CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205836Orig1s000
205837Orig1s000
205838Orig1s000

PHARMACOLOGY REVIEW(S)

Tertiary Pharmacology Review

By: Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology, OND IO
NDA: 205836 (tablet), 205837 (injection) and 205838 (oral solution)
Submission date: 11/24/2014
Drug: brivaracetam
Applicant: UCB Inc.
Indication: adjunctive therapy in the treatment of partial onset seizures in epilepsy

Reviewing Division: Division of Neurology Products

Discussion:

The primary and secondary pharmacology/toxicology reviewers concluded that the nonclinical information submitted for brivaracetam was sufficient to support approval for the indication listed above. The primary reviewer recommended follow up reproductive and developmental toxicity studies in the rat. The reviewer concluded that the high doses were not high enough because maternal and paternal toxicity was not achieved. The secondary reviewer concluded that repeating the rat reproductive and developmental toxicity studies was not needed because: 1) higher doses may not be possible because of toxicity, 2) higher doses are only likely to produce modest increases in exposure and 3) the doses tested in the rat already provide a 30 fold margin between the NOAEL and the human exposure. I also note that adverse findings were observed in the rabbit embryofetal study and there is only a margin of 4 between the NOAEL and the human exposure so defining a higher NOAEL in the rat may not be particularly informative.

No Established Pharmacologic Class is proposed for the draft labeling. The mechanism by which brivaracetam exerts its anticonvulsant activity is unknown so not including an Established Pharmacologic Class at this time is acceptable.

Conclusions:
The pharmacology/toxicology reviewer and supervisor conducted a thorough evaluation of the nonclinical information submitted in support of this NDA. I agree that the application can be approved from the pharmacology/toxicology perspective and that repeating the rat reproductive and developmental toxicity studies is not necessary.

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/s/

PAUL C BROWN
02/18/2016

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: January 23, 2016

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDAs 205-836, 205-837, and 205-838 (brivaracetam; ucb 34714)

NDAs 205-836, 205-837, and 205-838 have been submitted by the sponsor (UCB, Inc.) to support approval of brivaracetam (proposed tradename, Briviact) as adjunctive therapy in the treatment of partial onset seizures in epilepsy patients ≥16 years of age. NDA 205-836 is for a tablet (10, 25, 50, 75, 100 mg); NDA 205-837 is for an injection (10 mg/mL); NDA 205-838 is for an oral solution. Oral is to be the primary route of administration, with the intravenous route to be used in situations in which oral administration is not feasible.

To support the oral route of administration, a comprehensive battery of nonclinical studies was conducted, including primary and secondary pharmacology, safety pharmacology, PK/ADME, chronic toxicity, reproductive and developmental, carcinogenicity, and genotoxicity studies, all of which were submitted under NDA 205-836. To support short-term intravenous (IV) administration, the sponsor conducted one-month IV toxicity studies in rat and dog. These data have been reviewed in detail by Dr. Fisher (*cf. Pharmacology/Toxicology Review and Evaluation NDA 205-836, NDA 205-837, NDA 205-838, J. Edward Fisher, Ph.D., December 2, 2015*). Based on his review, Dr. Fisher has concluded that the nonclinical data support approval but that further assessment of reproductive and developmental toxicity should be conducted post-approval.

This memo provides a brief summary of selected nonclinical findings and conclusions and recommendations based on these findings. A detailed description and discussion of all the nonclinical data are provided in Dr. Fisher's review.

Pharmacology

Brivaracetam is a high-affinity synaptic vesicle protein 2A (SV2A) ligand. SV2 is comprised of a family of transmembrane proteins (SV2A, SV2B, SV2C), which are

located in all synaptic vesicles; SV2A is widely distributed in the CNS, but its functions are not well understood. The role of SV2A in the pathophysiology of epilepsy is suggested by the observation that levetiracetam (Keppra), an approved anticonvulsant, is a ligand for the SV2A protein and has what has been characterized as a unique or distinctive pharmacological profile (*cf.* Lynch BA *et al. PNAS 101(26):9861-9866, 2004*). Brivaracetam is a structural analog of levetiracetam, with up to 30 times higher in vitro binding affinity for the SV2A (K_i of 226 nM) compared to levetiracetam (*cf.* Ferlazzo E *et al. Neuropsychiatr Dis Treat* 11:2967-2973, 2015; Gillard M *et al. Eur J Pharmacol* 664:36-44, 2011) and no affinity for 50 other receptors/binding sites. In vivo, brivaracetam was active in multiple animal models of partial (e.g., fully 6 Hz and corneally-kindled seizures; ED_{50}'s of 62 and 1.2 mg/kg IP, respectively, in NMRI mouse) and generalized epilepsy (e.g., spontaneous spike and wave discharges in genetic absence epilepsy rats from Strasbourg [GAERS] and audiogenic seizures in sound-susceptible mouse; ED_{50}'s of 2.6 and 2.4 mg/kg IP, respectively).

Brivaracetam's anticonvulsant activity in vivo appears attributable to the parent compound; the only major circulating metabolite in humans (ucb-100406-1) was inactive in selected animal models of anticonvulsant activity (e.g., audiogenic seizures in sound susceptible DBA mouse) at 229 mg/kg IP. One additional metabolite (ucb-107092-1), which circulates at substantially higher plasma levels in severely renally impaired patients, was also inactive in various animal models (e.g., audiogenic seizures in sound susceptible DBA mouse, MES- and PTZ-induced seizures in NMRI mouse, fully amygdala-kindled seizures) at doses up to 229-413 mg/kg IP; in contrast, brivaracetam was active in these models, with ED_{50}'s of 2.4-113 mg/kg IP.

Safety Pharmacology: A number of safety pharmacology studies were conducted to investigate potential effects of brivaracetam on CNS, cardiovascular, respiratory, and GI systems.

Effects on the CNS were tested in normal rat (Sprague-Dawley, Wistar) and mouse (NMRI), in fully corneally kindled mouse and rat, and in GAERS. Effects on spontaneous motor activity (SMA) were tested in Sprague-Dawley rat at acute doses of 2.1-212 mg/kg IP; significant decreases in SMA were observed at the two highest doses tested (46 and 66% at 118 and 212 mg/kg IP, respectively). Using the Irwin test, dose-dependent incidence and severity of CNS depression (clinical signs included decreased SMA, passivity, abnormal posture/decreased body tone, and decreased startle and response to touch and pain) was demonstrated in fasted Wistar rat at acute doses of 100, 300, 600 (F only), 1000, and 1500 (M only) mg/kg; premature sacrifice (1/group) at the two highest doses resulted in sacrifice of all animals in those groups 5 and 4 hrs, respectively, post dose. To assess food effects on response to brivaracetam, an acute oral dose of brivaracetam (600 mg/kg) was administered to fasted and non-fasted Wistar rat (no concurrent controls). Clinical signs of CNS depression were evident in both fasted and non-fasted animals; however, the incidence and severity were clearly greater in the fasted animals. Rotarod performance was impaired in a dose-dependent manner in fully corneally kindled animals (ED_{50}'s of 55, 163, and 177 mg/kg IP in NMRI mouse, Sprague-Dawley rat, and GAERS, respectively).

Effects on cognitive function were tested in normal and fully kindled Sprague-Dawley rat using the Morris Water maze. At doses of 2.1-21 mg/kg IP, no adverse effects were observed. In an in vitro study conducted in hippocampal slices from Sprague-Dawley rats, brivaracetam (3-30 μM) had no effect on NMDA-dependent long-term potentiation.

The cardiovascular effects of brivaracetam were tested in a series of in vitro and in vivo studies. In in vitro studies, brivaracetam had no effect on hERG channel current or human cardiac sodium channels (hNav1.5) in stably transfected HEK293 cells at concentrations up to 100 μM and only a minimal effect on L-type calcium current in CHO cells overexpressing human Cav1.2 calcium channels (~8% at 100 μM vs 3.6% in control). In isolated canine Purkinje fibers (electronically paced at 0.5, 1, or 3 Hz), brivaracetam (2-200 μg/mL) had no effect on action potential duration, maximum rate of depolarization, upstroke amplitude, or resting membrane potential.

In vivo studies in Beagle dog assessed effects of brivaracetam on both cardiovascular and respiratory parameters following IV or PO administration. In one of the studies in anesthetized dogs, brivaracetam was administered IV (10-min infusion) at ascending doses of 5, 50, and 150 mg/kg (actual drug concentrations were only ~89-94% of nominal) at 60-min intervals. Primary effects were decreases in heart rate and increases in respiratory rate and minute volume at 50 and 150 mg/kg, and increases in QTc (Bazett's, Fridericia's, and Van de Waters corrections) and decreases in blood pressure (DAP, SAP, MAP) and left ventricular pressure at 150 mg/kg. No effects were observed at 5 mg/kg. In a second study in anesthetized dogs, brivaracetam was administered IV (10-min infusion) at ascending doses of 5, 15, and 45 mg/kg, at 30-min intervals. Minimal or no effects were observed on the cardiovascular or respiratory parameters assessed. In an in vivo study in conscious telemeterized dogs, effects on cardiovascular parameters were assessed following oral ascending oral doses of 5, 50, and 150 mg/kg, with a 2-day washout period between doses. There were no clear drug-related effects in males. In females, decreases in blood pressure (DAP, SAP, MAP) were observed at 50 and 150 mg/kg (4-8 hrs post dose), with effect being prolonged at 150 mg/kg (still evident 20 hrs post dose); heart rate was elevated at 50 and 150 mg/kg (53 and 31 bpm, respectively) at 1 hr post dose. ECG waveform findings in females included shortening of the RR and PR intervals and increases in QT_cF at 50 and 150 mg/kg; when QT_c was calculated using an animal-specific correction (QT_cQ), QT_cQ was prolonged only at 150 mg/kg but for up to 4 hrs post dose. Differences in plasma exposure could not account for the differences in response between males and females, based on 2-hr post dose data; plasma levels at 2 hrs post dose were similar between sexes.

In a respiratory safety pharmacology study in Wistar rat using whole body plethysmography, brivaracetam produced a decrease in expiratory and relaxation times, suggesting respiratory stimulation, at acute doses of 100, 300, and 600 mg/kg PO; no effects were observed at 30 mg/kg PO.

Effects on GI transit (30 min following a charcoal meal) were assessed in Wistar rat following acute oral doses of 100, 300, and 600 mg/kg. Brivaracetam inhibited GI transit

at 300 and 600 mg/kg (~60 and 80% decrease in distance travelled, respectively). In comparison, morphine (20 mg/kg PO) resulted in an ~50% decrease in distance travelled. Gastric emptying was also inhibited at the same doses, with stomach weights being increased (43 and 63%, respectively); morphine had no effect on gastric emptying.

Metabolites: Metabolite, ucb-107092-1, demonstrated no effects in safety pharmacology studies (CNS in Sprague-Dawley rat at 10-100 mg/kg IV; cardiovascular [in vitro dog isolated cardiac Purkinje fibers, in vitro hERG assay, in vivo cardiovascular study in conscious telemeterized Beagle dog at 15 and 150 mg/kg IV], respiratory in Sprague-Dawley rat at 10-100 mg/kg IV, and GI transit in Sprague-Dawley rat at 10-100 mg/kg IV).

PK/ADME

The PK/ADME of oral and IV brivaracetam was assessed primarily in NMRI mouse, Wistar rat, Beagle dog, and cynomolgus monkey. PK data following acute IV or PO doses are summarized in the following table. In rat, dosing in the fasted (F) state resulted in ~30% higher plasma exposure compared to dosing in the non-fasted (NF) state.

SPECIES	DOSE (mg/kg)	F/NF	PARAMETERS						
			C_{max}/C_0 (ng/mL)	T_{max} (hr)	AUC (µg*hr/mL)	$t_{1/2}$ (hr)	Cl (mL/min/kg)	Vd (L/kg)	F (%)
rat	10 IV	F	16.4	--	42.2	1.73	3.95	0.590	--
	10 PO		12.9	0.5	42.5	1.78	--	--	101
	600 PO	F	292	2	1995	--	--	--	--
		NF	166	1	1547	--	--	--	--
dog	5 IV	F	--	--	26.3±4.5	--	3.24±0.57	0.66	--
	5 PO		6.94±0.92	1	28.5±5.0	--	--	--	107.0±14.2
monkey	5 IV	F	9.7-6.2	--	4.7-3.4	0.3	21-29	0.61-0.77	--
	5 PO		0.08-0.22	0.5-1	--	--	--	--	--

Serum protein binding was low (12-20.7% bound) in all species tested, including human.

Urine was the major route of elimination in NMRI mouse (5, 100 mg/kg PO), Wistar rat (5, 100 mg/kg PO), Beagle dog (5 mg/kg IV, PO), and cynomolgus monkey (5 mg/kg IV, PO) (~80-88, 80-84, 85-91, and 73-83% of dose, respectively).

Tissue distribution studies were conducted in male Wistar rat and in non-pregnant and pregnant female Wistar rats. In male rat (non-fasted), ^{14}C-brivaracetam was administered orally for one week at a single dose of 5 mg/kg (Days 1 and 7) or 5 mg/kg BID (12-hr interval; Days 2-6); tissues were collected for up to 24 hrs after the dose on Day 1 and up to 336 hrs after the last dose (Day 7). Peak levels of radioactivity were detected at the first time point (one hour post dose) in plasma and all tissues assessed except for urinary bladder and fur (T_{max} = 4 hrs post dose), even with repeat dosing. The highest tissue concentrations (>10 µg eq/g) were detected in urinary bladder, preputial gland, and kidney, while the lowest (<3 µg eq/g) were detected in brain (cerebrum, cerebellum), spinal cord, lens, and fur.

In a separate study, fasted male and female (non-pregnant and pregnant [GD 16]) rats were administered ^{14}C-brivaracetam at an acute oral dose of 5 mg/kg. Selected tissues were collected for up to 96 (pregnant animals) or 336 hrs (males and non-pregnant females) post dose. In pregnant animals, ≤2% of dose radioactivity was detected in placenta, amniotic fluid, and fetal tissue at 1 hr post dose (T_{max}).

In a study in pigmented rat (acute dose of 5 mg/kg PO, ^{14}C-brivaracetam), no increased binding in pigmented tissues (compared to albino rat) was detected.

Toxicology

The pivotal general toxicity studies were conducted in Wistar rat (4-, 13-, and 26-week PO; 4-week IV), Beagle dog (4- and 26-week PO; 4-week IV), and cynomolgus monkey (4- and 39-week PO).

Oral studies: In rat, brivaracetam was administered either by gavage (BID, 6-hr interval) (4- and 13-week studies) or by a combination of dietary admixture and gavage (BID, 6-hr interval) (26-week study). Dose-ranging studies were conducted at acute doses up to 2000 mg/kg/day or doses of 0, 200, 400, and 600 mg/kg QD for 7 days or 0, 100, 300 and 1000 mg/kg QD for 2 weeks. An acute dose of 2000 mg/kg resulted CNS signs and the moribund sacrifice of females. In the 7-day study, all doses were associated with liver findings (increased liver weight, hepatocellular hypertrophy) and increases in CYP450 in males but were well-tolerated in males and females. In the 2-week study, the HD resulted in reduced body weight gain (8%) in males; liver findings (hepatocellular hypertrophy) and increases in CYP 450 were observed at all doses.

In the 4-week study (0, 100, 300, 1000, and 1500 mg/kg/day, given BID, 6-hr interval), 7 HD (mostly M; main-study and TK-satellite) animals were sacrificed moribund on Days 1-9, resulting in early termination of that group; 3 MDM were sacrificed moribund on Days 7-100, but all were TK-satellite animals. At the lower doses tested in the 13-week (0, 50, 100, 200, and 400 mg/kg/day, given BID, 6-hr interval) and 26-week (0/0, 100/50, 100/130, and 100/350 mg/kg/day [diet admixture/gavage (BID, 6-hr interval)]) studies, all doses were well-tolerated. (Also, in a dietary admixture/gavage (QD) dose-ranging study, doses of 0/0, 100/100, 300/150, and 1000/300 mg/kg/day were well-tolerated.)

The primary drug-related target organ identified in all the pivotal studies in rat was liver, with histopathology findings consisting of centrilobular hypertrophy, bile duct hyperplasia, bile duct pigment (lipofuscin, porphyrin), and/or mononuclear cell (peribiliary) inflammation. NOAELs for these findings (based on the incidence and/or severity) were 300 and 400 mg/kg/day in the 4- and 13-week oral gavage studies and 100/350 mg/kg/day in the 26-week dietary admixture/gavage study. In the 26-week study, renal hyaline droplet nephropathy was observed at all doses in males; therefore, no overall NOAEL was established in males.

Increases in liver CYP content and activity were demonstrated in dose-ranging and pivotal (4- and 13-week) studies. In general, plasma exposures (AUC) were lower with repeated dosing, consistent with enzyme induction.

In dog, brivaracetam was administered by oral gavage in the pivotal studies (BID, 6-hr interval in the 4- and 13-week studies; TID, 8-hr interval in the 26-week study). Liver was the primary target organ.

In a 2-week dose-ranging study (0, 100, 200, and 300 mg/kg/day), one HDF was sacrificed on Day 13, with liver toxicity. Histopathology findings in liver (including single cell necrosis, apoptosis, multifocal mononuclear inflammatory cell infiltrate, pigment deposition) were evident at all doses and were associated with increases in alkaline phosphatase, ALT, AST, and serum bile acids. In the 4-week study (0, 6, 15, 37.5, and 94 mg/kg/day), transient clinical signs (e.g., incoordination, unsteady gait) were observed at the HD. Liver findings (pigment [lipofuscin, porphyrin] deposition, single cell necrosis, mineral concretions in gallbladder lumen), associated with increases in alkaline phosphatase, ALT, and AST, were evident at the two highest doses tested. However, in the 13-week study (0, 6, 15, and 37.5 mg/kg/day; 4-week recovery), no liver histopathology was observed. The lack of effect on liver at the HD could not be explained by difference in plasma exposure between the 4- and 13-week studies; C_{max} and AUC were fairly similar between studies.

In the 26-week study (0, 15, 37.5, and 75 mg/kg/day), liver and biliary tract findings (pigment deposition ["consistent" with porphyrin pigment] in hepatocytes, Kupffer cells, and bile canaliculi, centrilobular fibrosis, hepatocyte single cell necrosis, concretions in lumen of gallbladder), associated with increases in ALT, SDH, GGT, alkaline phosphatase, and 5'-NT, were observed at all but the lowest dose tested, associated with plasma C_{max} and $AUC_{(0\text{-}24\ hr)}$ for brivaracetam of 4.88 ± 0.31 µg/mL and 34.7 ± 3.3 µg*hr/mL, respectively. (For comparison, the expected plasma C_{max} and $AUC_{(0\text{-}24\ hr)}$ at the proposed human daily dose of 200 mg/day [given 100 mg BID] are 3.5 µg/mL and 55 µg*hr/mL, respectively.)

The sponsor attributed the liver findings to "dog-specific porphyria," supported primarily by data from studies of a structurally related compound (ucb-101747-1), not brivaracetam. However, Dr. Fisher reviewed the sponsor's supportive data and has concluded that the brivaracetam data support the sponsor's proposed mechanism. In addition, the liver findings were associated with increases in clinically monitorable clinical pathology parameters; therefore, the relevance of the findings can more definitively be addressed by the clinical data.

In monkey, the pivotal (4- and 39-week) oral toxicity studies were conducted at doses of 0, 300, 600, and 900 mg/kg/day (given BID, 10-hr interval). Dose selection was based on the results of two oral dose-ranging studies. In a single dose (200, 400, and 800 mg/kg, given as two equal doses at a 6-hr interval) and 7-day MTD (1200, 1600, and 3200 mg/kg/day, given BID, 6-hr interval) dose-ranging study, the 1200 mg/kg/day dose was identified as the MTD, based on severe toxicity (prostration, blood in vomit associated

with marked erosion and hemorrhaging in the cardiac area of stomach; moribund sacrifice) at 3200 mg/kg/day. The C_{max} and $AUC_{(0\text{-}24\ hr)}$ at 1200 mg/kg (M-F) were 272-240 µg/mL and 2544-3503 µg*hr/mL, respectively. In a 2-week dose ranging study (0, 100, 300, and 900 mg/kg/day, given BID, 10-hr interval), the high dose was identified as an NOAEL but was associated with transient clinical signs and increased liver weight (associated with increases in triglycerides, ALT, and GGT), and dark area of the cardia (stomach) in one female. C_{max} and $AUC_{(0\text{-}24\ hr)}$ at 900 mg/kg/day were 149 µg/mL and 1265 µg*hr/mL, respectively.

In the pivotal studies, the highest dose tested (900 mg/kg/day) was identified as the NOAEL, associated only with transient clinical signs and increases in liver weight. There were no histopathological correlates in the 4-week study; in the 39-week study, hepatocellular hypertrophy (characterized as minimal/slight) and brown pigment deposition were observed in liver at the high dose. Plasma exposures at 900 mg/kg/day were as follows:

- 4-week: 149 µg/mL and 1265 µg*hr/mL for C_{max} and $AUC_{(0\text{-}24\ hr)}$, respectively
- 39-week: 161 µg/mL and 1518 µg*hr/mL for C_{max} and $AUC_{(0\text{-}24\ hr)}$, respectively

IV studies: in rat, brivaracetam was administered by continuous IV infusion at doses of 0, 200, 600, and 1000 mg/kg/day for 4 weeks in the pivotal study. Dose selection was based on data from a 7-day dose-ranging study at doses of 0, 200, 600, and 1200 mg/kg/day given by continuous IV infusion. Transient effect (clinical signs in HDF; reduced body weight gain in MDM and HDM; reduced food consumption in MD and HD animals) were observed for the first 3 days of dosing; liver findings (centrilobular hypertrophy, increased mitotic rate) were observed primarily at the MD and HD; the LD was identified as the NOAEL in both males and females.

In the pivotal 4-week study (2-week recovery period), the primary findings consisted of microscopic changes in liver (centrilobular hypertrophy at the MD and HD) and thyroid (follicular cell hypertrophy at all dose in males and in MDF and HDF). The NOAEL in females was the MD, whereas no NOAEL was identified in males because of chronic progressive nephropathy at all doses. Plasma brivaracetam exposures were as follows:

- Plasma concentrations
  - Day 1
    - Peak levels (M-F): 24.9-34.5, 71.3-143, and 144-300 µg/mL at LD, MD, and HD, respectively
  - Day 28
    - males: ~6-8, 20-29, and 25-34 µg/mL at LD, MD, and HD, respectively
    - females: ~19-23, 35-50, and 100-150 µg/mL at LD, MD, and HD, respectively
- Plasma AUC (M-F)
  - Day 1: 461-816, 1709-2945, and 3260-6795 µg-eq*hr/mL at LD, MD, and HD, respectively

- Day 28: 168-518, 578-992, and 710-3061 µg-eq*hr/mL at LD, MD, and HD, respectively

In dog, brivaracetam was administered by continuous IV infusion at doses of 0, 30, 100, and 150/300/200 mg/kg/day for 4 weeks. Dose selection was based on data from an MTD/dose-ranging study in which acute (10, 30, 60, 100, and 150 mg/kg/day, each for 3 days with 2-3 day washout between doses) and multiple (75 mg/kg/day for 2 days, followed by 150 mg/kg/day for 5 days) doses, administered by continuous IV infusion, were well-tolerated.

In the pivotal 4-week study (2-week recovery period), the high dose was titrated up to 300 mg/kg/day (by Day 3). Because of decreased body weight (up to 10%) at 300 mg/kg, the high dose was reduced to 200 mg/kg (from D16/15 on) in both males and females. No drug-related effects were observed on ECG parameters, assessed on Days 1, 8, and 28. Effects on liver, similar to those observed in the oral studies (including hepatocellular apoptosis, inflammatory cell infiltrates, gallbladder concretions), were observed at all but the LD, which was identified as the NOAEL. Plasma brivaracetam levels on Day 28 were ~2-3, 8-9, and 24-29 µg/mL at the LD, MD, and HD, respectively. Plasma brivaracetam AUCs were as follows:

- Day 1: 116 ± 12, 498 ± 52, and 828 ± 138 µg-eq*hr/mL at the LD, MD, and HD (150 mg/kg), respectively
- Day 28: 58.4 ± 4.4, 205 ± 25, and 624 ± 95 µg-eq*hr/mL at the LD, MD, and HD (200 mg/kg), respectively

IV toxicity studies of metabolite, ucb-107092-1, did not identify toxicities other than those likely attributable to procedural issues (e.g., infection, cannula placement) or local toxicity. In a pivotal 13-week toxicity study in Wistar rat at doses up to 2000 mg/kg/day (continuous infusion), the high dose was identified as an NOAEL.

Genetic Toxicology

A standard battery of genetic toxicology studies were conducted on brivaracetam. Brivaracetam was negative in the Ames assay, the *in vitro* chromosomal aberration assay in CHO cells, and the *in vivo* micronucleus assay in Wistar rat (0, 500, 1000, and 2000 mg/kg/day PO).

In an *in vitro* mouse lymphoma *tk* assay, increases in mutant fraction (MF) were observed in the absence of metabolic activation (4-hr exposure) in two separate experiments. However, brivaracetam may be considered negative in this assay because: (1) in the first experiment, the increase in MF observed (80 x 10^{-6} at 4800 µg/mL) did not exceed the GEF criterion for a positive response (i.e., 169 x 10^{-6}) and (2) in the second experiment, while the increase in MF observed (342 x 10^{-6}) exceeded the GEF criterion for a positive response, it was observed only at a concentration (4200 µg/mL) associated with an RTG of 10%, which should not be considered a positive response (*cf.* ICH S2(R1), June 2012).

A standard battery of genetic toxicity studies (Ames assay, *in vitro* mouse lymphoma tk assay, *in* vivo micronucleus assay in rat) of metabolite, ucb-107092-1, demonstrated no evidence of genotoxic potential.

Carcinogenicity

The carcinogenic potential of brivaracetam was tested in 2-year dietary/gavage carcinogenicity studies in CD-1 mouse (0/0, 300/100, 300/250, and 300/400 mg/kg/day; total doses: 0, 400, 550, and 700 mg/kg/day) and Wistar rat (0/0, 100/50, 100/130, 100/350, and 100/600 mg/kg/day; total doses: 0, 150, 230, 450, and 700 mg/kg/day). Drug-related neoplastic findings are summarized in the following tables.

MOUSE TISSUE	**FINDING**	**MALES**			
		0	**400**	**550**	**700**
Liver (hepatocytes)	adenoma	7/60	9/60	16/60	17/60*
	carcinoma	0/60	2/60	3/60	9/60*
	adenoma + carcinoma	7/60	9/60	17/60*	18/60*

*statistically significant by trend and pair-wise analyses

RAT TISSUE	**FINDING**	**FEMALES**				
		0	**150**	**230**	**450**	**700**
Thymus (epithelial cell; thymoma)	benign	2/50	2/48	4/48	5/50	11/50*
	malignant	0/50	1/48	0/48	0/50	0/50
	benign + malignant	2/50	3/48	4/48	5/50	11/50*

*statistically significant by trend and pair-wise analyses

Reproductive and Developmental Toxicology

The reproductive and developmental toxicology of brivaracetam was tested in Wistar rat (fertility and early embryonic, embryofetal, and pre- and postnatal development) and New Zealand White rabbit (embryofetal development).

The effects of brivaracetam on fertility and early embryonic development were assessed at oral doses of 0, 100, 200, and 400 mg/kg/day (given BID, 6-hr interval). Males were dosed for approximately 28 days prior to mating, throughout the mating period, and for approximately 2 weeks following the mating period; females were dosed for 2 weeks prior to mating, throughout the mating period, and to gestation day (GD) 6. No maternal toxicity and no adverse effects on fertility or developmental parameters were observed.

Effects of brivaracetam on embryofetal development were assessed in rat at oral doses of 0, 150, 300, and 600 mg/kg/day (given BID, 6-hr interval) administered during GDs 6-17. The only drug-related finding in dams was an increase in clinical signs (salivation, ptosis) at the high dose; no fetal effects were observed.

In the embryofetal development study in rabbit, brivaracetam was administered orally at doses of 0, 30, 60, 120, and 240 mg/kg/day (given BID, 6-hr interval). Dose selection was based on data from two dose-ranging studies, one in non-pregnant animals (0, 100,

200, and 400 mg/kg QD for 3 days, each dose separated by 3-4 day washout; 300 mg/kg QD for 7 days) and one in pregnant animals (0, 50, 100, 200 and 300 mg/kg/day [given BID, 6-hr interval] on GDs 6-19). In non-pregnant females, 300 mg/kg/day was identified as an MTD, based on decreased fecal output and body weight loss accompanied by decreases in food consumption; in pregnant animals, similar findings were noted at ≥200 mg/kg/day, in addition to an increase in post-implantation loss at 300 mg/kg/day.

In the pivotal study, there was a dose-related decreased fecal output and body weight loss, followed by decreases in body weight gain for the first week of dosing; however, body weights were similar among groups by GD 19. Five females were sacrificed moribund following persistent decreases in food consumption and body weight loss; however, the incidence was not dose-related (2, 0, 1, and 2 females at 30, 60, 120, and 240 mg/kg/day, respectively). Post-implantation loss was increased at the HD, resulting in a decrease in the number of live fetuses at that dose. Fetal effects consisted primarily of increases in the number of runts at the high dose and minor variations (including 27 rather than 26 presacral vertebrae) at all doses.

In the pre- and postnatal development study in rat, brivaracetam was administered at oral doses of 0, 150, 300, and 600 mg/kg/day (given BID, 10-hr interval) from GD 6 to lactation day (LD) 20. No toxicity was noted in the dams; therefore, the HD was the maternal NOAEL. Findings in the pups consisted primarily of decreases in body weight and delayed (2 days) vaginal patency in female pups at the high dose. In addition, Dr. Fisher noted evidence of adverse effects on learning and memory tasks (e.g., "…decreased auditory startle reactivity… and impaired Biel maze learning and memory…"), although most findings were not significantly affected.

Based on review of the data from the battery of reproductive and developmental toxicity studies in rat, Dr. Fisher concluded that sufficiently high doses had not been achieved in any of these studies, as evidenced by the lack of parental toxicity, and recommended that the entire battery be repeated at higher doses post-marketing (i.e., as post-marketing requirements). However, Dr. Fisher did note that the pre- and postnatal development study should be repeated only "…if the repeat rat embryofetal development study shows that significantly higher doses can be administered to pregnant rats."

The TK data (at the last time point sampled in each study), as well as accumulation ratios, from the most relevant toxicity studies in rat are summarized in the following tables, as well as the TK data from the reproductive and developmental toxicity studies. Plasma AUC data were calculated over a 12 or 24-hr period. Because of the short $t_{1/2}$ and the 6-hr dosing interval use in most of the gavage studies, the 0-12 hr interval was considered by the sponsor to capture exposure over a 24-hr period; therefore, the $AUC_{(0\text{-}12\ hr)}$ value should not be doubled to obtain $AUC_{(0\text{-}24\ hr)}$.

Taking into consideration the duration of dosing for each of the reproductive and developmental toxicity studies, the most relevant toxicity studies were conducted using gavage (BID) administration only and were of 2-weeks' duration for the embryofetal development study), 4-weeks' duration for the female fertility and pre- and postnatal

development studies, and 13-weeks' duration for the male fertility study. (AUCs were not calculated in the fertility study.) TK data from these studies are summarized below.

MALES

STUDY	DOSES (mg/kg)							
	30	50	100	200	300	400	1000	1500
C_{max} (µg/mL)								
2-wk	21.9		54.0		81.1		116.1	
4-wk			24.7		58.4		98.2	n/d
13-wk		13.8	20.9	37.8		72.6		
AUC* (µg•hr/mL)								
2-wk	54.2		146.9		368.7		888.8	
4-wk			78.5		265		603	n/d
13-wk		70.7	99.5	177		317		

*values calculated as $AUC_{(0\text{-}24\ hr)}$ for the 2-week study and $AUC_{(0\text{-}12\ hr)}$ for the 4- and 13-week studies; n/d = not determined because of premature sacrifice of group

STUDY	DOSES (mg/kg)		
	100	200	400
$C_{(0\text{-}5\ hr)}$# (µg/mL)			
fertility	27.7 ± 7.8	42.3 ± 12.7	52.1 ± 18.6

measured 0.5 hrs after 2nd daily dose (6 hrs between doses)

FEMALES

STUDY	DOSES (mg/kg)							
	30	50	100	200	300	400	1000	1500
C_{max} (µg/mL)								
2-wk	29.8		66.7		116.1		195.4	
4-wk			39.4		70.0		114	n/d
13-wk		21.1	39.8	77.8		111		
AUC* (µg•hr/mL)								
2-wk	97.8		312.1		803.5		2466.3	
4-wk			169		432		1135	n/d
13-wk		121	251	440		743		

*values calculated as $AUC_{(0\text{-}24\ hr)}$ for the 2-week study and $AUC_{(0\text{-}12\ hr)}$ for the 4- and 13-week studies; n/d = not determined because of premature sacrifice of group

STUDY	DOSES (mg/kg)					
	100	150	200	300	400	600
C_{max} (µg/mL)						
fertility	38.6 ± 6.6		55.9 ± 10.8		79.2 ± 33.0	
EFD		55.9		93.4		184
pre/post		38.0		57.0		74.9
$AUC_{(0\text{-}24\ hr)}$ (µg•hr/mL)						
fertility	--		--		--	
EFD		586		1099		1801
pre/post		278		377		964

Accumulation (Week 2-13 vs D1 ratios) at doses most relevant to the reproductive and developmental toxicity studies is summarized in the following table.

STUDY	DOSES (mg/kg)				
	100	200	300	400	1000
MALES					
Cmax					
2-wk	0.85		0.78		0.78
4-wk	0.67		0.67		0.79
13-wk	0.81	0.81		0.89	
AUC					
2-wk	0.50		0.45		0.44
4-wk	0.47		0.43		0.50
13-wk	0.57	0.61		0.44	
FEMALES					
Cmax					
2-wk	0.93		0.88		0.92
4-wk	0.96		0.85		0.61
13-wk	0.91	1.11		0.98	
AUC					
2-wk	0.74		0.57		0.95
4-wk	0.80		0.56		0.65
13-wk	0.89	0.96		0.88	

In males, premature deaths occurred at 1000 and 1500 mg/kg/day (4-week study); therefore, the highest dose tested in the fertility study was 400 mg/kg/day. Plasma exposures at that dose in the 13-week study and at 1000 mg/kg/day in the 4-week study were as follows:

- C_{max}: 72.6 and 98.2 µg/mL at 400 and 1000 mg/kg/day, respectively
- AUC: 317 and 603 µg*hr/mL at 400 and 1000 mg/kg/day, respectively

These data suggest that a repeat male fertility study at a high dose between 400 and 1000 mg/kg/day would provide an assessment of reproductive toxicity at plasma exposures ≤50% higher than those likely to have been achieved in the completed study.

In females, the results of the toxicity studies suggest that 1000 mg/kg/day is the highest dose that would have been tolerated, based on premature deaths at 1500 mg/kg in the 4-week study. Plasma exposures obtained at the highest dose (600 mg/kg) used in the embryofetal development study and those obtained in the 2-week study at 1000 mg/kg were as follows:

- C_{max}: 184 and 195.4 µg/mL at 600 and 1000 mg/kg/day, respectively
- AUC: 1801 and 2466.3 µg*hr/mL at 600 and 1000 mg/kg/day, respectively

Plasma exposures at 1000 mg/kg/day were <40% higher than that at the highest dose tested in the embryofetal development study.

While the plasma AUC at 1000 mg/kg/day in the 2-week study was substantially higher than that obtained at 600 mg/kg/day in the pre- and postnatal development study (964 µg*hr/mL), plasma exposures were lower after 4 weeks of dosing at 1000 mg/kg, suggesting continued enzyme induction between 2 and 4 weeks of dosing. Therefore, plasma exposures obtained at the highest dose (600 mg/kg) used in the pre- and postnatal development study and that obtained in the 4-week study at 1000 mg/kg/day were as follows:

- C_{max}: 74.9 and 114 µg/mL at 600 and 1000 mg/kg/day, respectively
- AUC: 964 and 1135 µg*hr/mL at 600 and 1000 mg/kg/day, respectively

Plasma exposures at 1000 mg/kg/day were 52 and 18% higher for C_{max} and AUC, respectively, compared to those at the highest dose tested in the pre- and postnatal development study.

In the fertility study, the highest dose tested was 400 mg/kg/day. The plasma concentration at 0.5 hrs (~C_{max}), the only sampling time, was 79 µg/mL. In the only pivotal study testing the 400 mg/kg/day dose (i.e., the 13-week study), plasma exposures were 111 µg/mL and 743 µg*hr/mL for C_{max} and AUC, respectively; TK data were not collected at Week 4. If one assumes the AUC would have been similar in the 4-week and fertility studies, the AUC would have only been approximately 50% higher if brivaracetam had been tested at 1000 mg/kg/day in the fertility study.

It is difficult to compare plasma exposure among studies, particular considering the differences in doses tested and the less-than linear TK resulting from enzyme induction with multiple dosing. However, based on the data and reasonable estimates of plasma exposure, it appears that testing brivaracetam at the higher doses (possibly 600 mg/kg/day in males and 1000 mg/kg/day in females) would not have resulted in sufficiently higher plasma exposure throughout the dosing periods to warrant repeat studies. The plasma AUCs achieved in the 1-month IV (continuous infusion) toxicity study at the highest dose tested (1000 mg/kg/day) were higher than those achieved in the oral studies; however, administration by continuous infusion is not feasible for fertility or pre- and postnatal development studies. While continuous infusion may be feasible in an embryofetal development study, the plasma AUC at the highest dose of brivaracetam tested in the oral embryofetal development study provides a substantial safety margin (>30 times) compared to exposures anticipated in humans (55 µg*hr/mL) at the maximum recommended daily dose of 100 mg BID.

Juvenile Animal Toxicology

Although all NDAs submitted for brivaracetam propose use in epilepsy patients at least 16 years of age, the sponsor conducted juvenile animal toxicology studies in juvenile Wistar rat and Beagle dog.

In the study in juvenile rat, brivaracetam was administered at oral doses of 0, 150, 300 and 600 mg/kg/day (given BID, 10-hr interval) on postnatal days (PND) 4 through 70,

with a 30-day recovery period. Dose selection was based on data from two dose-ranging studies. In the first dose-ranging study, brivaracetam was administered at oral doses of 0, 150, 300, and 600 mg/kg/day (given BID, 10-hr interval) on PNDs 4-28; an increase in deaths was observed at 600 mg/kg/day (mortality rate: 12.5, 7.5, 16.25, and 40% at 0, 150, 300, and 600 mg/kg/day, respectively). In the second dose-ranging study using the same doses and dosing regimen, but with dosing only on PNDs 4-21, an increase in deaths was observed at 300 and 600 mg/kg/day in males (0, 0, 3, and 7 deaths at 0, 150, 300, and 600 mg/kg/day, respectively) and at 600 mg/kg in females (0, 3, 1, and 5 deaths at 0, 150, 300, and 600 mg/kg/day, respectively).

In the pivotal study, there was an increase in deaths at the HD in both males (9, 7, 8, and 28 deaths at 0, 150, 300, and 600 mg/kg/day, respectively) and females (10, 2, 12, and 41 deaths at 0, 150, 300, and 600 mg/kg/day, respectively); in the majority of animals, the cause of death was not determined. Dr. Fisher noted a number of adverse effects on postnatal development at the HD ("…delayed male sexual maturation … short and long-term neurobehavioral changes…and impaired reproductive performance…) and "…persistent decreases in brain weight and size at all doses." Clearly, brivaracetam exhibited greater sensitivity to brivaracetam-induced toxicity in juvenile animals than in adult animals, which cannot be explained by differences in plasma exposures. A comparison of plasma exposures in the 13-week study in adult rat (in which there were no drug-related deaths) and those in the juvenile study at the highest doses tested (400 and 600 mg/kg/day, respectively) is provided in the following table:

STUDY	SAMPLING TIME	MALES		FEMALES	
		C_{max} (µmL)	AUC* (µg*hr/mL)	C_{max} (µmL)	AUC* (µg*hr/mL)
13-week	Day 1	91.5	712	79.1	844
	Week 13	39.9	317	81.6	743
juvenile+	PND 21	45.9	246	42.0	196
	PND 70	59.0	309	127	855

+dosing initiated on PND 4; *0-12 hrs in the 13-week study and 0-24 hrs in the juvenile animal study

In the juvenile dog, brivaracetam was administered at oral doses of 0, 15, 30, and 100 mg/kg/day (given BID, 10-hr interval) on PNDs 4 through 276 (273 consecutive days), with a 56-day recovery period. Dose selection was based on the results of a dose-ranging study at doses of 0, 15, 50, and 100 mg/kg/day (given BID, 10-hr interval) on PNDs 4 to 31. All doses were well-tolerated, except for a decrease in body weight gain (≤30%) at all the LD; effects on bone parameters (bone mineral content and density, bone area; short femoral length) were observed in MDM and HDM.

In the pivotal study, the only findings observed were liver findings similar to those observed in adult animals, primarily at the HD in males and females. No bone effects were detected, which is inconsistent with the results of the dose-ranging study. Difference in plasma exposure in males cannot explain the inconsistence since plasma exposures at the MD (50 mg/kg) in the dose-ranging study were lower than that the HD (100 mg/kg) in the pivotal study.

STUDY	SAMPLING TIME	MD+		HD	
		C_{max} (µmL)	$AUC_{(0\text{-}24\ hr)}$ (µg*hr/mL)	C_{max} (µmL)	$AUC_{(0\text{-}24\ hr)}$ (µg*hr/mL)
dose-ranging	PND 4	21.4	271	34.8	482
	PND 31	17.9	105	37.8	275
pivotal	PND 4	12.9	181	41.8	596
	PND 31	9.73	59.5	28.4	205
	PND 276	13.1	86.5	43.9	342

+50 mg/kg/day in the dose-ranging, 30 mg/kg/day in the pivotal juvenile study

Conclusions and Recommendations

I concur with Dr. Fisher's conclusion that the nonclinical data submitted in the NDAs for brivaracetam are adequate to support marketing approval, with appropriate labeling. While I agree that the general lack of maternal toxicity in the reproductive and developmental toxicity studies raises a concern regarding the adequacy of testing, the available TK data (with the caveats discussed) suggest that higher plasma exposures, sufficient to warrant repeat studies, would not have been achieved at doses that would have been tolerated. Therefore, I do not believe repeat studies are needed and recommend no post-marketing requirements as a condition of approval.

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/s/

LOIS M FREED
01/23/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER(S):	205836 (tablets), 205837 (injection), 205838 (oral solution)
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	11/24/14
PRODUCT:	brivaracetam (ucb 34714)
INDICATION:	epilepsy (adjunctive therapy for partial onset seizures in patients 16 years of age and older)
SPONSOR:	UCB
REVIEW DIVISION:	Division of Neurology Products (DNP)
PHARM/TOX REVIEWER:	Ed Fisher
PHARM/TOX SUPERVISOR:	Lois Freed
DIVISION DIRECTOR:	Billy Dunn
PROJECT MANAGER:	Heather Bullock

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Note: All figures and tables in this review were excerpted from the sponsor's submission or literature.

I. EXECUTIVE SUMMARY

A. Drug

Trade name: Briviact

Generic name: brivaracetam

Code names: ucb 34714, BRV

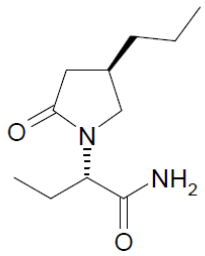
Chemical name: (2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1*H*-pyrrol-1-yl] butanamide

CAS registry number: 357336-20-0

Molecular formula: $C_{11}H_{20}N_2O_2$

Molecular weight: 212.29

Structure:



Drug class: anticonvulsant, synaptic vesicle protein 2A (SV2A) ligand

Indication: epilepsy; adjunctive treatment of POS in patients 16 years of age or older

Clinical dose: RSD is 100 mg/day and MRD is 200 mg/day

Dosage forms: oral tablets (NDA 205836), injection (N205837), oral solution (N205838)

Relevant INDs: 70205 (tablet), 103908 (iv solution), 110606 (oral solution)

B. Brief discussion of nonclinical findings

Brivaracetam (BRV, ucb 34714) was synthesized in a drug discovery program aimed at identifying selective and high affinity ligands for the levetiracetam (LEV) binding site, which is thought to represent synaptic vesicle protein 2A (SV2A), a widely distributed CNS protein thought to be involved in the coordination of synaptic vesicle exocytosis and neurotransmitter release. While the mechanism of action is unknown, binding to SV2A is highly correlated with anticonvulsant activity in animal models of epilepsy.

BRV binds to SV2A with an affinity ~10-fold greater than that of LEV. BRV was also shown to inhibit voltage-dependent Na^+ channels.

BRV was active in a variety of animal seizure models, with a profile similar to LEV but with greater potency. Nonclinical safety testing of BRV included safety pharmacology, general toxicology, genotoxicity, carcinogenicity, and reproductive and developmental toxicity studies. In the acute oral CNS safety testing in rats, transient signs of CNS depression were generally seen at doses of 100 mg/kg (parent AUC: 295 and 421 ug.hr/mL in males and females, respectively) or greater, and the lethal dose was >1000 mg/kg. In cardiovascular safety studies conducted in dogs, decreases in blood pressure, heart rate, and cardiac contractility and increases in QT and QTc were observed at iv and oral doses (≥50 mg/kg) that were associated with peak plasma levels of BRV above that measured in humans at the maximum recommended dose (MRD) of 100 mg BID (Cmax: 3.5 µg/mL in clinical study N1067).

BRV was rapidly and completely absorbed after oral administration (F ~100% in rats and dogs [also humans], <10% in monkeys due to high first-pass metabolism) and the half-life ranged from 2 h in rats to 0.3 h in monkeys (8 h in humans). Parent drug represented the most abundant circulating material in vivo in all species (including humans) except the cynomolgus monkey, which showed increased metabolic clearance compared to other species. In rodents, monkeys, and humans, ucb-100406-1 was the only metabolite exceeding 10% of the total circulating drug-related material. In dog, major metabolites included both ucb-100406-1 and ucb-102993-1, a derivative (with no pharmacological activity) resulting from the hydroxylation of the butyramide side-chain. Other metabolites were present in much smaller amounts. No in vivo metabolites were specific to humans. Coverage for the 3 primary human metabolites, ucb-100406-1 (major metabolite), ucb-42145, and ucb-107092-1, appeared adequate in the toxicology studies. However, because there was inadequate coverage for the minor metabolite ucb-107092-1 in subjects with severe renal impairment, the sponsor conducted stand-alone rat toxicity studies (safety pharmacology, 3-month general toxicity, genotoxicity, and embryofetal development) in which the metabolite was directly administered intravenously (iv). There was no indication of toxicity (NOAEL was the highest dose tested) at exposures much higher (30-50X) than those in subjects with severe renal impairment.

In chronic oral toxicity studies in the rat, dog, and monkey, effects on the liver were the most consistent findings. The changes seen in rat and monkey were mild and considered primarily adaptive, and there were adequate exposure margins between doses associated with toxicity in animals and human exposures (AUC) at the MRD (56 ug.h/mL in clinical study N1067). The no adverse effect level (NOAEL) in the chronic (26-week) rat study was considered to be 450 mg/kg/day (AUC: 257 and 464 ug.h/mL, in males and females, respectively); and in the chronic (39-week) monkey study, only adaptive liver changes were seen at the highest dose tested (900 mg/kg/day, AUC: 2351 ug.h/mL, combined sexes). However, more severe liver toxicity, including hepatocellular necrosis, was observed in dogs, and the NOAEL for hepatotoxicity after 26 weeks of repeated administration to dogs was 15 mg/kg/day (AUC: 35 ug.h/mL). The hepatotoxicity seen in dogs was attributed to what appears to be a species-specific mechanism involving the formation of a reactive oxidative metabolite with structural similarities to known porphyrogenic agents. This putative reactive metabolite is thought to alkylate CYP and result in the formation of *N*-alkylprotoporphyrin IX, which leads to CYP inactivation. CYP inactivation, in turn, induces heme synthesis, accelerating the accumulation of porphyrin precursors, which ultimately produces the liver effects observed.

To support the safety of the iv formulation, 1-month continuous infusion studies were conducted in the rat and dog. Effects similar to those seen in oral studies (adaptive liver changes and male rat-specific renal effects in rats; hepatobiliary effects in dogs, including protoporphyrin pigmentation, increased

hepatocellular apoptosis, inflammatory cell infiltration, and fibrosis in the liver, increased liver enzymes, and accumulation of dark concretions in the gallbladder) were observed at the highest doses tested (≥600 mg/kg/day in rats, ≥ 100 mg/kg/day in dogs). In dogs, exposure (AUC) to parent at the NOAEL (30 mg/kg/day) was 58 µg.h/mL (combined sexes).

There was no evidence of BRV-induced genotoxicity. In 2-year carcinogenicity studies, increased incidences of liver tumors (hepatocellular adenoma and carcinoma) were seen in male mice at oral doses >400 mg/kg/day (AUC at NOAEL: 82 and 51 ug.h/mL in males and females, 1-1.5X human AUC at MRD) and increased incidences of thymus tumors (benign thymoma) were seen in female rats at oral doses >450 mg/kg/day (AUC at NOAEL: 333 and 529 ug.h/mL in males and females, ~6-9X human). The clinical significance of the drug-related increases in these tumor types in rodents, although uncertain, appears to be limited.

No clear adverse effects on fertility or embryofetal development were detected at the highest oral doses tested in rats (400 and 600 mg/kg/day, respectively; AUCs: 743 and 1801 ug.h/ml, 13 and 32X human at MRD). However, based on the failure to achieve the expected level of maternal (paternal) toxicity at these doses, the studies may not have fully characterized the potential reproductive and developmental effects of BRV in rats and should be repeated postmarketing. Adverse effects on embryofetal development (increased postimplantation loss, decreased fetal body weight, increased incidences of fetal skeletal variations) were seen rabbits at the highest dose tested, which was also maternally toxic. The rabbit developmental NOAEL was 120 mg/kg/day (maternal AUC: 198 ug.h/mL, ~3.5X human). In an oral pre- and postnatal development study in rats, there was some evidence of developmental toxicity (slight decrease in offspring growth and [female] sexual development and altered behavior [decreased locomotor activity]) at the high dose, but based on the lack of maternal toxicity at this dose, it is recommended that the study be repeated if the repeat rat embryofetal development study (or dose range-finding study) shows that significantly higher doses can be administered to pregnant rats. The maternal AUC at the NOAEL for pre- and postnatal developmental toxicity in the rat (300 mg/kg/day, AUC: 377 ug.h/mL) was ~7X the human exposure to BRV at the MRD. Based on animal studies, the potential for developmental toxicity for BRV appears to be similar to that for levetiracetam, which has not been associated with teratogenic effects in humans based on limited epidemiological data.

In an oral juvenile rat study, a number of adverse developmental effects were observed (increased mortality, neurobehavioral changes, impaired reproductive performance, and persistent decreases in brain weight and size). The effect on brain weight and size was seen at the lowest dose tested (150 mg/kg/day, AUC: 120 µg.h/mL, ~2X human). The data suggest greater sensitivity to toxicity (mortality) and unique developmental effects of BRV in the juvenile rat compared to the adult. An oral juvenile dog study did not indicate any unique effects or increased sensitivity to effects seen in adult dogs, at AUCs up to ~10-fold that in humans at the MRD. The toxic effects of BRV in juvenile rats were not seen in a juvenile rat study of levetiracetam (cf. Keppra labeling).

C. Recommendations

The application is approvable from a pharmacology/toxicology standpoint. However, because the potential for toxicity may not have been fully characterized in the rat reproductive and developmental toxicity studies due to improper dose selection, the sponsor should attempt to increase the highest doses evaluated in those studies in Phase 4.

II. PHARMACOLOGY

A. Brief summary

Brivaracetam (ucb 34714; BRV) is a 2-pyrrolidone derivative structurally related to levitiracetam (LEV) but with a 10X higher affinity (p*K*i =7.1 compared to 6.1) for synaptic vesicle protein 2A (SV2A), a protein widely distributed in the CNS and believed to be involved in the coordination of synaptic vesicle exocytosis and neurotransmitter release. Binding affinity of LEV analogues to SV2A correlated with seizure protection in animal models of epilepsy. In addition to its affinity for SV2A, BRV has shown inhibitory effects on voltage-dependent Na^+ currents in rat cortical neurons in culture. In rat hippocampal slices in vitro, BRV (1–10 uM) significantly suppressed evoked epileptiform responses (population spikes, PSs) recorded in the CA3 area. Concentrations active in this model were 1/10 those of LEV (3.2 uM vs 32 uM). It was noted that BRV also reduced the occurrence of spontaneous bursts, considered a marker for drug-refractory epileptiform activity, while LEV was inactive.

BRV was active in a number of animal models of epilepsy. In the corneally kindled mouse model of partial epilepsy, BRV protected animals from secondarily generalized motor seizures (ED50 = 1.2 mg/kg, ip). In the same model, chronic pretreatment prior to corneal stimulation with LEV or 10-fold lower doses of BRV (1.7-54 *vs* 0.21-6.8 mg/kg ip, both dosed BID prior to corneal stimulation) led to a similar suppression of kindling development. In the amygdala-kindled rat model of focal epilepsy, BRV suppressed both motor seizure severity and after-discharge duration. In audiogenic seizure susceptible mice, BRV protected against clonic convulsions (ED50 = 2.4 mg/kg ip). BRV suppressed spike-wave-discharges in the genetic absence epilepsy rat from Strasbourg (GAERS). In the partially drug-resistant self-sustaining status epilepticus (SSSE) model in rats induced by perforant path stimulation (PPS), the cumulative duration of seizures was reduced dose-dependently to 11% and 0.8% of controls at BRV iv doses of 20 and 300 mg/kg, respectively. For comparison, iv doses of 200 mg/kg LEV and 10 mg/kg diazepam reduced seizure duration to 35 and 15% of controls, respectively. It was concluded that the potency of BRV in SSSE was approximately 10X greater than that of LEV at a similar dose. The combination of diazepam (1 mg/kg iv) and BRV (1 mg/kg iv) reduced the duration of active seizures to 3% of controls, while either drug alone at the same doses had little effect. BRV metabolites, ucb-107092-1, ucb-100023-1, ucb-100406, and ucb 42145, were found to have no anticonvulsant activity. Only one minor metabolite, the ketone metabolite ucb 47074, showed weak anticonvulsant activity, with approximately 1/20 the potency of BRV, indicating that the parent compound is responsible for the drug's pharmacological activity.

B. Safety Pharmacology

In acute oral CNS safety testing (Irwin test) of BRV in Wistar rats (0, 100, and 300 (both sexes), 600 (females only), 1000, and 1500 mg/kg (males only)), signs of CNS depression were observed, generally at oral doses ≥ 100 mg/kg. One male was sacrificed ~4.5h post dose at 1000 mg/kg and 1 male died ~3.5h after dosing at 1500 mg/kg. CNS signs at these doses included passivity, decreased alertness, ataxia, abnormal respiration, and decreased sensorimotor (decreased startle and touch responses), neuromuscular (decreased grip strength), and autonomic function (ptosis, salivation, increased pupil diameter). In a test of potential effects on cognitive function, BRV (2.1, 6.8, or 21 mg/kg ip) was administered to normal and kindled male SD rats 60 min before each learning session of the Morris water maze. There was no evidence that BRV altered spatial reference learning or memory in either normal or kindled rats, while the positive control (VPA, 300 mg/kg ip) significantly impaired spatial reference memory in normal rats.

Two cardiovascular safety pharmacology studies were conducted in the beagle dog. In a study in anesthetized dogs, iv doses of 50 and 150 mg/kg produced dose-related reductions in heart rate (-11 to -21% vs time-matched vehicle) and transient increases in respiration rate (+40 to 106% vs vehicle) and minute volume (+50 to 89% vs vehicle). Additional cardiovascular changes at the HD included increases in QT (max+21% vs vehicle), QTc intervals (max +13% vs vehicle), rapid and transient decrease in arterial blood pressure (mean, systolic and diastolic; max -31%, -31% and -35% vs vehicle respectively), with transient reductions in femoral blood flow (max -25% vs baseline), left ventricular systolic pressure (max -31% vs vehicle or -20% vs baseline) and peak positive and negative dP/dt (max -44 and -36% vs baseline, respectively). Peak effects generally occurred 10 min after the start of infusion. Plasma levels of BRV, 60min after the start of infusion, were 79.9 and 308 µg/mL at 50 and 150 mg/kg, respectively.

In a study in conscious beagle dogs, oral doses of 50 and 150 mg/kg produced a reduction in arterial blood pressure (max -24, -30, -27% for systolic, diastolic and mean vs time-matched vehicle, respectively) 4-6h following dosing and up to 20 h at the HD, and an increase in heart rate (up to +66%) 1 h after dosing in females only. The RR interval was reduced at 1 and 2 h after dosing, but QT interval was unaffected, which resulted in prolonged QTcF and QTcQ intervals (max +21% and + 13% vs vehicle, respectively). The PR interval was shortened at 0.5-4 h post dosing at the HD (max -24%). Plasma concentrations of BRV at 2h post dosing, which were similar in males and females, were 61.2 and 174 µg/mL at 50 and 150 mg/kg, respectively.

In a study in which single oral doses [0, 30, 100, 300 and 600 mg/kg] were administered to male Wistar rats, BRV slightly reduced the expiratory time (up to 16%) and relaxation time (up to 15%) at 30 or 90 min after administration of the 3 highest doses, although with no clear dose relationship, indicating a possible slight respiratory stimulant effect.

Because there was inadequate coverage for subjects with severe renal impairment, the hydroxy-acid metabolite, ucb-107092-1, was investigated in a battery of in vitro and in vivo safety pharmacology studies. This metabolite was devoid of pharmacological activity and did not produce any effects in the safety pharmacology assessment. In vitro cardiovascular safety pharmacology studies were also performed on the BRV (b) (4) (b) (4) which is present as an impurity. Concentrations of up to (b) (4) µg/mL had no significant effect on any of the action potential parameters measured in dog isolated Purkinje fibers and human cardiac potassium channels (hERG).

III. PHARMACOKINETICS

A. Brief Summary

After single oral dosing to animals at pharmacologically relevant doses (~1-10 mg/kg), BRV showed rapid and complete absorption. Peak plasma concentrations were typically achieved within 1 h after oral dosing. The oral bioavailability (F) of BRV was ~100% in rats and dogs. In Cynomolgus monkeys, F was <10%, thought to be related to the high first-pass metabolism, not to absorption issues.

Terminal elimination t½ after iv dosing varied across species, from 0.3 h in Cynomolgus monkey to 2 h in rats (mean PK parameters in **Table III.1**). Total plasma clearance inversely correlated with t1/2 values, being much higher in monkeys than in the other species. In vitro assays confirmed higher metabolic clearance in monkey when compared to other species. There was little evidence of sex differences in PK/TK parameters, except in the rat, in which females showed higher exposure and slower elimination. Nonlinear PK was observed in dog after iv dosing, but was not seen in other species tested.

Because of the short t1/2 of BRV in animals, to ensure proper coverage throughout the day, toxicology studies used multiple daily dosing (bid or tid oral gavage, with or without dietary administration). BRV levels decreased upon repeated dosing in rodents, rabbits, and dogs, a dose-dependent (D-D) finding related to auto-induction of metabolism (as confirmed by increase in metabolite formation, increase in hepatic drug metabolizing enzymes, and histopathological findings in liver). Monkeys did not show any signs of auto-induction.

Safety margins based on Cmax and AUC in toxicity studies conducted in rat, rabbit, dog, and monkey, relative to those in humans at the proposed MRHD of 100mg BID are shown in **Tables III.2-3**.

Table III.1. Key pharmacokinetic parameters of brivaracetam after single dosing

Species		Mouse	Rat		Dog		Cynomolgus monkey	
Parameter	mg/kg	0.82	10		5		5	
	Gender	M	M	F	M	F	M	F
C_{max}[2]	µg/mL	0.70	11.4	14.4	6.64	7.23	0.08	0.22
AUC[2]	µg·h/mL	0.79	32.7	52.6	31.4	25.5	<0.41	<0.28
t_{max}[2]	h	0.08	0.5	0.5	1.0	0.76	0.5	1.0
$t_{1/2}$[1]	h	0.6[2]	1.6	1.9	NC	NC	0.3	0.3
CL[1]	L/h/kg	0.89[2]	0.28	0.21	0.17	0.22	1.26	1.74
V_z[1]	L/kg	0.87[2]	0.63	0.55	0.66	0.67	0.61	0.77
F	%	-	92	108	104	110	<10	<10

[1] Following iv dosing; [2] Values after oral dosing (eg, apparent $t_{1/2}$, CL/F, V_z/F); NC=Not calculated because of the nonlinear pharmacokinetics.

Table III.2. Safety margins for brivaracetam based on Cmax in pivotal studies

Type of study	Species	Administration	NOAEL[a] (mg/kg/day)	C_{max} (µg/mL) at NOAEL[b]	Safety margin[c]
Repeat dose	Rat	26-week oral (bid) 4-week iv infusion	450 600	36.6 (males) 65.9 (females) 24.1 (C_{ss}, males) 41.3 (C_{ss}, females)	10 19 6.9 12
	Dog	26-week oral (tid) 4-week iv infusion	15 30	4.88 2.43	1.4 0.7
	Monkey	39-week oral (bid)	900	223	64
Carcinogenicity	Mouse	104-week oral	400 (males) 700 (females)	9.25 (males) 38.9 (females)	2.6 11
	Rat	104-week oral	700	79.6 (males) 81.3 (females)	23 23
Reproductive toxicity	Rat	Fertility oral	400	52.1 ($C_{0.5h}$, males)[d] 79.2 ($C_{0.5h}$, females)[d]	15 23
	Rat	EFD oral	300[e] 600[f]	93.4 184	27 53
	Rabbit	EFD oral	120[f]	35.8	10
	Rat	PPND oral	600[g] 300[h]	74.9 57	21 16
Juvenile toxicity	Rat	9-week oral	300	86.7 on PND4 (first dose)[i] 38.9 on PND21 44.2 (males, on PND70) 61.6 (females, on PND70)	25 11 13 18
	Dog	9-month oral	30	13.6 on PND4 (first dose) 10.2 on PND31 12.1 on PND276	3.9 2.9 3.5

a: In rat studies, due to male rat-specific change of hyaline droplet nephropathy, no NOAEL could be determined in most studies. Male rat exposure at the NOAEL determined for female rats is given for information. Please see Section 1.3.1 for detailed data;
b: C_{max}, unless otherwise stated. Gender and time point of determination are only specified if the difference was considered relevant. Otherwise, average values are given;
c: For calculation C_{max}, ss at the MRHD (100mg bid) was used, ie, 3.5µg/mL (UCB study number N01067);
d: Plasma level 0.5h after the second daily sub-dose;
e: Maternal NOAEL;
f: NOAEL for embryo-fetal development;
g: NOAEL for maternal effect, reproductive toxicity, functional/neurobehavioral development;
h: NOAEL for neonatal/postnatal development;
i: Toxicokinetics from Study NCD1550 (Module 2.6.4 Table 1-25).

Table III.3. Safety margins for brivaracetam based on AUC in pivotal studies

Type of study	Species	Administration	NOAEL[a] (mg/kg/day)	AUC_{0-24h} (µg.h/mL) at NOAEL[b]	Safety margin[c]
Repeat dose	Rat	26-week oral (bid) 4-week iv infusion	450 600	257 (males) 464 (females) 578 (males) 992 (females)	4.6 8.3 10 18
	Dog	26-week oral (tid) 4-week iv infusion	15 30	34.7 58.4	0.6 1.0
	Monkey	39-week oral (bid)	900	2351	42
Carcinogenicity	Mouse	104-week oral	400 (males) 700 (females)	82.2 (males) 160 (females)	1.5 2.9
	Rat	104-week oral	700	510 (males) 635 (females)	9.1 11
Reproductive toxicity	Rat	Fertility	400	ND	
	Rat	EFD oral	300[d] 600[e]	1099 1801	20 32
	Rabbit	EFD oral	120[e]	198	3.5
	Rat	PPND oral	600[f] 300[g]	964[f] 377[g]	17 6.7
Juvenile toxicity	Rat	Oral	300	1099 on PND4 (first dose)[h] 168 on PND21 253 (males on PND70) 493 (females on PND70)	20 3.0 4.5 8.8
	Dog	Oral	30	190 on PND4 (first dose) 63.5 on PND31 78.1 on PND276	3.4 1.1 1.4

a: In rat studies, due to male rat-specific change of hyaline droplet nephropathy, no NOAEL could be determined in most studies. Male rat exposure at the NOAEL determined for female rats is given for information. Please see Section 1.3.1 for detailed data;
b: Gender and time point of determination are only specified if the difference was considered relevant. Otherwise, average values are given;
c: For calculation 2xAUC_{0-12} at the MRHD (100mg bid) was used, ie, 56µg.h/mL (UCB study number N01067);
d: Maternal NOAEL;
e: NOAEL for embryo-fetal development;
f: NOAEL for maternal effect, reproductive toxicity, functional/neurobehavioral development;
g: NOAEL for neonatal/postnatal development;
h: Toxicokinetics from Study NCD1550 (Module 2.6.4 Table 1-25).

In all species studied, BRV displayed a volume of distribution (Vz) close to total body water content (ca 0.6L/kg). Distribution studies in pigmented rats showed that [14C]-BRV distributed rapidly throughout the body following oral administration; the highest concentrations of radioactivity were found in the GI tract, liver, and kidney, as well as the preputial and clitoral glands. The elimination of radioactivity from tissues generally paralleled that from plasma, with levels returning to background by 24 h. However, elimination from the preputial and clitoral glands required up to 72 h. The affinity for the preputial and clitoral glands (not observed in mice) was fully reversible, associated with parent drug (not seen with metabolites), and found not to involve covalent binding. Data indicated that neither BRV nor its metabolites bind to melanin.

PK/PD studies in audiogenic seizure-prone mice showed that BRV distributed rapidly to the brain, where concentrations peaked 15 min after oral dosing and directly paralleled pharmacological activity, without any time delay or hysteresis. In mice and rats, brain-to-plasma ratios equilibrated very rapidly and were close to unity across dosing routes, sex, and sampling time.

BRV was shown to readily cross the placenta in rats. From 1 h post-dose, radioactivity levels in fetuses, amniotic fluid, and placenta were similar to those in maternal blood. In vitro distribution studies showed that BRV (from 0.5-1 to 100 µg/mL) distributed evenly between blood cells and plasma (ratio of ca 1), and had a low plasma protein binding (12-27% range vs 21% in human), across the tested concentrations and species.

The level of unchanged BRV recovered in urine and feces was low in animals (5, 6, 4, and 0% in mice, rats, dogs, and monkeys, respectively) and in humans. Following po administration, the recovery of total drug-derived radioactivity was >90% in mice, rat, dog, and monkey at 48 to 168 h post-dose, and shown to be independent of sex, route, dose, and/or pregnancy state. In rodents, most of the radioactivity was renally excreted, with minimal biliary excretion. Following single po dosing of 14C-BRV at 5 mg/kg to lactating female rats, radioactivity was secreted in milk and rapidly reached levels similar to those in plasma.

B. Metabolism

Parent drug represented the most abundant circulating material in vivo for all species (including humans) except the cynomolgus monkey, which showed increased metabolic clearance compared to other species. The major metabolic route involves the stereoselective hydroxylation of the propyl chain to produce ucb-100406-1, both in animals and humans (**Figure III.2**). In rodents, monkeys, and humans, ucb-100406-1 was the only metabolite exceeding 10% of the total circulating material. In dog, major metabolites included both ucb-100406-1 and ucb-102993-1, a derivative resulting from the hydroxylation of the butyramide side-chain. The other identified metabolic routes involved the hydrolysis of acetamide moiety to the acid derivative, ucb 42145, which can be then be hydroxylated to ucb-107092-1, and the oxidation of ucb-100406-1 to the corresponding ketone, ucb 47074. The other metabolites and/or the other metabolite isomers were present in much smaller amounts.

No in vivo metabolites were specific to humans. Coverage for the three primary human metabolites, ucb-100406-1 (only major metabolite based on 10% limit), ucb-42145, and ucb-107092-1 (**Table III.4-5**), appeared adequate. Separate stand-alone toxicology studies were conducted for ucb-107092-1, since this metabolite was present in higher amounts in renally-impaired human subjects than in animal species (**Table III.6**). No identified metabolites contain structural alerts. However, it is thought that the bioactivation of the butyramide side-chain, combined with other precipitating factors, might lead to the formation of porphyrogenic derivatives, particularly in dogs. The ultimate causative metabolite could not be identified, but ucb-102993-1, which was considered a surrogate for the putative activated metabolite, was seen in some animal species (especially in dog) but not in humans. In liver microsomes and hepatocytes, the cynomolgus monkey showed the highest transformation rate when compared to other species, with humans showing the lowest (2% parent transformed after 2 h incubation with liver microsomes). Across test systems and species, including humans, ucb-100406-1 appeared as the major metabolite. Liver microsomal data confirmed that ucb-102993-1 was produced in some animal species (especially dog), but not in humans.

Figure III.2. BRV metabolic pathways

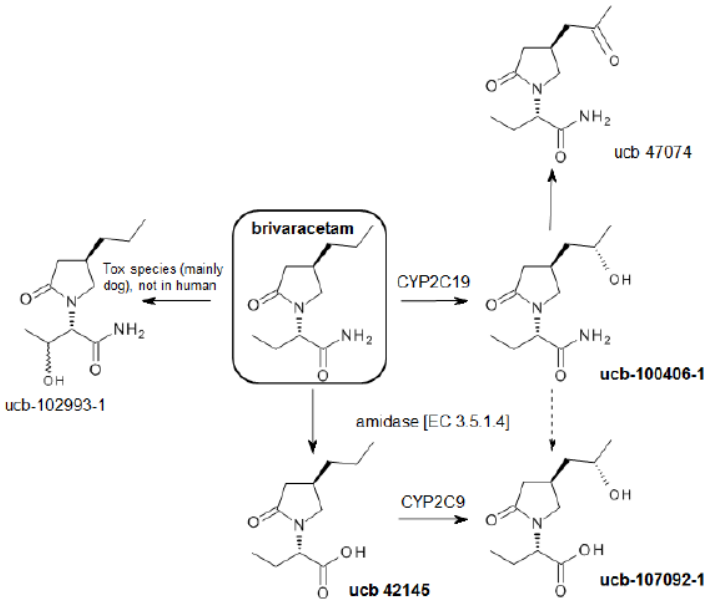


Table III.4: Human plasma exposures (µg.h/mL) to BRV and metabolites following iv and oral dosing

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%

BRV=brivaracetam; CSR=clinical study report; CV=coefficient of variation; iv=intravenous

[a] "Percent of sum4" is the proportion of BRV and each metabolite in plasma, relative to the sum of the mean plasma exposures of BRV and metabolites together, which was set to 100%.

[b] "Mean oral" represents the average of the 2 groups from N01259 (gemfibrozil control+rifampicin control).

Data sources: N01259 CSR Table 11:2; N01259 CSR Table 11:3; N01256B CSR Table 11:5

Table III.5 Safety margins for ucb-100406-1 and ucb-107092-1 in pivotal studies with BRV based on AUC: ratios of AUC0-24h in animals at the NOAEL relative to AUC0-inf in healthy volunteers and in human subjects with severe renal impairment

Species	Administration	NOAEL[a] (mg/kg/day)	AUC_{0-24h} (µg.h/mL) at NOAEL	Safety margin in HVs[b]	Safety margin in severe renally impaired subjects[c]
ucb-100406-1					
Rat	26-week oral (bid)	450	276	20	4.8
	4-week iv infusion	600	338	24	5.9
Dog	26-week oral (tid)	15	28.5	2.0	0.50
	4-week iv infusion	30	70.9	5.0	1.23
Monkey	39-week oral (bid)	900	1209	85.7	21.0
ucb-107092-1					
Rat	26-week oral (bid)	450	4.64	2.8	0.13
	4-week iv infusion	600	3.73	2.2	0.10
Dog	26-week oral (tid)	15	1.23	0.74	0.03
	4-week infusion	30	2.29	1.37	0.06
Monkey	39-week oral (bid)	900	37.6	22.5	1.05

a: In rat studies, due to male rat-specific change of hyaline droplet nephropathy, no NOAEL could be determined in most studies. Mean exposure (male and female) at the NOAEL determined for female rats is given for information. Please see Section 1.3.1 for detailed data;
b: For calculation AUC at 200mg in healthy volunteers was used, ie, for ucb-100406-1: 14.1µg.h/mL, for ucb-107092-1: 1.67µg.h/mL (UCB study number N01109);
c: For calculation AUC at 200mg in subjects with severe renal impairment was used, ie, for ucb-100406-1: 57.5µg.h/mL, for ucb-107092-1: 35.8µg.h/mL (UCB study number N01109);
HVS=Healthy volunteers.

Table III.6. Safety margins for ucb-107092-1 in pivotal studies with ucb-107092-1 based on AUC

Type of study	Species	Administration	NOAEL[a] (mg/kg/day)	Css (µg/mL) at NOAEL	Safety margin[a,b]	AUC_{0-24h} (µg.h/mL) at NOAEL	Safety margin[a]
Repeat dose	Rat	13-week iv infusion	2000	50.8 (males) 75.7 (females)	>59 >87	1220 (males) 1818 (females)	34 51
Reproductive toxicity	Rat	EFD iv infusion	1000	33.8	>39	810	23

a: For calculation C_{max} and $AUC0_{-inf}$ of ucb-107092-1 at the MRHD of 200mg brivaracetam/day in subjects with severe renal impairment were used, ie, 0.868µg/mL and 35.8µg.h/mL (UCB study number N01109);
b: based on comparison versus C_{max} after a single dose of 200mg, no data available after 100mg bid.

IV. TOXICOLOGY

Acute and subchronic general toxicity (up to 13 weeks oral and 1-month iv) and genotoxicity studies were previously reviewed (IND 70205 review dated 8/26/04 by Kathleen Young and IND 103908 review dated 12/11/08 by Christopher Toscano)

A. CHRONIC TOXICITY

1. ucb 34714: 26 Week Oral (Dietary and Gavage) Administration Toxicity Study in the Rat (Study Number PSM1029, conducted by (b) (4), report dated 6/30/05, GLP)

a. Methods

Wistar rats (Crl:WI (Glx/BRL/Han)BR, 20/sex/grp + 12/sex/grp TK) received 0 + 0 (unsupplemented diet and vehicle: 1% methylcellulose 400 cps in sterile water), 100 + 50, 100 + 130, or 100 + 350 mg/kg/day (diet and gavage respectively) BRV (batch #: C02-P714-110R) for 26 weeks. The gavage doses were split into two equal doses (5 mL/kg) given 6 hrs apart. Mortality and clinical observations were recorded daily and BW and food consumption weekly throughout the study. Ophthalmoscopy was performed on all main study groups at baseline and once in week 25 in C and HD animals. Hematology, coagulation, and clinical chemistry parameters were measured in all main study groups at 13 and 26 weeks. Additional blood samples were taken from all main study animals at 4 week for clinical chemistry only, and at the week 27 necropsy for measurement of serum total bile acids. Urine samples were collected from all main study animals at 3, 12, and 25 week for urinalysis. At the end of the dosing period, main study animals were necropsied, selected organs were weighed, and macroscopic and microscopic examinations were performed (full battery of tissues).

In TK groups, blood samples were taken on day 2 and week 26 at 1, 3, 6, 7, 9, 12, 18, and 24 hrs after the first daily dose. Additional blood samples were taken in week 13, at 24 hours after the first daily dose only. Samples were analyzed for ucb 34714 and its metabolites, ucb 42145, ucb-100406-1, ucb-107092-1, and ucb-102993-1.

Doses were based on the results of a 28-day range-finding study in rats (UCB Study # PSM1005) in which doses of 100 + 100, 300 + 150 or 1000 + 300 mg/kg/day (dietary + gavage QD) were administered and a 13-week oral study in rats by gavage (Study # PSM0813) in which doses of 50, 100, 200 or 400 mg/kg/day (given BID, 6 hrs apart) were administered. In the 28-day study, brown pigment in the bile duct and/or peribiliary inflammation were seen in HD males, increased liver weights were seen at the MD and HD, and centrilobular hepatocyte hypertrophy occurred in all animals, with a dose-related severity. Male rat-specific hyaline droplet nephropathy was also noted at all doses. In the 13-week study, increased liver weights, centrilobular hepatocyte hypertrophy, and the presence of brown pigment in centrilobular hepatocytes were seen at >100 mg/kg/day in males and >50 mg/kg/day in females. ALT was increased slightly (35%, SS) in HD females.

b. Results

i. Mortality and Clinical Observations

There were no drug-related deaths. Clinical signs consisted of salivation and/or paddling, seen at the MD and HD throughout the dosing period.

ii. Body Weight

There were no effects of drug on BW gain or BWs.

iii. Ophthalmoscopy

There were no effects of drug.

iv. Clinical Pathology

There were no drug-related changes in hematological parameters. Plasma cholesterol and glucose were increased at all doses in both sexes (up to 30 and 70%, respectively, at HD, both SS) and triglycerides were increased (up to 30%, SS) at the HD. A slight increase in urine volume was seen in females at all doses at week 25.

v. Necropsy

Liver weights (relative to BW) were increased (SS) at all doses in both sexes (**Table IV.A1.1**), and increased adrenal and kidney (14% and 7% respectively, compared to C) and thymus weights were decreased (21%) in HD females.

Table IV.A1.1. Liver weight (BW adjusted)

Group (dose in mg/kg/day[1])	Adjusted Liver Weight (g) *(% from Controls)*	
	Males	Females
1 (0)	8.664	5.513
2 (100 + 50)	9.220* *(+6%)*	6.103*** *(+11%)*
3 (100 + 130)	9.780*** *(+13%)*	6.059** *(+10%)*
4 (100 + 350)	10.548*** *(+22%)*	6.835*** *(+24%)*

[1] in diet + gavage
*P<0.05 **P<0.01 ***P<0.001

Hypertrophy of centrilobular hepatocytes with brown pigment in cytoplasm was seen in animals from all dose groups with evidence of a dose-response relationship (**Table IV.A1.2**). In the spleen, extramedullary hematopoiesis was decreased at all doses in males and at the HD in females (**Table IV.A1.3**). Brown pigment deposits in macrophages of the red pulp were seen in animals from all groups, but the severity was increased in MD and HD females. Hyaline droplets within the cytoplasm of proximal tubular epithelial cells, focal basophilic tubules, granular casts, and karyomegaly (collectively regarded as hyaline droplet nephropathy) were seen in males from all dose groups, with evidence of a dose-response relationship (**Table IV.A1.4**). In the thyroid, diffuse hypertrophy of follicular cells was seen in

a small number of males from all dose groups and brown pigment in follicular cells was also seen in some affected animals (**Table IV.A1.5**). Altered colloid with basophilic deposits was seen in animals from all groups, but the incidence and severity were increased in MD and HD males. Increased follicular diameter was recorded in 3/19 HD males.

Table IV.A1.2. Incidence of drug-related liver findings

	Male				Female			
Group (dose in mg/kg/day [1])	**1 (0)**	**2 (100+50)**	**3 (100+130)**	**4 (100+350)**	**1 (0)**	**2 (100+50)**	**3 (100+130)**	**4 (100+350)**
Number examined	20	20	19	19	20	20	20	20
Hypertrophy, hepatocellular, centrilobular								
Minimal	0	14	3	0	0	11	1	0
Slight	0	6	16	5	0	9	17	3
Moderate	0	0	0	14	0	0	2	17
Total	0	20	19	19	0	20	20	20
Pigment, brown, hepatocellular, centrilobular								
Minimal	0	15	9	6	3	9	6	5
Slight	0	0	2	8	0	9	12	11
Moderate	0	0	0	0	0	0	0	2
Total	0	15	11	14	3	18	18	18

[1] In diet + gavage

Table IV.A1.3. Incidence of drug-related spleen findings

Sex	**Male**				**Female**			
Dosage level ucb 34714 (mg/kg/day)	0	100/ 50	100/ 130	100/ 350	0	100/ 50	100/ 130	100/ 350
Number examined	20	20	19	19	20	20	20	20
Haematopoiesis, extramedullary, erythroid								
Minimal	8	4	1	1	8	10	9	5
Pigment, brown, red pulp								
Minimal	19	18	16	17	8	7	0	0
Slight	0	1	1	1	12	13	20	15
Moderate	0	0	0	0	0	0	0	5
Total	19	19	17	18	20	20	20	20

Table IV.A1.4. Incidence of drug-related kidney findings

	Male				Female			
Group (dose in mg/kg/day [1])	**1 (0)**	**2 (100+50)**	**3 (100+130)**	**4 (100+350)**	**1 (0)**	**2 (100+50)**	**3 (100+130)**	**4 (100+350)**
Number examined	20	20	19	19	20	2	2	20
Basophilic tubes								
Minimal	1	5	7	9	1	0	0	0
Hyaline droplets, proximal tubules, prominent								
Minimal	1	14	17	7	0	0	0	0
Slight	0	0	0	12	0	0	0	0
Total	1	14	17	19	0	0	0	0
Karyomegaly, tubular epithelium, prominent								
Minimal	0	2	3	10	0	0	0	0
Casts, granular, medulla								
Minimal	0	0	0	1	0	0	0	0

[1] In diet + gavage

Table IV.A1.5. Incidence of drug-related thyroid findings

	Male				Female			
Group (dose in mg/kg/day [1])	**1 (0)**	**2 (100+50)**	**3 (100+130)**	**4 (100+350)**	**1 (0)**	**2 (100+50)**	**3 (100+130)**	**4 (100+350)**
Number examined	20	20	19	19	20	0	0	19*
Hypertrophy, follicular cells, diffuse								
Minimal	0	1	2	3	0	-	-	1
Slight	0	0	0	1	0	-	-	0
Total	0	1	2	4	0	-	-	1
Pigment, brown, Follicular cells								
Minimal	0	2	2	3	0	-	-	0
Altered colloid, basophilic deposits								
Minimal	4	4	5	7	1	-	-	2
Slight	1	2	2	4	0	-	-	0
Moderate	0	1	2	0	0	-	-	0
Total	5	7	9	11	1	-	-	2
Increased follicular diameter								
Minimal	0	0	0	2	0	-	-	0
Slight	0	0	0	1	0	-	-	0
Total	0	0	0	3	0	-	-	0

[1] In diet + gavage

* no sections of thyroid gland available for one Group 4 female

iv. Toxicokinetics

TK parameters for ucb 34714 and its measured metabolites are shown in **Table IV.A1.6**. Exposure to parent increased dose-proportionally and was ~2-fold higher in females than males. There was a significant decrease in exposure with repeated administration.

Table IV.A1.6. PK parameters for ucb 34714 and metabolites in rat

Parameter	Unit	Dose (mg/kg/day)					
		100 [a] + 50 [b]		100 [a] + 130 [b]		100 [a] + 350 [b]	
		Males	Females	Males	Females	Males	Females
Day 2							
ucb 34714							
C_{max}	(µg/mL)	14.1	22.9	21.4	37.3	45.2	122
C_{min}	(µg/ mL)	1.96	4.43	0.871	2.74	0.656	2.79
AUC(0-24 h)	(µg.h/ mL)	108	217	124	254	300	1056
ucb 42145							
AUC(0-24 h)	(µg.h/ mL)	2.93	6.27	3.71	7.10	9.17	29.9
ucb-100406-1							
AUC(0-24 h)	(µg.h/ mL)	81.1	78.0	127	124	256	291
ucb-107092-1							
AUC(0-24 h)	(µg.h/ mL)	1.94	2.05	3.21	2.91	6.33	7.45
ucb-102993-1							
AUC(0-24 h)	(µg.h/ mL)	3.36	2.91	5.77	5.13	17.4	17.0
Week 26							
ucb 34714							
C_{max}	(µg/ mL)	8.63	15.2	17.5	33.0	36.6	65.9
C_{min}	(µg/ mL)	0.537	2.06	0.883	1.57	0.878	0.716
AUC(0-24 h)	(µg.h/ mL)	65.2	144	116	196	257	464
ucb 42145							
AUC(0-24 h)	(µg.h/ mL)	1.68	3.11	4.11	5.98	7.86	12.3
ucb-100406-1							
AUC(0-24 h)	(µg.h/ mL)	75.4	82.6	151	151	276	276
ucb-107092-1							
AUC(0-24 h)	(µg.h/ mL)	1.37	1.35	2.90	2.63	4.94	4.33
ucb-102993-1							
AUC(0-24 h)	(µg.h/ mL)	3.67	3.66	6.87	6.02	16.3	14.4

[a]: in diet; [b]: gavage bid (2 equal subdoses ca 6 hours apart)

c. Conclusions

Administration of oral (diet + gavage) doses of 100 + 50, 100 + 130, or 100 + 350 mg/kg/day BRV to Wistar rats for 26 weeks resulted in clinical chemistry changes (increased cholesterol, triglycerides and glucose), increased liver weights, and histopathological changes in the liver (hepatocellular hypertrophy and brown pigment deposits in both sexes at all doses), kidney (hyaline droplet nephropathy in males at all doses), spleen (decreased extramedullary hematopoiesis in MD and HD males and HD females, increased brown pigment deposits in macrophages of the red pulp in MD and HD females), and thyroid (hypertrophy and brown pigment in follicular cells and altered colloid with basophilic deposits in males at all doses). The sponsor considered these all adaptive responses or male rat specific, so the HD was considered the NOAEL. Exposure (AUC (0-24h)) to the parent compound at week 26 was 257 and 464 µg.h/mL, in males and females, respectively, at this dose (human AUC 56 ug.h/mL at MRD of 100 mg BID).

2. ucb 34714: 26 Week Oral Gavage (Three Times Daily Administration) Toxicity Study in The Dog (Study Number PSM1013, conducted by [redacted](b) (4), report dated 9/8/05, GLP)

a. Methods

Beagle dogs (4/sex/grp) received oral (gavage,) doses of 0 (vehicle: 1% methylcellulose 400 cps in sterile water), 15, 37.5, or 75 mg/kg/day BRV (batch #: C02-P714-110R) for 26 weeks. The doses were split into three equal doses (5 mL/kg) given 8 hrs apart. Mortality and clinical observations were recorded daily and body weight weekly throughout the study. Ophthalmoscopy was performed at baseline and on day 2 and week 25. ECG was recorded twice at baseline and on day 2 and weeks 4, 12, and 25. Hematology, clinical chemistry, and urinalyisis were measured at baseline and at 4, 13, and 26 weeks. At necropsy, selected organs were weighed and a macroscopic examination was performed. A full battery of tissues was then sampled, preserved in the appropriate fixatives, and examined microscopically.

Blood samples for TK analysis were taken on day 1 and week 26 pre-dose and at 1, 4, 8, 9, 12, 16, 17, 20, and 24 hours and analyzed for ucb 34714 and its metabolites, ucb 42145, ucb-100406-1, ucb-107092-1, and ucb-102993-1. Doses were based on the results of a 28-day oral range-finding study (UCB Study PSM0943) in which doses of 15, 37.5, and 75 mg/kg/day were administered orally (TID gavage dosing) and increases in plasma ALT, ALP and AST, minimal single hepatocyte necrosis, brown pigment in bile canaliculi and Kuppfer cells, and minimal hypertrophy of thyroid follicular epithelium were seen at the HD.

b. Results

i. Mortality and Clinical Observations

There were no mortalities and no drug-related clinical signs.

ii. Body Weight

BW gain during the dosing period was similar between control and dose groups and there were no group differences in final BW.

iii. ECG and Ophthalmoscopy

There was no effect of drug on heart rate. There were no noteworthy changes in the ECG parameters. There were no effects of drug on ophthalmoscopy.

iv. Clinical Pathology

There were no drug-related changes in hematological or urinalysis parameters. Increases in mean plasma ALT, ALK PHOS, AST, GGT, 5'-nucleotidase (5'-ND), and sorbitol dehydrogenase (SDH) were seen in dose groups (**Table IV.A2.1**). These increases were generally similar in both sexes, relative to baseline values, at weeks 4, 13, and 26 (5- to 7X for ALT, 2- to 4X for ALK PHOS, GGT, 5'-ND, and SDH at HD). All or most individual values were outside the historical background or control ranges, with the exception of SDH. In addition, an increase in mean serum bile acids (SBLA) was noted at the HD (SS in females at week 13 and males at week 26).

Table IV.A2.1. Clinical chemistry

Occasion: Week 26

	Test article	Control		ucb 34714	
	Group	1	2	3	4
	Level (mg/kg/day)	0	15	37.5	75

Group/ Sex	AST IU/L	ALT IU/L	GAMMA GT IU/L	ALK PHOS IU/L	Na mmol/L	K mmol/L	Cl mmol/L
1M Mean	28	44	3	188	147	4.2	113
SD	4	10	1	50	3	0.1	3
2M Mean	26	40	3	184	146	3.9	112
SD	4	10	1	72	2	0.2	1
3M Mean	26	45	3	287	147	4.1	112
SD	6	15	1	77	2	0.2	1
4M Mean	42*	249*	4	559***	148	4.0	114
SD	9	47	1	127	2	0.3	3
Statistics	A2	A2	A2	A2T	A2	A2	A2
1F Mean	30	40	3	168	147	4.0	113
SD	7	8	1	18	1	0.1	2
2F Mean	33	47	4	254	147	4.0	113
SD	8	16	1	57	1	0.4	1
3F Mean	36	126	5	437**	147	3.9	115
SD	13	159	2	176	1	0.2	1
4F Mean	48*	346***	9***	1201***	146	4.2	112
SD	7	211	2	491	1	0.4	1
Statistics	A2	A2	A2	A2T	A2	A2	A2

Table IV.A2.1. (cont.)

Group/ Sex	Ca mmol/L	IN PHOS mmol/L	UREA mmol/L	T BILI umol/L	CREAT umol/L	T PROT g/L	ALBUMIN g/L
1M Mean	2.67	1.4	3.9	1.1	77	56	31
SD	0.09	0.1	0.4	0.7	4	2	1
2M Mean	2.66	1.3	4.4	1.4	77	55	33
SD	0.10	0.1	0.5	0.4	8	2	1
3M Mean	2.71	1.4	3.9	1.3	76	57	34
SD	0.06	0.1	0.3	0.2	3	2	1
4M Mean	2.68	1.4	4.0	1.5	78	54	31
SD	0.08	0.1	0.5	0.4	8	3	2
Statistics	A2	A2	A2	J	A2	A2	A2
1F Mean	2.66	1.2	4.2	1.5	71	56	33
SD	0.02	0.1	0.1	0.3	4	2	1
2F Mean	2.61	1.2	4.2	1.7	74	55	32
SD	0.05	0.1	0.6	0.3	3	1	2
3F Mean	2.57	1.3	4.0	1.8	76	55	30
SD	0.06	0.1	0.7	0.3	1	2	2
4F Mean	2.62	1.4	4.1	2.3	74	55	29**
SD	0.11	0.2	0.3	0.7	13	1	3
		DR*		DR*			
Statistics	A2	A2	A2	A	A2	A2	A2

Group/ Sex	SBLA umol/L
1M Mean	7.1
SD	1.4
2M Mean	7.4
SD	0.6
3M Mean	7.1
SD	1.8
4M Mean	11.2*
SD	1.7
Statistics	A2
1F Mean	8.1
SD	3.7
2F Mean	6.6
SD	0.9
3F Mean	8.1
SD	1.1
4F Mean	9.0
SD	2.1
Statistics	A2

Group/ Sex	GLOBULIN g/L	AG RATIO	TOT CHOL mmol/L	TRIGS mmol/L	GLUC mmol/L
1M Mean	25	1.3	3.2	0.32	5.1
SD	2	0.1	0.7	0.15	0.4
2M Mean	23	1.5	3.4	0.31	6.0**
SD	3	0.2	0.6	0.09	0.3
3M Mean	24	1.4	3.1	0.27	5.9**
SD	2	0.1	0.5	0.03	0.2
4M Mean	23	1.4	2.7	0.29	5.9**
SD	1	0.1	0.3	0.07	0.2
Statistics	A2	A2	A2	A2T	A2
1F Mean	23	1.5	3.5	0.44	5.2
SD	2	0.2	1.3	0.20	0.5
2F Mean	23	1.4	2.9	0.24	5.6
SD	1	0.1	0.3	0.02	0.2
3F Mean	24	1.2	3.1	0.25	6.0*
SD	1	0.1	0.7	0.10	0.3
4F Mean	26	1.2*	2.2*	0.24	5.7
SD	3	0.3	0.6	0.05	0.5
	DR*			DR*	
Statistics	A2	A2	A2	A2T	A2

Table IV.A2.1. (cont.)

Group/ Sex	5'-ND IU/L	SDH IU/L
1M Mean	0.4	7.0
SD	0.2	0.8
2M Mean	0.5	6.8
SD	0.2	1.0
3M Mean	0.4	7.8
SD	0.1	1.3
4M Mean	0.9	16.8***
SD	0.5	7.8

Statistics	A2T	A2
1F Mean	0.6	7.3
SD	0.2	1.3
2F Mean	0.5	7.3
SD	0.2	1.3
3F Mean	0.9	7.0
SD	0.7	0.8
4F Mean	1.9*	11.3
SD	1.0	4.0

Statistics	A2T	A2

* P<0.05
** P<0.01
*** P<0.001
DR = significant dose response test

A2 = two-way ANOVA, regression and Dunnett's
J = Kruskal-Wallis, Terpstra-Jonckheere, Wilcoxon
A = ANOVA, regression and Dunnett's

v. Necropsy

Liver weights were increased (BW adjusted 17%) in HD males. This change was mainly due to 2 males (#13 and 16) with macroscopic findings (large, dark liver) in the liver. There was no change in females. In addition to the 2 HD males, large liver was noted in 1 MD male (#12) and dark liver was noted in 2 HD females (# 31 and 32).

Centrilobular fibrosis and hyperplasia of oval cells/bile ducts and brown pigment in canaliculi, hepatocytes and/or Kupffer cells were seen in a few MD animals and in most HD animals (**Table IV.A2.2**). Single hepatocyte necrosis and centrilobular inflammation were seen in all HD animals. The severity of all these changes was generally dose-related and similar between males and females. Concretions in the lumen were seen in 1 HD male (#16) and 1 HD female (#31).

Table IV.A2.2. Incidence of microscopic liver changes (sexes combined)

Dosage level ucb 34714 (mg/kg/day)	0	15	37.5	75
Number examined	**8**	**8**	**8**	**8**
Fibrosis, centrilobular (bridging)				
Minimal	0	0	1	2
Slight	0	0	0	4
Marked	0	0	0	1
Total	0	0	1	7
Hyperplasia, oval cells/bile ducts, centrilobular				
Minimal	0	0	2	2
Slight	0	0	0	4
Moderate	0	0	0	1
Total	0	0	2	7
Pigment, brown, canaliculi				
Minimal	0	0	2	0
Slight	0	0	1	4
Moderate	0	0	0	4
Total	0	0	3	8
Pigment, brown, hepatocellular, prominent				
Minimal	0	0	1	4
Pigment, brown, Kupffer cells				
Minimal	0	0	3	0
Slight	0	0	0	3
Moderate	0	0	0	5
Total	0	0	3	8
Necrosis, hepatocellular, single cell				
Minimal	0	0	0	8
Inflammation, centrilobular				
Minimal	0	0	0	6
Slight	0	0	0	2
Total	0	0	0	8

vi. Toxicokinetics

TK parameters for ucb 34714 and its metabolites are shown in **Table IV.A2.3**. There were no clear sex differences. Exposure to parent decreased with repeated administration, presumably due to auto-induction.

Table IV.A2.3. TK parameters for ucb 34714 and its metabolites in dogs (sexes combined)

Parameter	Unit	Dose[a] (mg/kg/day)		
		15	37.5	75
Day 1				
ucb 34714				
C_{max}	(µg/mL)	5.25 ± 0.46	13.8 ± 1.3	31.7 ± 2.6
C_{min}	(µg/mL)	0.161 ± 0.089	1.09 ± 0.44	5.75 ± 2.48
AUC(0-24 h)	(µg.h/mL)	48.7 ± 4.6	149 ± 15	404 ± 59
ucb 42145				
AUC(0-24 h)	(µg.h/mL)	4.84 ± 0.66	12.4 ± 1.3	44.6 ± 10.4
ucb-100406-1				
AUC(0-24 h)	(µg.h/mL)	26.6 ± 3.2	48.2 ± 8.3	81.0 ± 9.3
ucb-107092-1				
AUC(0-24 h)	(µg.h/mL)	0.836 ± 0.132	1.50 ± 0.33	2.53 ± 0.58
ucb-102993-1[b]				
AUC(0-24 h)	(µg.h/mL)	9.57 ± 1.92	30.5 ± 5.88	80.0 ± 20.3
Week 26				
ucb 34714				
C_{max}	(µg/mL)	4.88 ± 0.31	10.4 ± 1.0	23.5 ± 2.7
C_{min}	(µg/mL)	**0.023** ± 0.013	**0.037** ± 0.022	0.265 ± 0.161
AUC(0-24 h)	(µg.h/mL)	34.7 ± 3.3	79.1 ± 11.2	192 ± 23
ucb 42145				
AUC(0-24 h)	(µg.h/mL)	2.82 ± 0.44	6.19 ± 1.10	14.7 ± 2.8
ucb-100406-1				
AUC(0-24 h)	(µg.h/mL)	28.5 ± 4.0	59.9 ± 5.1	106 ± 12
ucb-107092-1				
AUC(0-24 h)	(µg.h/mL)	1.23 ± 0.30	2.49 ± 0.32	4.66 ± 1.00
ucb-102993-1[b]				
AUC(0-24 h)	(µg.h/mL)	11.8 ± 1.59	40.8 ± 10.8	117 ± 25

[a] : daily dose split into 3 equal subdoses given approximately 8 hours apart.
[b] : semi-quantitative result.
Bold values are below the limit of quantitation (0.05 µg/mL)

c. Conclusions

Administration of oral (gavage) doses of 15, 37.5, or 75 mg/kg/day BRV to beagle dogs for 26 weeks resulted in clinical chemistry changes (dose-related increases in ALT, SDH, ALK PHOS, 5'-ND, and GGT), increased liver weights, and hepatobiliary histopathological changes (brown pigment deposits in hepatocytes, Kupffer cells, and bile canaliculi, fibrosis and hyperplasia of oval cells/bile ducts, hepatocyte necrosis and inflammation, gallbladder concretions), primarily at MD and HD. The LD was considered the NOAEL. Exposure (AUC (0-24h)) to parent drug at this dose was 34.7 µg.h/mL (sexes combined) at 26 weeks, which is lower than that measured in humans at the MRD (56 ug.h/mL at 100 mg BID).

3. ucb 34714: 39 Week b.i.d Oral (Gavage) Toxicity Study in the Cynomolgus Monkey (Study # PSM1140, conducted by (b) (4), report dated 7/1/05, GLP)

a. Methods

Cynomolgus monkeys (4/sex/grp) received oral (gavage) doses of 0 (vehicle: 1% methylcellulose 400 cps in sterile water), 300, 600, or 900 mg/kg/day BRV (batch #: C02-P714-111R and C02-P714-112R) for 39 weeks. The doses were split into 2 equal daily doses (5 mL/kg) given 10 hrs apart. An additional female was added at the HD following the first of 2 accidental deaths in this group. The first day of dosing for this additional female was day 35 and this animal was sacrificed after 34 weeks of dosing. Observations consisted of daily morbidity/mortality checks, clinical examinations (after each dose), and weekly body weight measurements for each animal. Physical examination and detailed clinical examination were performed at regular intervals during the study. Ophthalmology was performed pre-test, during weeks 12/13, 26, and at the end of the dosing period. ECG, clinical pathology, and blood sampling for TK was performed pre-test, during weeks 4 (hepatic markers only for clinical laboratory determinations), 12/13, 26/25, and at the end of the dosing period. In addition to these intervals, the additional group 4 female was examined and sampled on the same calendar days as the other animals, which corresponded to the 7/8th and 21st weeks of administration for this animal. Hematology and clinical chemistry determinations were also performed during week 20 for all animals except the additional female. Selected organs were weighed and tissue samples were fixed and preserved at necropsy for all animals. A full battery of tissues from all animals was examined histopathologically.

Blood samples for TK were taken at weeks 4 and 26, before and at 1, 10 (immediately before the second daily dose), 11, and 24 hrs after the first daily dose, and at week 13 and at the end of the study (weeks 34 or 39) before and 0.5, 1, 3, 6, 10 (i.e., immediately before the second dose), 10.5, 11, 13, 16, and 24 hours after the first daily dose. In addition to these intervals, blood samples were collected from HD female no. 2683 on the same calendar day as the other animals, which corresponded to weeks 8 and 21.

Doses were based on the results of a previous 4-week oral (gavage) toxicity study at the same doses in the monkey (UCB Study RRLE03G1402). The only drug-related findings in that study consisted of sporadic and transient vomiting and mildly increased liver weights, at all doses, which were not considered to be of toxicological significance.

b. Results

i. Mortality and Clinical Observations

Two deaths occurred on days 29 (#2680) and 77 (#2682) in HD females. For both animals, macroscopic findings at necropsy and histopathological changes in the lungs and trachea were consistent with gavage error as the cause of death.

Drug-related clinical signs consisted of vomiting, hypersalivation, reduced activity, clumsy movements, and loss of balance, primarily at the MD and HD during the first week of dosing. Hypersalivation continued to be seen throughout the dosing period, but the other signs were observed only sporadically.

ii. Body Weight

BW gain during the dosing period was increased somewhat in dose groups, but final BWs were not different among groups.

iii. ECG and Ophthalmoscopy

Although not dose-related and sporadic in occurrence, an increase in QT duration (+12 to +31%, relative to pre-dose), QTcF (+8 to +26%), and QTcV (+7 to +21%) was noted in 2 MD males (#s 2659 and 2660) at week 4 and in 2 HD females (#s 2679 and 2681) during week 26. There were no other changes in CV parameters.

iv. Clinical Pathology

There was a slight decrease in RBC parameters (up to –14, -9 and –15% compared to pre-test for RBC, HB, and PCV, respectively) at the MD and HD in both sexes throughout the study (weeks 12, 20, 26, and 39). A decreased (SS) APTT was seen in individual MD and HD females.

The only consistent, dose-related clinical chemistry changes were increased triglyceride concentrations in treated animals of both sexes (**Table IV.A3.1**) and increased ALT (up to 56%, SS at MD and HD) and glutamate dehydrogenase (up to 2X, SS at MD and HD) in males. The latter change was also seen in treated females at some intervals, but was not dose-related.

There were no T-R urinalysis changes.

Table IV.A3.1. Triglyceride concentrations (mmol/L and % control)

	Males				Females			
Group/sex	M1	M2	M3	M4	F1	F2	F3	F4
mg/kg/day	0	300	600	900	0	300	600	900
Week 12/13	0.69	0.68 (-1)	1.09* (58)	1.44* (109)	0.76	0.69 (-9)	1.18 (55)	1.51 (99)
Week 20	0.96	0.81 (-16)	1.88 (96)	2.03 (111)	1.07	0.71 (-34)	1.44 (35)	2.22 (107)
Week 25/26	0.72	0.67 (-7)	1.24 (72)	1.67** (132)	0.70	0.70 -	1.24 (77)	0.97 (39)
Week 39	0.68	0.76 (12)	1.59* (134)	2.03* (199)	0.62	0.66 (6)	1.37 (121)	1.88 (203)

* =p<0.05; ** = p<0.01

Values in brackets correspond to the percentage difference from controls.

v. Necropsy

Mean liver weight (corrected for BW) was significantly increased (31% compared to C) in HD males.

Diffuse hypertrophy of hepatocytes was seen in 3/7 HD animals and brown pigment was noted in hepatocytes of 2/7 animals at this dose. According the pathology report, the increased pigment deposition in these animals "could be related to a slight increase in turnover of cellular membranes over a prolonged period." The report also stated that "there were no changes that appeared to be directly linked to altered serum enzyme levels of ALAT and GLDH."

vi. Toxicokinetics

TK parameters for ucb 34714 and its metabolites are shown in **Table IV.A3.2**. There were no clear sex differences and no evidence of auto-induction.

Table IV.A3.2. PK parameters for ucb 34714 and its metabolites in monkeys

Parameter	Unit	Dose (mg/kg/day)								
		300			600			900		
Week 13										
C_{max}	µg/mL	56.5	±	10.4	120	±	19	171	±	59
$C_{10\,h}$	µg/mL	*0.037*	±	0.025	0.576	±	0.370	4.84	±	6.51
$C_{24\,h}$	µg/mL	0.009	±	0.009	0.151	±	0.203	1.82	±	3.76
AUC(0-24 h)	µg.h/mL	269	±	62	965	±	193	1730	±	789
ucb 42145 *		0.07	±	0.01	0.07	±	0.01	0.07	±	0.01
ucb-100406-1 *		2.48	±	0.83	1.13	±	0.30	0.80	±	0.38
ucb-107092-1 *		0.08	±	0.03	0.04	±	0.01	0.03	±	0.01
ucb-102993-1 *		0.16	±	0.04	0.22	±	0.05	0.20	±	0.06
Week 39										
C_{max}	µg/mL	60.2	±	17.3	133	±	25	223	±	73
$C_{10\,h}$	µg/mL	*0.022*	±	0.015	0.273	±	0.259	3.07	±	3.49
$C_{24\,h}$	µg/mL	*0.109*	±	0.151	*0.115*	±	0.143	1.73	±	3.10
AUC(0-24 h)	µg.h/mL	267	±	101	1133	±	223	2351	±	822
ucb 42145 *		0.07	±	0.01	0.07	±	0.01	0.07	±	0.02
ucb-100406-1 *		2.73	±	1.39	0.93	±	0.27	0.62	±	0.38
ucb-107092-1 *		0.09	±	0.04	0.03	±	0.01	0.02	±	0.01
ucb-102993-1 *		0.15	±	0.04	0.20	±	0.03	0.16	±	0.03

Underlined values are BLQ (< 0.01 µg/mL); italic values include BLQ values.
* AUC(0-24 h) metabolite / AUC(0-24 h) ucb 34714.

c. Conclusions

Oral administration of BRV (300, 600 and 900 mg/kg/day dosed BID) to cynomolgus monkeys for 39 weeks produced transient (during the first week) CNS signs (reduced activity, clumsy movements, loss of balance), a slight reduction in RBC parameters, increased triglyceride concentrations (both sexes) and ALT (males only) and GDH activities (both sexes) at the MD and HD and increased liver weights, hepatocellular hypertrophy, and increased brown pigment deposition in the liver at the HD. At the NOAEL (LD) based on the CNS and clinical chemistry effects, plasma exposures to the parent compound (AUC = 270 ug.hr/mL, combined sexes) were approximately 5-fold that measured in humans at the MRD (56 ug.h/mL at 100 mg BID).

B. CARCINOGENICITY

1. ucb 34714: 104 - Week Oral (Dietary and Gavage) Carcinogenicity Study in CD-1 Mice (UCB Study # NCD1304, conducted by [redacted] (b) (4) report dated 8/26/09, GLP)

a. Methods

BRV (lot#s E04-83162, C05P714-117, C05P714-119, and CB14000016) was administered orally (diet + gavage, 5 mL/kg, BID) to mice (Crl:CD1(ICR), 60/sex/grp + 8 [C] or 18/sex/group TK) at total daily doses of 0 (1% w/v methylcellulose vehicle), 400, 550, or 700 mg/kg/day for 104 weeks (**Table IV.B1.1**). In treated groups, the dose given by dietary admix was 300 mg/kg/day and doses administered by gavage were 100, 250 and 400 mg/kg/day, split into two equal daily doses given 6 hours apart. Mortality and clinical signs were monitored daily. Animals received a detailed clinical examination and palpation weekly throughout treatment. Body weights and food consumption were recorded at pre-determined intervals from pre-dosing until the end of the dosing period. Blood samples were collected from main study animals for hematology during week 105 prior to sacrifice. All surviving main study animals and dead or moribund animals were necropsied and a macroscopic examination performed. A full battery of tissues was sampled, fixed, and examined microscopically. In TK satellite groups, blood samples were taken during weeks 13, 26, and 52 for determination of plasma concentration of ucb 34714 and three metabolites, ucb 42145, ucb-100406-1, and ucb-107092-1. Additional blood samples were taken from a subset of main study animals during week 104.

Dose selection was based on the results of a 13-week oral (gavage) study in CD-1 mice (see Exec-CAC minutes dated 9/20/05). The sponsor originally proposed total doses of 0, 450, 675, and 1000 mg/kg/day in males, and 0, 525, 750, and 1000 mg/kg/day in females. The Exec-CAC considered the highest doses too high based on deaths in the 13-week study and recommended total daily doses of 0, 125, 250, and 500 mg/kg/day.

Table IV.B1.1 Dose groups in mouse study

Group	Treatment (mg/kg/day)			Animal Numbers			
				Main Study		Satellite Study[3]	
	In Diet[1]	Gavage[2]	Total	Males	Females	Males	Females
1/Control	0	0	0	1-60	304-344, 346-363, 611	61-69	364-372
2/Low	300	100 (2x50)	400	70-129	373-432	130-147	433-450
3/Intermediate	300	250 (2x125)	550	148-207	451-510	208-225	511-528
4/High	300	400 (2x200)	700	226-285	529-574, 608, 576-588	286-303	589-595, 597-602, 604-607, 610

Animal 603 was replaced by Animal 610 during pretrial
Animal 575 was replaced by Animal 608 on Day 1 of dosing. This animal received it's first full dose on Day 2.
Animals 345 and 596 were replaced by animals 611 and 607 respectively on Day 3 of the study.
[1] The test item was administered by dietary admix only from the first day of treatment (Day 0) onwards and until the end of the study.
[2] The test item was administered by gavage from Day 1 onwards and until the end of the study. Doses by gavage were split into 2 equal daily subdoses given 6 h apart.
[3] Satellite animals dedicated to blood sampling for toxicokinetics.

b. Results

i. Mortality and body weight

There were no drug effects on survival (**Table IV.B1.2**).

BW gain over the dosing period was decreased in all treated groups (-32, -42, and -24% in males; -34, -21, and -24% in females at LD, MD, and HD; statistically significant (SS) in males at all doses and in LD females), but there was no dose relationship. At the end of the dosing period, mean BW was SS lower in LD and MD males and in LD female.

Table IV.B1.2 Mortality in 2-year mouse carcinogenicity study (# of animals)

Group (Dose Level mg/kg/day)	Males	Females
1 (0)	26 [19, 7]	38 [34, 4]
2 (300/100)	33 [30, 3]	40 [37, 3]
3 (300/250)	35 [28, 7]	40 [35, 5]
4 (300/400)	31 [28, 3]	40 [35, 5]

[ ] = number killed, number found dead

ii. Microscopic pathology

Neoplastic

In the sponsor's analysis, the incidence of hepatocellular adenoma or carcinoma showed a SS trend and the incidence of hepatocellular adenoma was increased (SS) in MD and HD males (**Table IV.B1.3**). Hepatocellular carcinoma was only seen in treated animals (SS trend), with a SS increase at the HD. The incidence of hepatocellular tumors was not increased in females. Hepatocellular carcinoma was only seen in treated animals, with a SS increase in HD males. The incidence of hepatocellular carcinomas in LD and MD males was greater than C, but within the historical control range.

There was a trend for increased incidences of benign luteoma and Sertoli cell tumors in treated females, but group differences did not reach SS (**Table IV.B1.4**). According to the sponsor, these finding should be considered of limited biological importance given the absence of other significant alterations in the female reproductive tract. There was no evidence of an effect of treatment on other tumor types.

The FDA statistical reviewer found SS dose response relationships in the incidences of hepatocellular adenoma, hepatocellular carcinoma, and combined hepatocellular adenoma and carcinoma in male mice. In female mice, the incidence of benign Sertoli cell tumor in ovaries also showed a SS dose response relationship. The pairwise comparisons showed SS increased incidences of hepatocellular adenoma and carcinoma at the HD and a SS increased combined incidence of hepatocellular adenoma and carcinoma at the MD and HD.

Table IV.B1.3 Incidence of hepatocellular tumors

Sex	**Male**				**Female**			
Dosage level (mg/kg/day)	**0**	**300/ 100**	**300/ 250**	**300/ 400**	**0**	**300/ 100**	**300/ 250**	**300/ 400**
Number examined	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**
One ADENOMA	6	4	9	7	2	2	0	0
Two ADENOMAS	1	1	3	4	0	0	0	0
Three ADENOMAS	0	2	1	2	0	0	0	0
Four ADENOMAS	0	1	1	2	0	0	0	1
Six ADENOMAS	0	0	0	1	0	0	0	0
Seven ADENOMAS	0	1	2	1	0	0	0	0
One CARCINOMA	0	1	3	8	0	0	0	0
Two CARCINOMAS	0	1	0	1	0	0	0	0
Number with ADENOMA	7	9	16	17	2	2	0	1
Number with CARCINOMA	0	2	3	9	0	0	0	0
Total with ADENOMA OR CARCINOMA	7	9	17	18	2	2	0	1

Table IV.B1.4 Incidence of luteoma and Sertoli cell tumours in the ovary

Sex	**Male**				**Female**			
Dosage level (mg/kg/day)	**0**	**300/ 100**	**300/ 250**	**300/ 400**	**0**	**300/ 100**	**300/ 250**	**300/ 400**
Number examined	**0**	**0**	**0**	**0**	**60**	**60**	**60**	**60**
One BENIGN LUTEOMA	-	-	-	-	1	0	4	4
Two BENIGN LUTEOMAS	-	-	-	-	0	0	2	0
Number with BENIGN LUTEOMAS	-	-	-	-	1	0	6	4
One BENIGN SERTOLI CELL TUMOUR	-	-	-	-	0	0	0	3

Non-neoplastic

Non-neoplatic findings considered T-R consisted of hepatocellular hypertrophy (centrilobular or diffuse), brown pigment in hepatocytes and Kupffer cells, necrosis of single hepatocytes, and eosinophilic and clear cell altered foci in the liver at all doses (**Table IV.B1.5**). In females, vacuolation of periportal hepatocytes was increased at all doses. Brown pigment was considered likely related to the formation of lipofuscin as a result of breakdown of SER. All liver changes were considered by the sponsor to be adaptive and not adverse. Brown pigment deposition in the olfactory mucosa and hyperplasia of the mucosal glands were also seen in the majority of treated animals from all dose groups with dose related severity (**Table IV.B1.6**). As in the liver, the study pathologist considered these findings to be likely related to the formation of lipofuscin pigment resulting from breakdown of SER in secondary lysosomes and of limited toxicological importance.

Table IV.B1.5 Incidence of non-neoplastic lesions in the liver

Sex	**Male**				**Female**			
Dosage level (mg/kg/day)	**0**	**300/ 100**	**300/ 250**	**300/ 400**	**0**	**300/ 100**	**300/ 250**	**300/ 400**
Number examined	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**
Pigment, brown, Kupffer cells								
Grade 1 of 5 (minimal)	5	12	19	10	15	20	21	19
Grade 2 of 5 (slight)	1	5	7	8	1	2	0	4
Grade 3 of 5 (moderate)	0	0	1	1	0	0	0	0
Total	6	17	27	19	16	22	21	23
Necrosis, hepatocellular, single cell								
Grade 1 of 5 (minimal)	3	6	12	12	0	2	1	4
Grade 2 of 5 (slight)	0	4	3	5	0	0	0	0
Grade 3 of 5 (moderate)	0	0	0	2	0	0	0	0
Total	3	10	15	19	0	2	1	4

Hypertrophy, hepatocellular, centrilobular								
Grade 1 of 5 (minimal)	0	23	11	8	0	14	11	13
Grade 2 of 5 (slight)	1	20	21	19	0	3	14	4
Grade 3 of 5 (moderate)	0	4	9	10	0	0	1	0
Grade 4 of 5 (marked)	0	0	6	12	0	0	0	0
Total	1	47	47	49	0	17	26	17
Hypertrophy, hepatocellular, diffuse								
Grade 1 of 5 (minimal)	0	0	0	0	0	0	1	5
Grade 2 of 5 (slight)	0	0	0	3	0	1	1	1
Grade 3 of 5 (moderate)	0	0	3	3	0	0	0	0
Grade 4 of 5 (marked)	0	0	1	1	0	0	0	0
Total	0	0	4	7	0	1	2	6
Altered hepatocytes, eosinophilic, focal								
Grade 1 of 5 (minimal)	2	3	4	6	1	0	0	1
Grade 2 of 5 (slight)	0	0	1	2	0	0	0	0
Grade 3 of 5 (moderate)	0	0	0	1	0	0	0	0
Total	2	3	5	9	1	0	0	1
Altered hepatocytes, clear, focal								
Grade 1 of 5 (minimal)	1	1	4	3	0	0	1	1
Grade 2 of 5 (slight)	0	0	0	1	0	0	0	0
Grade 3 of 5 (moderate)	0	0	0	1	0	0	0	0
Grade 4 of 5 (marked)	0	0	0	1	0	0	0	0
Total	1	1	4	6	0	0	1	1
Vacuolation, hepatocellular, periportal								
Grade 1 of 5 (minimal)	2	0	0	1	1	7	7	12
Grade 2 of 5 (slight)	0	0	0	0	0	1	1	0
Total	2	0	0	1	1	8	8	12
Pigment, brown, hepatocellular, centrilobular								
Grade 1 of 5 (minimal)	0	7	10	6	0	0	0	0

Table IV.B1.6 Incidence of non-neoplastic lesions in the nasal cavity/head

Sex	**Male**				**Female**			
Dosage level (mg/kg/day)	**0**	**300/ 100**	**300/ 250**	**300/ 400**	**0**	**300/ 100**	**300/ 250**	**300/ 400**
Number examined	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**
Pigment, brown, mucosa								
Grade 1 of 5 (minimal)	1	36	28	15	2	32	19	27
Grade 2 of 5 (slight)	0	10	16	24	0	1	13	12
Grade 3 of 5 (moderate)	0	0	0	0	0	0	1	0
Total	1	46	44	39	2	33	33	39
Hyperplasia, glands, mucosal								
Grade 1 of 5 (minimal)	24	30	17	25	16	17	28	26
Grade 2 of 5 (slight)	8	9	12	6	2	3	3	6
Grade 3 of 5 (moderate)	1	1	2	2	0	0	0	1
Total	33	40	31	33	18	20	31	33

Toxicokinetics

Exposure to parent was higher in males than females and increased greater than dose-proportionally. Metabolite exposures were approximately 3-6, 120-290, and 1-3% of parent for ucb 42145, ucb-100406-1, and ucb-107092-1, respectively (**Table IV.B1.7**).

Table IV.B1.7 Plasma drug and metabolite exposures in mice

Parameter	Unit	300 [(a)] + 100 [(b)] mg/kg/day		300 [(a)] + 250 [(b)] mg/kg/day		300 [(a)] + 400 [(b)] mg/kg/day	
		males	females	males	Females [(c)]	males	females
Week 13							
C_{1h} ucb 34714	(µg/mL)	5.27	2.25	24.7	9.66	37.1	23.2
Week 26							
C_{1h} ucb 34714	(µg/mL)	7.77	2.81	21.2	13.6	46.9	38.1
Week 52							
C_{max} ucb 34714	(µg/mL)	9.25	4.85	32.8	*14.4*	51.3	38.9
C_{24h} ucb 34714	(µg/mL)	3.54	0.774	2.09	*0.466*	3.43	0.573
$AUC_{(0\text{-}24h)}$	(µg eq.h/mL)						
ucb 34714		82.2	51.4	136	*58.6*	252	160
ucb 42145		2.75	2.67	5.30	*4.38*	8.99	8.97
ucb-100406-1		155	148	241	*237*	314	341
ucb-107092-1		1.50	1.52	2.57	*5.15*	3.48	3.42
Week 105							
C_{1h} ucb 34714	(µg/mL)	7.76	4.70	24.3	11.1	24.5	22.3

(a) : in diet; (b) gavage (2 equal sub-doses given 6 hours apart); (c) : italic values are reported for information as on Week 52, 3 female mice from Group 3 (mid dose) received the second sub-dose of ucb 34714 after the blood sample was taken at 7h post first sub-dose. The C_{max} and $AUC_{(0\text{-}24h)}$ are probably underestimated.

c. Conclusions:

Oral (gavage and dietary) administration of ucb 34714 to CD1 mice for 2 years increased the incidences of hepatocellular tumors in males at the MD and HD (SS for hepatocellular adenoma and carcinoma at the HD and combined hepatocellular adenoma and carcinoma at the MD and HD). There was a trend for increased incidences of benign luteoma and Sertoli cell tumors in treated females, but group differences did not reach SS.

2. ucb 34714: 104-Week Oral (Dietary and Gavage) Carcinogenicity Study in Wistar Rats (UCB Study # *NCD1305*, conducted by (b) (4) report dated 7/15/09, GLP)

a. Methods:

Brivaracetam (lot#s E04-83162, C05P714-115, C05P714-117, C05P714-119, and CB14000016) was administered orally (diet + gavage, 5 mL/kg, BID) to rats (Han Wistar, 50/sex/grp + 5 [C] or 10/sex/group TK) at doses of 0 (1% w/v methylcellulose vehicle), 150, 230, 450, or 700 mg/kg/day for 104 weeks (**Table IV.B2.1**). In treated groups, the dose given by dietary admix was 100 mg/kg/day and doses administered by gavage were 50, 130, 350, and 600 mg/kg/day, split into two equal daily doses given 6 hours apart. Mortality and clinical signs were monitored daily. Animals received a detailed clinical examination and palpation weekly throughout treatment. Body weights and food consumption were recorded from pre-test until the end of the dosing period. Blood samples were collected from main study animals for hematological investigations during weeks 103/104. All main study animals, including dead or moribund animals, were necropsied and a macroscopic examination performed. A full panel of tissues from all animals was sampled, preserved in the appropriate fixative, and examined microscopically. In TK groups, blood samples were taken during weeks 13, 26, and 52 for determination of plasma concentration of ucb 34714 and three metabolites: ucb 42145, ucb-100406-1, and ucb-107092-1. Additional blood samples were taken from a subset of main study animals during week 104.

Doses were based on the results of a 26-week toxicity study in Wistar rats. The Exec-CAC agreed with the 4 doses proposed by the sponsor in females (0, 150, 230, 450, and 700 mg/kg/day) based on MTD (lethality), but recommended administration of only the lower 3 doses in males (0, 150, 230, and 450 mg/kg/day).

Table IV.B2.1 Dose groups

Group	Treatment (mg/kg/day)			Animal Numbers			
				Main Study		Satellite Study[3]	
	In Diet[1]	Gavage[2]	Total	Males	Females	Males	Females
1/Control	0	0	0	1-50	296-345	251-255	546-550
2/Low	100	50 (2x25)	150	51-100	346-395	256-265	551-560
3/Intermediate I	100	130 (2x65)	230	101-150	396-445	266-275	561-570
4/Intermediate II	100	350 (2x175)	450	151-200	446-495	276-285	571-580
5/High5	100	600 (2x300)	700	201-250	496-545	286-295	581-590

[1] The test item was administered by dietary admix only from the first day of treatment (Day 0) onwards and until the end of the study.
[2] The test item was administered by gavage from Day 1 onwards and until the end of the study. Doses by gavage were split into 2 equal daily subdoses given 6 h apart.
[3] Satellite animals dedicated to blood sampling for toxicokinetics.

b. Results:

Body weight and mortality

There was no clear effect of treatment on survival, although number found dead was increased slightly in HD males and females (**Table IV.B2.2**). There were no notable clinical signs that could be attributable to treatment. In males, body weight (BW) was statistically significantly (SS) lower from week 5 through to the end of the treatment period at all but the MD, and BW gain was lower (SS) in all treated groups over the treatment period, although the differences were not clearly dose-related (**Table IV.B2.3**). In females, BW and BW gain were lower in all treatment groups from week 3 until the end of the treatment period, but the differences were again not dose-related. There were no effects on hematology parameters that were considered to be drug-related.

Table IV.B2.2 Mortality in rats

Group (Dose Level mg/kg/day)	Males	Females
1 (0)	15 [15, 0]	10 [10, 0]
2 (100/50)	10 [9, 1]	12 [11, 1]
3 (100/130)	15 [14, 1]	16 [15, 1]
4 (100/350)	9 [8, 1]	10 [9, 1]
5 (100/600)	10 [6, 4]	13 [10, 3]

Figures in [] = number killed, number found dead

Table IV.B2.3 Body weights in rats

Male

(Group/Dose Level) (mg/kg/day)		Treatment Period (Weeks)										Body Weight Gain (g) (Week 0 - Week 104)
		95	96	97	98	99	100	101	102	103	104	
1 (0)	Number	40	39	39	39	37	36	35	35	35	35	35
	Mean	598	600	602	605	603	605	603	605	603	605	428
	SD	69	71	71	72	73	76	78	77	77	78	71
2 (150)	Number	45	45	45	44	44	43	42	42	41	40	40
	Mean	553	555	556	556	556	552	554	556	555	557	382
	SD	61	62	61	61	62	63	61	61	61	62	58
	Prob.	**	**	**	**	**	***	**	**	**	**	**
3 (230)	Number	42	41	40	40	38	38	36	36	36	35	35
	Mean	577	582	583	585	577	575	573	575	575	575	400
	SD	78	72	72	73	71	71	73	74	76	76	76
	Prob.											
4 (450)	Number	46	45	44	44	43	42	42	42	42	41	41
	Mean	560	561	562	565	557	555	553	555	554	555	378
	SD	68	69	69	70	61	60	60	61	63	65	57
	Prob.	*	**	**	**	**	**	**	**	**	**	***
5 (700)	Number	42	42	42	41	41	40	40	40	40	40	40
	Mean	566	567	567	571	568	566	565	567	564	566	387
	SD	65	64	65	66	66	65	64	65	64	63	57
	Prob.	*	*	*	*	*	*	*	*	*	*	**

Significantly different from the Control: * P<0.05, ** P<0.01, *** P<0.001

Female

(Group/Dose Level) (mg/kg/day)		Treatment Period (Weeks)										Body Weight Gain (g) (Week 0 - Week 104)
		95	96	97	98	99	100	101	102	103	104	
1 (0)	Number	45	45	45	45	44	44	42	42	40	40	40
	Mean	403	406	407	409	410	409	407	404	406	406	261
	SD	66	65	66	66	66	68	66	64	67	69	65
2 (150)	Number	45	44	43	43	42	42	38	38	38	38	38
	Mean	338	337	338	339	337	338	337	337	335	334	194
	SD	44	44	46	46	46	47	44	44	44	44	40
	Prob.	***	***	***	***	***	***	***	***	***	***	***
3 (230)	Number	43	42	41	40	39	38	35	34	34	34	34
	Mean	353	354	355	357	356	357	359	362	362	361	218
	SD	56	56	55	52	52	53	52	52	54	53	47
	Prob.	***	***	***	***	***	***	***	***	***	***	**
4 (450)	Number	41	41	41	41	40	40	40	40	40	40	40
	Mean	356	355	357	358	359	360	361	362	362	364	217
	SD	54	54	54	54	53	54	55	54	54	55	47
	Prob.	***	***	***	***	***	***	***	***	***	***	**
5 (700)	Number	40	40	39	38	38	38	38	38	37	37	37
	Mean	338	338	341	341	340	340	341	342	343	341	199
	SD	48	48	50	49	50	49	49	51	49	49	43
	Prob.	***	***	***	***	***	***	***	***	***	***	***

Significantly different from the Control: * P<0.05, ** P<0.01, *** P<0.001

Neoplastic

In the sponsor's analysis, there was a SS trend for increased incidence of benign or malignant thymoma in females and a SS difference from C at the HD (**Table IV.B2.4**). The historical control range for this tumor was 0.0 – 8.7%. According to the report, "This is a common tumor type in Han Wistar rats and the control incidence in females in this study is low in comparison with the control range from contemporaneous studies. The apparent increase in the incidence of thymoma was not considered to be toxicologically relevant." Incidences of thyroid follicular cell tumors were also increased in drug-treated rats but were not dose-related (**Table IV.B2.5**). The trend was SS in the combined sex analysis for adenomas and for overall thyroid tumor incidence.

In the FDA statistician's review, the analysis showed SS dose response relationships for the incidence of benign thymoma and combined incidences of benign and malignant thymoma in the thymus of female rats and the pairwise comparison showed SS increased incidences of benign thymoma and combined benign and malignant thymoma (same incidence as benign except one additional LD) in the thymus in HD females compared to C.

Table IV.B2.4 Incidence of epithelial tumors in the thymus

Sex	**Male**					**Female**				
Number examined	**48**	**47**	**44**	**48**	**49**	**50**	**48**	**48**	**50**	**50**
Dosage level ucb 34714 (mg/kg/day)	**0**	**100/ 50**	**100/ 130**	**100/ 350**	**100/ 600**	**0**	**100/ 50**	**100/ 130**	**100/ 350**	**100/ 600**
Benign thymoma	0	2	1	1	2	2	2	4	5	11
Malignant thymoma	1	0	0	0	0	0	1	0	0	0
Total	1	2	1	1	2	2	3	4	5	11

Table IV.B2.5 Incidence of follicular cell tumors in the thyroid gland

Sex	Male					Female				
Number examined	50	50	50	50	49	50	50	50	50	50
Dosage level ucb 34714 (mg/kg/day)	0	100/ 50	100/ 130	100/ 350	100/ 600	0	100/ 50	100/ 130	100/ 350	100/ 600
Adenoma	1	0	5	4	4	0	2	1	3	2
Carcinoma	0	0	1	0	1	0	0	1	0	0
Total	1	0	6	4	5	0	2	2	3	2

Non-neoplastic

Non-neoplastic findings considered drug-related were seen in the liver, thyroid (males), kidneys (males), and Harderian gland (males). In the liver, hypertrophy, brown pigment, and vacuolation of centrilobular hepatocytes were seen at all doses, with evidence of a dose response for hypertrophy and pigment (**Table IV.B2.6**). The liver hypertrophy and brown pigment deposition were considered to be adaptive responses to enzyme induction. Eosinophilic inclusions were also seen in hepatocytes of some affected animals. Bile duct hyperplasia and fibrosis were seen at all doses with some evidence of a dose response. Basophilic and eosinophilic foci of altered hepatocytes were seen in all groups, but the incidence appeared to be increased in drug-treated males compared to C.

In the kidney, hyaline droplets in proximal tubules were seen in males from all drug-treated groups with evidence of a dose response (**Table IV.B2.7**). Brown pigment in tubules was increased in males with evidence of a dose response. Focal mineralization in the papilla, chronic progressive nephropathy, and basophilic tubules also appeared to be increased in treated males.

The incidence of brown pigment in thyroid follicular cells was increased in drug-treated males. Focal hyperplasia of the Harderian gland was seen with an increased incidence in HD males.

Table IV.B2.6 Incidence of liver findings in rats

Sex	Male					Female				
Dosage level ucb 34714 (mg/kg/day)	0	100/ 50	100/ 130	100/ 350	100/ 600	0	100/ 50	100/ 130	100/ 350	100/ 600
Number examined	50	50	50	50	50	50	50	50	50	50
Hypertrophy, hepatocellular, centrilobular										
Grade 1 of 5 (minimal)	0	32	13	4	2	0	33	19	5	4
Grade 2 of 5 (slight)	0	12	32	16	6	0	13	28	39	20
Grade 3 of 5 (moderate)	0	0	3	30	41	0	0	1	6	25
Total	0	44	48	50	49	0	46	48	50	49
Pigment, brown, hepatocellular, centrilobular										
Grade 1 of 5 (minimal)	0	23	29	18	25	2	18	16	22	15
Grade 2 of 5 (slight)	0	1	4	14	11	0	6	16	11	19
Grade 3 of 5 (moderate)	0	0	0	3	3	0	0	1	10	9
Grade 4 of 5 (marked)	0	0	0	0	0	0	0	0	0	2
Total	0	24	33	35	39	2	24	33	43	45
Vacuolation, hepatocellular, centrilobular										
Grade 1 of 5 (minimal)	2	29	31	23	16	0	3	4	3	2
Grade 2 of 5 (slight)	0	5	0	1	1	1	0	0	0	0
Total	2	34	31	24	17	1	3	4	3	2
Inclusions, eosinophilic, hepatocellular										
Grade 1 of 5 (minimal)	0	1	1	5	6	1	0	1	3	0
Hyperpasia, bile ducts										
Grade 1 of 5 (minimal)	3	10	10	22	16	8	10	15	15	12
Grade 2 of 5 (slight)	0	0	0	1	0	0	2	0	0	0
Grade 3 of 5 (moderate)	0	0	0	0	0	0	1	0	1	0
Total	3	10	10	23	16	8	13	15	16	12
Fibrosis, bile ducts										
Grade 1 of 5 (minimal)	2	9	11	16	9	4	3	6	11	6
Altered hepatocytes, basophilic, tigroid, focal										
Grade 1 of 5 (minimal)	16	33	27	32	22	23	30	29	34	30
Grade 2 of 5 (slight)	0	0	1	0	0	16	8	13	11	7
Grade 3 of 5 (moderate)	0	0	0	0	0	6	8	1	1	0
Grade 4 of 5 (marked)	0	0	0	0	0	0	1	1	0	0
Total	16	33	28	32	22	45	47	44	46	37
Altered hepatocytes, eosinophilic, focal										
Grade 1 of 5 (minimal)	17	25	29	31	18	29	24	25	25	26
Grade 2 of 5 (slight)	0	0	3	5	4	3	2	3	8	6
Grade 3 of 5 (moderate)	0	0	0	1	0	0	0	0	0	0
Total	17	25	32	37	22	32	26	28	33	32

Table IV.B2.7 Incidence of kidney findings in rats

Sex	Male					Female				
Number examined	50	50	50	50	50	50	50	50	50	50
Dosage level ucb 34714 (mg/kg/day)	0	100/ 50	100/ 130	100/ 350	100/ 600	0	100/ 50	100/ 130	100/ 350	100/ 600
Number examined	50	50	50	50	50	50	50	50	50	50
Hyaline droplets, proximal tubules										
Grade 1 of 5 (minimal)	0	16	23	24	19	0	0	0	0	0
Grade 2 of 5 (slight)	0	2	3	12	15	0	0	0	0	0
Grade 3 of 5 (moderate)	0	0	0	1	0	0	0	1	0	0
Grade 4 of 5 (marked)	0	1	0	0	1	0	0	0	0	0
Total	0	19	26	37	35	0	0	1	0	0
Pigment, brown, tubules										
Grade 1 of 5 (minimal)	10	17	21	35	30	36	31	31	38	40
Grade 2 of 5 (slight)	0	1	0	5	4	2	0	2	2	3
Grade 3 of 5 (moderate)	0	0	0	1	1	0	0	0	1	0
Total	10	18	21	41	35	38	31	33	41	43
Mineralisation, papilla, focal										
Grade 1 of 5 (minimal)	1	4	10	9	10	6	9	6	4	4
Nephropathy, chronic, progressive/basophilic tubules										
Total	31	29	40	46	45	23	14	13	21	19

Toxicokinetics

Exposure to parent was higher (up to 1.5X) in females than males and increased greater than dose-proportionally (**Table IV.B2.8**). Metabolite exposures were approximately 3, 65-134, and 1-2% of parent for ucb 42145, ucb-100406-1, and ucb-107092-1, respectively.

Table IV.B2.8 Plasma drug and metabolite exposures in rats

Parameter	Unit	100 [a] + 50 [b] mg/kg/day		100 [a] + 130 [b] mg/kg/day		100 [a] + 350 [b] mg/kg/day		100 [a] + 600 [b] mg/kg/day	
		males	females	males	females	males	females	males	females
Week 13									
C_{1h}	(µg/mL)								
ucb 34714		8.76	16.5	19.1	25.5	36.0	68.6	61.1	70.9
Week 26									
C_{1h}	(µg/mL)								
ucb 34714		8.75	15.9	22.2	34.3	45.5	69.6	42.2	63.9
Week 52									
C_{max}	(µg/mL)								
ucb 34714		11.1	17.5	22.0	34.2	59.5	68.5	79.6	81.3
C_{24h}	(µg/mL)								
ucb 34714		2.28	2.00	1.55	2.29	1.26	1.29	1.28	1.68
$AUC_{(0-24h)}$	(µg eq.h/mL)								
ucb 34714		84.7	121	124	197	333	529	510	635
ucb 42145		2.39	3.05	3.61	5.10	10.2	13.7	14.1	16.0
ucb-100406-1		102	92.7	167	154	337	347	476	449
ucb-107092-1		1.97	1.07	3.02	2.11	5.94	4.98	9.24	7.38
Week 103/104									
C_{1h}	(µg/mL)								
ucb 34714		13.6	12.3	23.4	28.3	36.6	39.8	71.3	72.1

(a) : in diet; (b) gavage (2 equal sub-doses given 6 hours apart)

c. Conclusions:

Oral (gavage and dietary) administration of ucb 34714 to Wistar rats for 2 years increased the incidence of benign thymus tumors in females and produced a trend for increased thyroid follicular cell tumors in rats of both sexes. Non-neoplastic lesions in the liver, kidney, and thyroid were consistent with those observed in previous studies.

C. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY

1. ucb 34714 - Oral (Gavage) Fertility and Early Embryonic Development Study in the Rat (Report No. PSM0978; dated 11/27/03; conducted by (b) (4); GLP)

a. Methods

Wistar rats (Crl:WI (Glx/BRL/Han) BR VAF PLUS; 25/sex/grp) received 0 (vehicle: 1% methylcellulose), 100, 200, or 400 mg/kg/day BRV (batch #: C02-P714-109R) dosed BID (6 hr apart) by oral gavage (5 mL/kg) prior to (at least 28 days in males, 14 days in females) and during the mating period (maximum of 20 days). Males were dosed for at least 2 weeks post-mating and females until GD 6. Body weights, food consumption, and clinical observations were regularly recorded throughout the study. Estrous cycles were monitored in females for 10 days before pairing. Blood samples for TK evaluations were collected from 10/sex/group on one day towards the end of the pre-pairing period at 0.5 hours after the second daily dose. Females were sacrificed and necropsied on GD 13 and the number of corpora lutea and number and distribution of implantations were recorded. Two weeks after the end of the mating period, males were sacrificed and testes and epididymides were weighed. Samples of sperm suspension were immediately assessed for motility and concentration using CASA (computer assisted sperm motility analysis) technology and a smear was prepared for microscopic examination of morphology. The testes from all males were examined microscopically in a stage aware manner. Doses were based on the results of the 13-week oral gavage toxicity study in Wistar rats (doses of 0, 50, 100, 200, and 400 mg/kg/day given BID) in which the HD induced liver effects in both sexes, including increased ALT, liver weights, centrilobular hypertrophy, and the presence of brown pigment identified as lipofuscin in centrilobular hepatocytes.

b. Results

i. Mortality and Clinical Observations

There were no deaths considered treatment-related (TR). One MD male (number 59) was sacrificed on day 6 of dosing with noisy, labored breathing, but there were no findings at necropsy and this was considered an incidental death. The only clinical sign was excessive salivation immediately post-dosing in all MD and HD animals throughout the dosing period and at the LD for a few days.

ii. Body Weight

There were no effects on body weight (BW) or BW gain in males (**Figure IV.C1.1**). In females, BW gains were slightly reduced at the MD and HD (-13 % in both groups) during GDs 7 to 13 (i.e., after dosing stopped). However, BWs were comparable to C throughout gestation (**Figure IV.C1.2**).

Figure IV.C1.1. Male body weight

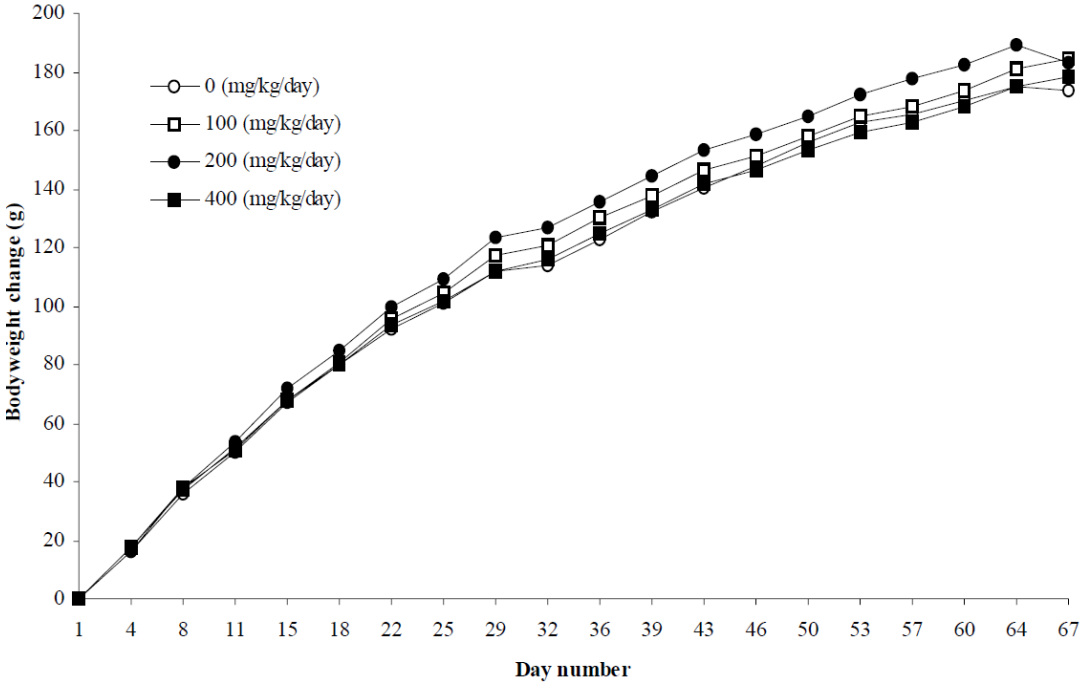


Figure IV.C1.2. Female body weight

Premating

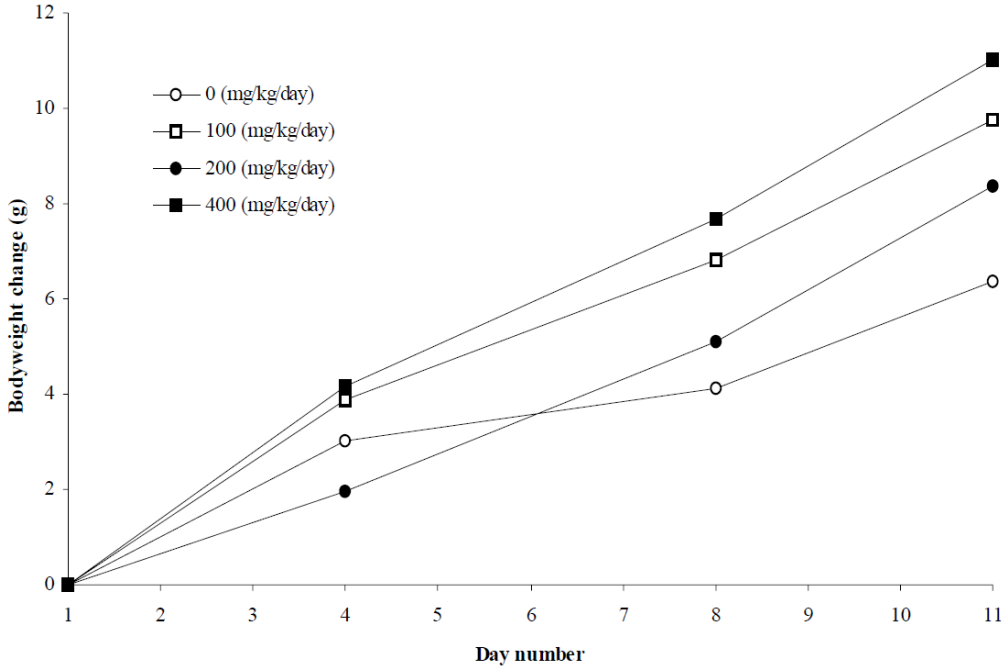
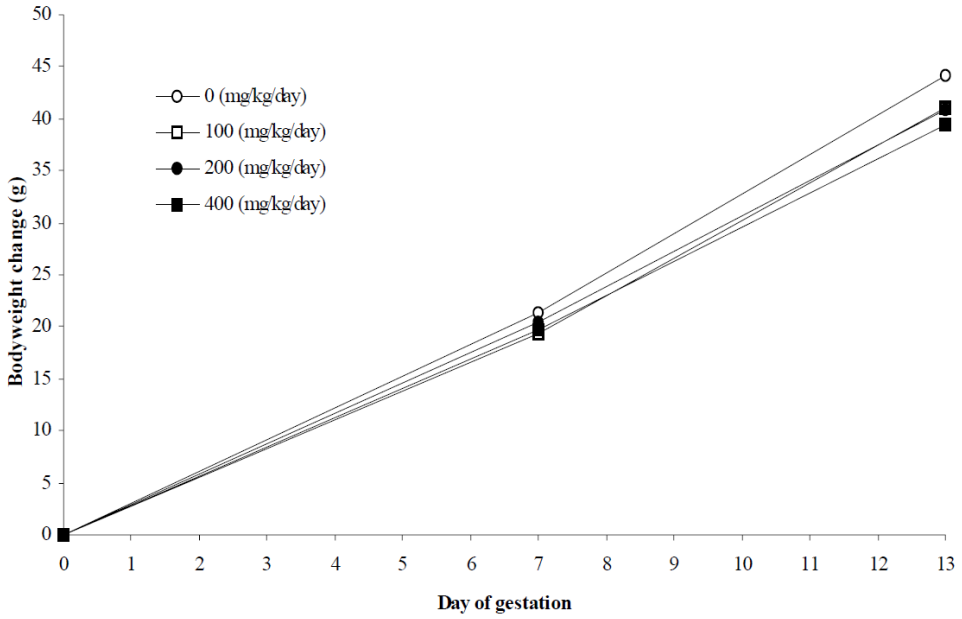


Figure IV.C1.2.(cont.)

Gestation



iii. Male and female reproductive indices

Estrous cycling, mating, and fertility parameters were unaffected by treatment (**Tables IV.C1.1 and IV.C1.3**). All rats in cohabitation mated with the exception of one C male and one MD male. There were no effects on sperm parameters that were considered T-R by the sponsor, although there were some apparent increases (NS) in abnormal sperm in treated males (**Table IV.C1.2**).

Table IV.C1.1 Pre-mating estrus cycles

Group	: 1	2	3	4
Treatment	: Control		ucb 34714	
Dosage (mg/kg/day)	: 0	100	200	400

Mean number of complete oestrous cycles ± S.D.

Group	N	Pre-pairing smears (10 days)
1	25	2.0 ± 0.0
2	25	2.0 ± 0.2
3	25	1.8 ± 0.4
4	25	1.9 ± 0.3

N = number of animals in mean

Table IV.C1.2 Sperm morphology

Group	: 1	2	3	4
Treatment	: Control		ucb 34714	
Dosage (mg/kg/day)	: 0	100	200	400

Parameter	Group 1	2	3	4
N	25	25	24	25
No. normal #	197 ± 3	197 ± 2	196 ± 3	197 ± 3
No. headless #	1.84 ± 2.56	1.80 ± 1.71	2.13 ± 2.38	1.44 ± 1.16
No tailless (with mid piece) #	0.28 ± 0.54	0.36 ± 0.70	0.54 ± 0.72	0.52 ± 0.77
No. with reduced hook #	0.36 ± 0.76	0.40 ± 0.71	0.67 ± 1.27	0.64 ± 1.85
Miscellaneous abnormalities #	0.24 ± 0.52	0.40 ± 0.71	0.63 ± 1.01*	0.44 ± 0.65

N = number of animals in mean
# = statistically analysed * = p<0.05

Table IV.C1.3 Mating and fertility parameters

Group	:	1	2	3	4
Treatment	:	Control		ucb 34714	
Dosage (mg/kg/day)	:	0	100	200	400

Group	Sex	Number paired	Number mated	Number fertile	Copulation index#	Fertility index#
1	M	25	24	24	96.0	100.0
2	M	25	25	23	100.0	92.0
3	M	24	23	23	95.8	100.0
4	M	25	25	23	100.0	92.0

Group	Sex	Number paired	Number mated	Number fertile	Copulation index#	Fertility index#
1	F	25	25	25	100.0	100.0
2	F	25	25	23	100.0	92.0
3	F	25	25	23	100.0	92.0
4	F	25	25	23	100.0	92.0

= statistically analysed

iv. Litter parameters

No treatment effects on C-sectioning or litter parameters were apparent (**Table IV.C1.4**). There was an increase in the mean number of corpora lutea at the HD compared with concurrent and historical Cs, which was considered to be coincidental and not of toxicological significance.

Table IV.C1.4 Caesarean-Sectioning Observations

Group	: 1	2	3	4
Treatment	: Control		ucb 34714	
Dosage (mg/kg/day)	: 0	100	200	400

	Group 1	Group 2	Group 3	Group 4
Number of females with implantations at scheduled kill	25	23	23	23
Number of corpora lutea	325	314	314	327
Mean number per female#	13.0	13.7	13.7	14.2*
Standard deviation	1.4	2.2	1.5	1.6
Number of implantations	285	285	292	294
Mean number per female#	11.4	12.4	12.7	12.8
Standard deviation	2.8	2.5	1.6	2.9
Mean % pre-implantation loss#	12.5	8.9	6.8	10.1
Number of early embryo/foetal deaths	16	15	11	12
Number of dead embryos	0	0	0	0
Mean % post-implantation loss#	5.7	5.7	3.8	3.8
Number of live embryos	269	270	281	282
Mean number per female#	10.8	11.7	12.2	12.3
Standard deviation	2.9	2.7	1.8	2.8
Mean % of implantations	94.3	94.3	96.2	96.2

= statistically analysed *=p<0.05

v. Necropsy

There were no effects on testes weights or other necropsy observations. There was no effect of treatment on the histopathology of the testes or the stages of spermatogenesis.

vi. Plasma level data

Plasma BRV concentrations measured at the end of the pre-mating period at 0.5 hours after the second daily dose are summarized in **Table IV.C1.5**.

Table IV.C1.5 BRV mean plasma concentrations (µg/mL) after repeat oral administration

	Dose [1] (mg/kg/day)		
	100	200	400
Males	27.7 ± 7.8	42.3 ± 12.7	52.1 ± 18.6
Females	38.6 ± 6.6	55.9 ± 10.8	79.2 ± 33.0

[1] Doses were split into 2 equal subdoses given 6 hours apart.

c. Conclusions

Treatment of male and female rats with BRV (oral gavage doses of 100, 200, or 400 mg/kg/day, given BID, 6 hr apart) prior to and during mating and throughout gestation resulted in only minor clinical signs of toxicity and slight effects on parental body weight gain and produced no apparent adverse effects on mating and fertility or on C-sectioning parameters. Dose selection was questionable since toxicity at the HD was not limiting in the 13-week study (AUCs 317 and 743 ug.h/mL in males and females) and did not produce the expected level of parental toxicity in this study. In a 4-week rat toxicity study (oral gavage doses of 100, 300, 1000, and 1500 mg/kg/day given BID, 6 hr apart), the HD was not tolerated and some males were sacrificed moribund at the MHD; however, it appears that there is an adequate dose gap between 400 and 1000 mg/kg/day to justify a recommendation that the study be repeated in an attempt to reach the expected level of parental toxicity.

2. ucb 34714: Oral (Gavage) Embryo-Fetal Toxicity Study in the Rat (Study No. PSM0853, report dated 9/9/02, conducted by [redacted] [(b) (4)] GLP)

a. Methods

Female Wistar rats (Crl:(WI, Glx/BRL/Han) BR VAF PLUS; 24/grp + 12/grp TK) were treated with 0 (1% methylcellulose vehicle), 150, 300, or 600 mg/kg/day BRV (dosed BID, 6 hr apart; batch #105) by oral gavage (5 mL/kg) on GDs 6 through 17. Dams were observed for viability, clinical signs, premature deliveries, and deaths. Body weights (BW) and food consumption were recorded during the dosing and postdosing period. Blood samples for TK determinations were collected on GD 6 or 17 from 3 mated satellite females/group/time point, at 1, 3, 6, 7, 9, and 24 hrs after the first daily dose. Main study animals were sacrificed on GD 20 and C-sectioned. Numbers of corpora lutea was recorded and uteri were examined for pregnancy, number and distribution of implantation sites, early and late resorptions, and live and dead fetuses. Half of the fetuses in each litter were fixed in Bouin's solution for subsequent examination of the brain by free-hand serial sectioning and of the viscera using microdissection. The remaining fetuses were placed in alcohol for light fixation before being examined for skeletal and visceral abnormalities.

Dose selection: Doses were based on an embryofetal range-finding study in Wistar rats in which a dose of 600 mg/kg/day (dosed BID, 6 hr apart) induced maternal clinical signs: hypoactivity, lethargy, unsteady gait, noisy breathing, and partially closed eyes.

b. Results

i. Maternal effects

There were no maternal deaths. Salivation was observed immediately after the first and second dose on each day and partially closed eyes were also observed at between 1.25 and 1.5 hours post-dosing in all HD females. There were no effects on maternal BW gain over the treatment period (**Table IV.C2.1**). One HD dam (#75) was found to have an abnormal kidney (bilateral pelvic dilatation) at necropsy. Four LD females were not pregnant, but all other main study females were pregnant with live fetuses on GD 20. In the TK groups, 1 MD and 1 HD female were not pregnant. TK parameters for BRV are shown in **Table IV.C2.2**.

Table IV.C2.1 Maternal Body Weight Changes

Group	:	1	2	3	4
Treatment	:	Control		ucb 34714	
Dosage (mg/kg/day)	:	0	150	300	600

Group sex		Day number Gain# 6-7	Gain# 6-8	Gain# 6-9	Gain# 9-12	Gain# 12-15	Gain# 15-18	Gain# 6-18	Gain# 18-20
1F	Mean	2.7	6.3	9.6	14.2	16.5	28.7	69.0	22.3
	S.D.	2.1	3.4	4.4	4.0	5.4	7.6	13.4	6.2
	N	24	24	24	24	24	24	24	24
2F	Mean	3.9	6.8	10.6	13.9	16.4	29.9	70.8	23.9
	S.D.	2.9	3.6	5.1	3.7	3.8	5.6	12.0	6.2
	N	20	20	20	20	20	20	20	20
3F	Mean	4.3*	7.5	11.0	15.3	16.1	29.8	72.3	23.5
	S.D.	3.2	3.0	3.3	4.1	4.2	7.1	15.0	4.1
	N	24	24	24	24	24	24	24	24
4F	Mean	5.3**	7.2	9.7	14.6	18.7	28.1	71.0	21.4
	S.D.	2.5	3.3	4.1	3.7	5.7	7.0	13.2	7.8
	N	24	24	24	24	24	24	24	24

- statistically analysed *=p<0.05 **=p<0.01 ***=p<0.001

Table IV.C2.2 TK parameter values of ucb 34714 in pregnant female rats

Parameter	Unit	Dose (mg/kg/day)		
		150	300	600
Day 1 of treatment [(a)]				
C_{max1}	(µg/mL)	45.7	71.5	77.3
t_{max1}	(h)	1	3	6
C_{max2}	(µg/mL)	59.9	81.3	155
t_{max2}	(h)	7	7	7
AUC (0-24h)	(µg.h/mL)	717	1163	1913
C_{24h}	(µg/mL)	4.15	7.12	31.7
Day 12 of treatment [(b)]				
C_{max1}	(µg/mL)	55.3	48.4	77.2
t_{max1}	(h)	1	1	3
C_{max2}	(µg/mL)	55.9	93.4	184
t_{max2}	(h)	7	7	7
AUC (0-24h)	(µg.h/mL)	586	1099	1801
C_{24h}	(µg/mL)	0.118	1.30	7.39

Sampling time refers to the first daily sub-dose
(a) Day 6 of pregnancy
(b) Day 17 of pregnancy

ii. Litter parameters and fetal evaluations

There were no effects of treatment on litter parameters at C-sectioning (**Table IV.C2.3**). An increase in preimplantation loss at the HD was attributed to 1 HD female (#75) with a high rate (73%).

There were 4 HD fetuses from 3 litters with malformations (classified as major abnormalities) compared to none in C fetuses (**Table IV.C2.4-8**). Two fetuses from the same HD litter (female #75) had kidney abnormalities (absent kidneys, small kidneys, and absence of a uterine horn), while bifid sternum and transposition of the aortic and pulmonary arch were found in two fetuses from two different litters (female #s 84 & 94). There were also single incidences of fetal malformations at the LD (malrotated hind-limb) and MD (absent kidney). There were apparent dose-related increases in incidences of combined (SS at HD) and individual minor abnormalities (what would not be considered variations; e.g., irregular ridging of palate, uneven occipital ossification, decreased ossification of caudal vertebrae).

Table IV.C2.3 Caesarean-sectioning observations

Group :	1	2	3	4
Treatment :	Control		ucb 34714	
Dosage (mg/kg/day) :	0	150	300	600

	Group 1	Group 2	Group 3	Group 4
Number of females with implantations at scheduled kill	24	20	24	24
Number of corpora lutea	265	237	269	281
Mean number per female	11.0	11.9	11.2	11.7
Standard deviation	1.9	1.5	1.6	1.1
Number of implantations	243	213	246	245
Mean number per female	10.1	10.7	10.3	10.2
Standard deviation	2.8	2.7	2.3	2.7
Mean % pre-implantation loss	9.3	11.1	8.9	13.0
Number of early embryo/foetal deaths	16	13	8	13
Number of late embryo/foetal deaths	1	0	0	1
Number of dead foetuses	0	0	0	0
Mean % post-implantation loss	7.8	7.5	3.1	6.0
Number of live foetuses	226	200	238	231
Mean number per female	9.4	10.0	9.9	9.6
Standard deviation	2.9	3.1	2.1	2.7
Mean % of implantations	92.2	92.5	96.9	94.0
Number of male foetuses	124	103	113	122
Number of female foetuses	102	97	125	109
Mean % male foetuses	55.4	50.7	47.6	53.9
Mean litter weight	35.9	38.6	38.2	36.1
Standard deviation	9.6	11.1	8.9	10.3
Mean foetal weight	3.89	3.91	3.85	3.80
Standard deviation	0.37	0.56	0.42	0.54
Mean foetal weight - males only	4.00	4.00	3.93	3.86
Standard deviation	0.47	0.57	0.44	0.58
Mean foetal weight - females only	3.78	3.83	3.78	3.72
Standard deviation	0.32	0.57	0.40	0.51
Mean placental weight	0.48	0.49	0.48	0.50
Standard deviation	0.05	0.09	0.06	0.07
Mean gravid uterus weight	56.8	61.2	59.9	58.1
Standard deviation	14.5	15.3	12.3	14.8

Table IV.C2.4 Fetal Abnormalities – Summary

Group	:	1	2	3	4
Treatment	:	Control		ucb 34714	
Dosage (mg/kg/day)	:	0	150	300	600

	Group 1	Group 2	Group 3	Group 4
Combined examination (external/visceral/skeletal)				
Total number of litters examined	24	20	24	24
Total number of foetuses examined	226	200	238	231
Number with major abnormalities	0	1	1	4
Mean % of foetuses examined	0.0	0.5	0.4	3.6
Number of litters affected	0	1	1	3
Number with minor abnormalities	82	60	91	103*
Mean % of foetuses examined	37.5	31.1	39.0	44.8
Number of litters affected	24	19	24	24
Number with variations	144	131	142	138
Mean % of foetuses examined	63.5	67.5	59.6	60.0
Number of litters affected	24	20	24	24

* = significantly different from Controls, p<0.05 (Fishers test and Cochran Armitage Trend test)

Table IV.C2.5 External examination: number of fetuses affected (group mean percent)

Group	:	1	2	3	4
Treatment	:	Control		ucb 34714	
Dosage (mg/kg/day)	:	0	150	300	600

Key	Finding	Type	Group 1	Group 2	Group 3	Group 4
	Total number of foetuses examined		226	200	238	231
	Total number of litters examined		24	20	24	24
	Neck					
1	entire: oedema	minor	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
	Body					
2	entire: runted foetus	minor	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
	Hindlimb					
A	entire- uni- or bilateral: malrotated	major	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)

Table IV.C2.6 Fresh visceral examination: number of fetuses affected (group mean percent)

Group	:	1	2	3	4
Treatment	:	Control		ucb 34714	
Dosage (mg/kg/day)	:	0	150	300	600

Key	Finding	Type	Group 1	Group 2	Group 3	Group 4
	Total number of foetuses examined		120	105	126	122
	Total number of litters examined		24	20	24	24
	Thoracic cavity					
3	innominate artery: absent	minor	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
B	aortic and pulmonary arch: transposition of great vessels	major	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
	Abdominal cavity					
a	kidney- uni- or bilateral: increased pelvic cavitation	variant	0 (0.0)	0 (0.0)	2 (1.7)	1 (1.0)
C	kidney- uni- or bilateral: absent	major	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)
b	ureter- uni- or bilateral: dilated	variant	9 (7.6)	7 (7.5)	8 (7.2)	5 (4.2)
c	umbilical artery: left sided	variant	18 (16.9)	12 (10.5)	14 (10.4)	10 (7.4)

Table IV.C2.7 Visceral examination: number affected (group mean percent)

Group	:	1	2	3	4
Treatment	:	Control		ucb 34714	
Dosage (mg/kg/day)	:	0	150	300	600

Key	Finding	Type	Group 1		Group 2		Group 3		Group 4	
	Total number of foetuses examined		106		95		112		109	
	Total number of litters examined		24		20		24		24	
	Brain									
4	lateral ventricle: enlarged	minor	0	(0.0)	0	(0.0)	1	(2.1)	2	(1.4)
	Oral cavity									
5	palate: irregular ridging	minor	5	(4.7)	0	(0.0)	8	(6.4)	11	(8.5)
	Thoracic cavity									
6	thorax: situs inversus	minor	0	(0.0)	0	(0.0)	1	(0.8)	0	(0.0)
	Abdominal cavity									
7	abdomen: situs inversus	minor	0	(0.0)	0	(0.0)	1	(0.8)	0	(0.0)
8	abdomen: haemorrhage	minor	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)
9	liver: small area protruding in thorax, no displacement of viscera	minor	5	(4.6)	2	(1.8)	2	(1.9)	2	(1.7)
a	kidney- uni- or bilateral: increased pelvic cavitation	variant	11	(9.9)	6	(5.9)	7	(6.0)	5	(5.1)
C	kidney- uni- or bilateral: absent	major	0	(0.0)	0	(0.0)	1	(0.8)	0	(0.0)
D	kidney- uni- or bilateral: reduced in size	major	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)
b	ureter- uni- or bilateral: dilated	variant	9	(8.8)	7	(12.2)	3	(3.3)	1	(0.8)
10	testis- uni- or bilateral: laterally displaced towards urinary bladder	minor	0	(0.0)	0	(0.0)	1	(0.8)	0	(0.0)
E	uterus- horn - left: absent	major	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)
c	umbilical artery: left sided	variant	16	(14.7)	17	(17.0)	8	(6.8)	12	(10.8)

Table IV.C2.8 Skeletal examination: number of fetuses affected (group mean percent)

Group	:	1	2	3	4
Treatment	:	Control		ucb 34714	
Dosage (mg/kg/day)	:	0	150	300	600

Key	Finding	Type	Group 1		Group 2		Group 3		Group 4	
	Total number of foetuses examined		120		105		126		122	
	Total number of litters examined		24		20		24		24	
	Skull									
11	frontal- uni- or bilateral: incomplete ossification	minor	0	(0.0)	1	(1.0)	0	(0.0)	1	(0.7)
12	frontal- uni- or bilateral: uneven ossification	minor	6	(4.2)	2	(1.5)	5	(3.4)	7	(5.0)
13	parietal- uni- or bilateral: incomplete ossification	minor	8	(5.6)	5	(8.5)	5	(3.6)	8	(5.7)
14	parietal- uni- or bilateral: uneven ossification	minor	45	(44.0)	37	(33.4)	52	(43.2)	59	(46.3)
d	interparietal: incomplete ossification	variant	33	(33.7)	26	(26.6)	53	(43.1)*	46	(35.9)
15	interparietal: uneven ossification	minor	26	(20.4)	25	(24.0)	25	(18.9)	33	(25.9)
e	occipital: incomplete ossification	variant	46	(41.6)	34	(34.3)	49	(39.7)	54	(40.7)
16	occipital: uneven ossification	minor	0	(0.0)	1	(1.7)	2	(1.3)	6	(4.6)*
17	zygomatic arch- uni- or bilateral: incomplete ossification	minor	1	(0.7)	2	(2.1)	2	(1.3)	4	(3.1)
18	squamosal- uni- or bilateral: incomplete ossification	minor	3	(2.1)	1	(0.8)	2	(1.5)	3	(2.4)
19	zygomatic arch and maxilla- uni- or bilateral: partial fusion	minor	2	(1.4)	2	(1.7)	1	(0.8)	2	(1.4)
20	hyoid: not ossified	minor	0	(0.0)	1	(1.0)	1	(0.7)	2	(1.3)
f	hyoid: incomplete ossification	variant	12	(9.3)	4	(3.5)	6	(4.0)	13	(9.0)

Vertebra										
21	number of presacral vertebrae: 27	minor	2	(2.1)	4	(3.9)	5	(4.3)	5	(3.6)
Cervical vertebra										
g	one or more centra: ossified	variant	116	(97.3)	103	(98.5)	124	(98.7)	116	(94.4)
22	one or more neural arch: incomplete ossification	minor	4	(2.8)	4	(3.3)	6	(4.2)	1	(0.7)
Thoracic vertebra										
23	number of vertebra: 14	minor	10	(8.0)	7	(6.1)	11	(8.4)	6	(4.9)
h	one or more centra: incomplete ossification	variant	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
i	one or more centra: bilobed ossification	variant	15	(15.3)	10	(12.7)	19	(15.2)	16	(14.1)
24	one or more centra: asymmetrically ossified	minor	1	(0.7)	0	(0.0)	1	(0.7)	1	(2.1)
25	one or more centra: bipartite ossification	minor	0	(0.0)	1	(0.8)	1	(0.7)	0	(0.0)
26	one or more neural arch: incomplete ossification	minor	3	(2.1)	0	(0.0)	1	(0.8)	1	(0.7)
Lumbar vertebra										
27	number of vertebra: 5	minor	10	(8.0)	5	(4.6)	8	(5.6)	5	(4.0)
28	number of vertebra: 7	minor	2	(2.1)	2	(2.5)	2	(1.5)	4	(2.8)
29	one or more centra: bilobed ossification	minor	1	(0.7)	0	(0.0)	2	(1.2)	0	(0.0)
30	one or more neural arch: incomplete ossification	minor	3	(2.1)	1	(0.8)	4	(4.2)	5	(3.5)
Sacral vertebra										
31	one or more centra: not ossified	minor	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
32	one or more neural arch: incomplete ossification	minor	11	(8.8)	8	(6.8)	12	(11.0)	20	(14.0)
33	one or more neural arch: not ossified	minor	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Caudal vertebra										
34	number of centra: <=2	minor	0	(0.0)	1	(0.8)	2	(2.1)	2	(1.4)
35	number of neural arches: 0	minor	1	(0.7)	4	(3.8)	8	(8.5)*	10	(6.8)**
Rib										
36	rib- uni- or bilateral: cervical	minor	5	(3.7)	9	(9.0)	9	(7.3)	10	(9.1)
37	one or more: wavy	minor	26	(22.2)	16	(17.9)	17	(14.3)	22	(19.3)
38	one or more: incomplete ossification	minor	0	(0.0)	0	(0.0)	0	(0.0)	2	(1.4)
39	14th- uni- or bilateral: extra	minor	10	(8.0)	7	(6.1)	11	(8.4)	6	(4.9)

j	14th- uni- or bilateral: vestigial	variant	67	(52.7)	54	(52.1)	60	(47.5)	52	(42.2)
Sternum										
40	1st sternebra: incomplete ossification	minor	1	(0.7)	1	(0.8)	1	(0.7)	1	(0.6)
41	2nd sternebra: not ossified	minor	0	(0.0)	0	(0.0)	1	(0.7)	3	(2.1)
42	2nd sternebra: incomplete ossification	minor	1	(0.7)	3	(6.5)	3	(3.1)	2	(1.4)
43	3rd sternebra: incomplete ossification	minor	1	(0.7)	1	(0.8)	2	(1.5)	2	(1.5)
44	4th sternebra: not ossified	minor	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.7)
45	4th sternebra: incomplete ossification	minor	1	(0.7)	2	(5.8)	2	(2.1)	2	(1.5)
46	one or more: bilobed ossification, bipartite ossification, mis-shapen or misaligned	minor	10	(6.8)	5	(4.6)	2	(1.5)	1	(0.7)
k	5th sternebra: not ossified	variant	8	(5.4)	5	(3.8)	6	(4.6)	14	(9.6)
m	5th sternebra: incomplete ossification	variant	8	(5.4)	9	(11.2)	9	(7.4)	10	(7.3)
n	6th sternebra: not ossified	variant	0	(0.0)	1	(0.8)	1	(0.7)	4	(2.8)
o	6th sternebra: incomplete ossification	variant	3	(2.4)	3	(6.5)	2	(2.2)	6	(4.2)
F	one or more: bifid	major	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.8)
Pelvic girdle										
47	entire: asymmetric insertion	minor	1	(0.7)	0	(0.0)	1	(0.6)	3	(2.4)
48	pubis- uni- or bilateral: incomplete ossification	minor	0	(0.0)	1	(0.8)	1	(0.7)	0	(0.0)
Forelimb										
49	one or more metacarpal: incomplete ossification	minor	1	(0.7)	3	(2.4)	2	(2.0)	2	(1.4)
p	5th metacarpal- uni- or bilateral: not ossified	variant	40	(32.3)	24	(21.5)	29	(24.0)	39	(30.8)
q	one or more phalange: ossified	variant	38	(30.8)	51	(49.1)**	43	(32.4)	38	(35.1)
Hindlimb										
r	astragalus- uni- or bilateral: ossified	variant	0	(0.0)	4	(5.6)*	4	(3.3)	4	(3.5)
50	one or more metatarsal: not ossified	minor	0	(0.0)	1	(0.8)	1	(0.7)	0	(0.0)
51	one or more metatarsal: incomplete ossification	minor	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.7)
s	one or more phalange: ossified	variant	0	(0.0)	4	(5.2)*	6	(5.0)*	6	(5.6)*

* = significantly different from Controls, P<0.05 (Fishers test and Cochran Armitage Trend test)
** = significantly different from Controls, P<0.01 (Fishers test and Cochran Armitage Trend test)

c. Conclusions

Treatment of pregnant rats with BRV (oral gavage doses of 150, 300, or 600 mg/kg/day, given BID, 6 hr apart) throughout the period of organogenesis (GDs 6-17) produced some evidence of adverse effects on development (slight increases in total incidences of major and minor fetal abnormalities) at the HD. The sponsor dismissed these findings as spontaneous rather than T-R due to their low incidence and sporadic occurrence. The sponsor also seemed to suggest a familial basis for the malformations found in 2 fetuses from the same HD litter, since the dam was found to have a kidney abnormality at necropsy and also had a high rate of preimplantation loss, although it is not clear how these findings are related. However, maternal toxicity at the HD was less than generally expected; and the exposure margin, while high (~30X human at MRD), did not reach the ICH limit of 50X. Therefore, the study cannot be considered to have fully evaluated effects on embryofetal development. Although the results of the 4-week rat toxicity study (oral gavage doses of 100, 300, 1000, and 1500 mg/kg/day, given BID, 6 hr apart) in which the HD was not tolerated and some males were sacrificed moribund at the MHD indicate that it may not be possible to achieve much higher doses, it is recommended that an effort be made to reach a minimally maternally toxic dose in a repeat rat embryofetal development study.

3. ucb 34714- oral (gavage) embryo-fetal toxicity study in the rabbit (Study # PSM0860, report dated 11/15/02, conducted by (b) (4) GLP)

a. Methods

Female (timed-mated) rabbits (New Zealand White, Harlan, UK; 20/group) were treated with 0 (1% methylcellulose vehicle), 30, 60, 120, or 240 mg/kg/day BRV (dosed BID, 6 hr apart; batch #105) by oral gavage (2 mL/kg) on GDs 6 through 19. Does were observed for viability, clinical signs, premature deliveries, and deaths. Body weights (BW) and food consumption were recorded during the dosing and postdosing period. Blood samples were collected from the marginal ear vein on GDs 6 and 19 for TK at 1, 3, 6 (before the second daily dose), 7, 9, and 12 hrs after the first dose. Animals were sacrificed on GD 28 and C-sectioned. Pregnancy status was assessed, the gravid uterus was weighed, and the numbers of corpora lutea, implantations, and live fetuses recorded. Live fetuses were weighed, sexed, and examined for external abnormalities. The placental weights were also recorded. Live fetuses were then killed and half in each litter were decapitated and the heads fixed in Bouin's solution for subsequent serial sectioning. The remaining intact fetuses and the bodies of the decapitated fetuses were fixed in alcohol for subsequent microdissection. The viscera were examined and the fetuses were then eviscerated and the carcasses cleared and stained with Alizarin red S for skeletal examination.

Dose selection: Doses were based on a dose range-finding study in pregnant rabbits in which a dose of 300 mg/kg/day given BID (6 hr apart) reduced maternal BW gain (but did not produce maternal mortality) and increased postimplantation loss (22%, SS).

b. Results

i. Maternal effects

Five treated females (2 LD, 1 MHD, and 2 HD) were sacrificed early for humane reasons due to sustained decreases in food consumption and excessive body weight losses

(**Table IV.C3.1**). In addition, 1 LD female (#29) was sacrificed on GD 15 due to a gavage accident (catheter lodged in throat) and 1 MHD doe (#66) aborted 1 fetus on GD 24 and was sacrificed. During the treatment period, there was a higher incidence of reduced fecal output in treated groups (19, 17, 19, and 19 at LD, MD, MHD, and HD, respectively) compared to C (10). There was a transient, generally dose-dependent increase in BW loss in treated groups early in gestation (**Figure IV.C3.1**), but subsequently BW gain was increased in treated groups so that over the entire dosing period no SS effect on BW gain was seen (**Table IV.C3.2**). There were 19, 16, 18, 17, and 17 females with live fetuses at scheduled necropsy on Day 28 of pregnancy (1, 3, 2, 1, and 0 non-pregnant), at the C, LD, MD, MHD, and HD, respectively. One HD female (#86) was pregnant (1 implantation) but had total resorption. TK parameters for BRV are shown in **Table IV.C3.3**.

Table IV.C3.1 Maternal deaths

Dose level (mg/kg/day)	Female number	Day of sacrifice (Day of pregnancy)	Bodyweight loss between Day 6 and Day of sacrifice
30	23	16	580 g (16%)
	39	15	510 g (16%)
120	65	15	590 g (15%)
240	81	16	360 g (11%)
	92	14	320 g (10%)

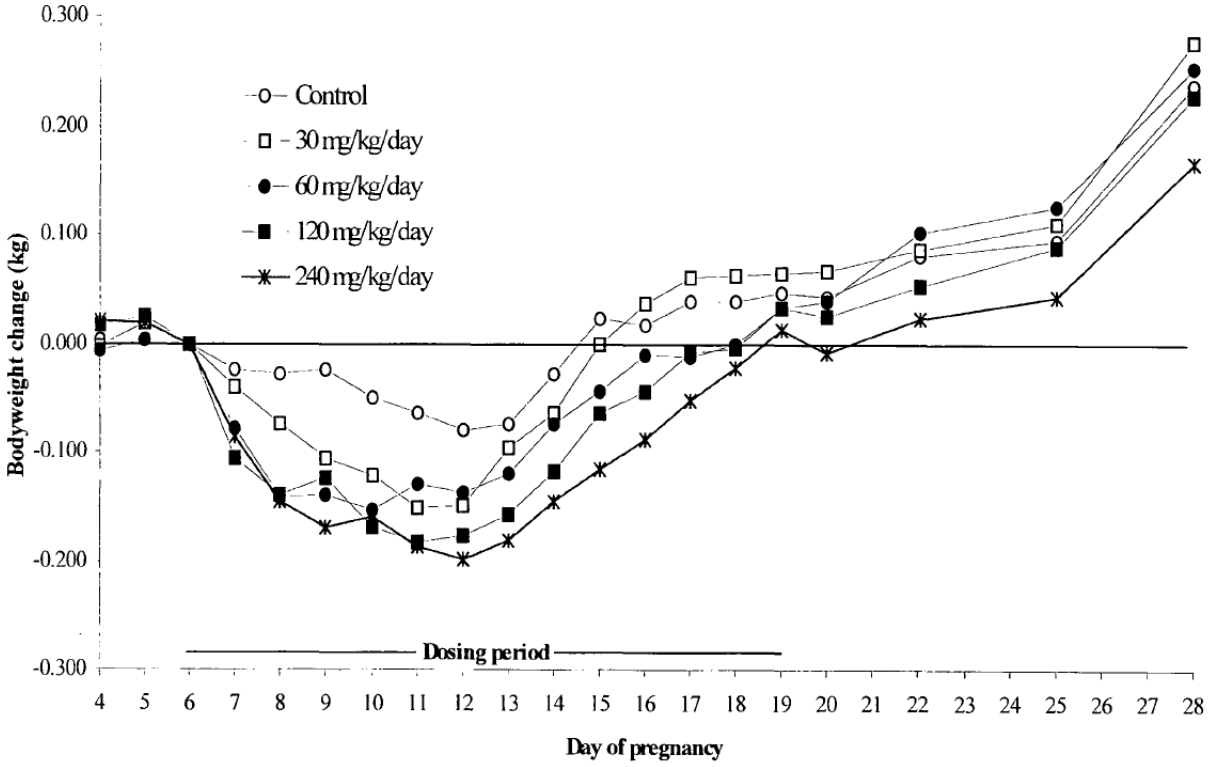


Figure IV.C3.1 Maternal body weight

Table IV.C3.2 Maternal body weight

Group : 1 2 3 4 5

Test article : Control ucb 34714

Dosage (mg/kg/day) : 0 30 60 120 240

Group sex		Day number Gain# 4-6	Gain# 6-7	Gain# 6-8	Gain# 6-9	Gain# 6-12	Gain# 12-15	Gain# 15-18	Gain# 18-20	Gain# 20-22	Gain# 22-25
1F	Mean	-0.002	-0.025	-0.029	-0.025	-0.082	0.104	0.016	0.004	0.037	0.015
	S.D.	0.084	0.067	0.077	0.074	0.118	0.079	0.059	0.042	0.055	0.040
	N	19	19	19	19	19	19	19	19	19	19
2F	Mean	0.004	-0.050	-0.082*	-0.116***	-0.163	0.134	0.064	0.003	0.021	0.023
	S.D.	0.051	0.052	0.065	0.080	0.129	0.117	0.101	0.045	0.035	0.045
	N	17	17	17	17	17	17	16	16	16	16
3F	Mean	0.007	-0.079**	-0.142***	-0.140***	-0.138	0.094	0.043	0.040	0.062	0.024
	S.D.	0.073	0.052	0.102	0.114	0.113	0.102	0.052	0.038	0.064	0.070
	N	18	18	18	18	18	18	18	18	18	18
4F	Mean	-0.018	-0.103***	-0.159***	-0.134***	-0.204**	0.092	0.058	0.029	0.027	0.035
	S.D.	0.068	0.055	0.082	0.085	0.138	0.141	0.091	0.063	0.043	0.052
	N	19	19	19	19	19	19	18	18	18	17
5F	Mean	-0.038	-0.078***	-0.139***	-0.167***	-0.207**	0.070	0.092**	0.015	0.030	0.022
	S.D.	0.092	0.057	0.059	0.066	0.110	0.111	0.098	0.053	0.053	0.050
	N	20	20	20	20	20	19	18	18	18	18

Non-pregnant females; excluded from group mean
- statistically analysed *=p<0.05 **=p<0.01 ***=p<0.001

Group : 1 2 3 4 5

Test article : Control ucb 34714

Dosage (mg/kg/day) : 0 30 60 120 240

Group sex		Day number Gain# 25-28	Gain# 6-19	Gain# 12-20	Gain# 20-28
1F	Mean	0.142	0.045	0.124	0.195
	S.D.	0.113	0.137	0.100	0.094
	N	19	19	19	19
2F	Mean	0.167	0.064	0.215*	0.210
	S.D.	0.085	0.088	0.086	0.068
	N	16	16	16	16
3F	Mean	0.127	0.033	0.177*	0.214
	S.D.	0.088	0.133	0.083	0.056
	N	18	18	18	18
4F	Mean	0.138	0.008	0.190*	0.202
	S.D.	0.114	0.148	0.106	0.094
	N	17	18	18	17
5F	Mean	0.122	0.013	0.191*	0.173
	S.D.	0.114	0.143	0.116	0.107
	N	18	18	18	18

Non-pregnant females; excluded from group mean
- statistically analysed *=p<0.05 **=p<0.01 ***=p<0.001

Table IV.C3.3 Maternal plasma drug levels

Parameter	Unit	Dose (mg/kg/day)			
		30	60	120	240
Day 1 of treatment [(a)]					
C_{max1}	(µg/mL)	8.46	17.3	37.4	76.6
t_{max1}	(h)	3	3	1	1
C_{max2}	(µg/mL)	10.5	23.5	52.6	135
t_{max2}	(h)	7	7	9	7
AUC(0-12h)	(µg.h/mL)	83.7	172	390	904
C_{12h}	(µg/mL)	4.07	7.01	22.6	64.0
Day 14 of treatment [(b)]					
C_{max1}	(µg/mL)	8.61	12.0	25.5	45.3
t_{max1}	(h)	1	3	1	1
C_{max2}	(µg/mL)	8.06	17.0	35.8	77.1
t_{max2}	(h)	7	7	7	7
AUC(0-12h)	(µg.h/mL)	62.2	106	198	445
C_{12h}	(µg/mL)	1.66	3.79	5.34	14.7

Time refers to the first daily subdose

(a) Day 6 of pregnancy

(b) Day 19 of pregnancy

ii. Litter parameters and fetal evaluations

Postimplantation loss was increased at the HD (25% vs 14% in C, SS) and there was a decrease in the number of live fetuses per female at that dose (6.6 vs 7.3 in C). These values are partially skewed by the total litter loss in HD female #86. If this litter is not included, there were 11/17 (65%) HD litters with greater than 10% postimplantation loss compared to 9/19 (47%) C litters, mean postimplantation loss at the HD was 20%, and the number of live fetuses/female was 7. Fetal BW was also slightly decreased (6%) at the HD compared to C (**Table IV.C3.4**). The decrease in fetal BW at the LD could be attributed to the increased litter size in this group (8.9 fetuses per female).

Increases in the incidence of major and/or minor abnormalities and variations were seen at all doses, although differences were not strictly dose-related; the LD group appeared to be something of an outlier, but this could be at least partially due to the increased litter size/decreased BWs at that dose (**Table IV.C3.5**). There was no discernable pattern in the individual major abnormalities. Abnormalities that were generally dose-related (and acknowledged as drug-related by the sponsor) were: runted fetuses at the HD and an increased number of fetuses with 27 presacral vertebrae (instead of 26), 13 thoracic vertebrae (instead of the usual 12), and supernumerary (13^{th}) ribs at all doses (SS). These are particularly common skeletal variations in the rabbit. There were also increases in the incidence of other minor abnormalities and variants related to the extent of ossification at all doses, but these were not clearly dose-related.

Table IV.C3.4 Caesarean-sectioning observations

Group :	1	2	3	4	5
Treatment :	Control		ucb 34714		
Dosage (mg/kg/day) :	0	30	60	120	240

	Group 1	Group 2	Group 3	Group 4	Group 5
Number of females with implantations at scheduled kill	19	16	18	17	18
Number of corpora lutea	208	171	186	180	189
Mean number per female	10.9	10.7	10.3	10.6	10.5
Standard deviation	2.1	1.7	1.6	1.8	4.0
Number of implantations	160	153	148	147	156
Mean number per female	8.4	9.6	8.2	8.6	8.7
Standard deviation	3.1	1.9	2.6	2.4	4.4
Mean % pre-implantation loss	22.4	9.8	19.9	19.0	21.9
Number of early embryo/foetal deaths	13	5	13	14	21
Number of late embryo/foetal deaths	8	6	2	6	16
Number of dead foetuses	0	0	0	0	0
Mean % post-implantation loss	13.7	6.6	8.7	12.2	24.6
Number of live foetuses	139	142	133	127	119
Mean number per female	7.3	8.9	7.4	7.5	6.6
Standard deviation	3.0	1.6	2.2	2.3	3.3
Mean % of implantations	86.3	93.4	91.3	87.8	75.4
Mean litter weight	279.7	321.8	277.4	292.3	248.7
Standard deviation	108.3	64.1	73.1	77.9	92.0
Mean foetal weight	39.1	36.3	38.2	39.9	36.9
Standard deviation	3.1	3.5	3.8	4.0	5.3
Mean foetal weight - males only	38.6	36.8	39.2	40.5	37.1
Standard deviation	3.4	3.6	3.7	4.3	4.8
Mean foetal weight - females only	38.7	35.9	36.6	39.5	36.3
Standard deviation	4.2	4.0	5.5	3.8	5.7
Mean placental weight	4.40	3.86	4.06	4.09	4.07
Standard deviation	1.21	0.59	0.73	0.71	0.90
Mean gravid uterus weight	438.8	500.8	424.0	448.9	412.4
Standard deviation	161.8	95.7	107.7	120.5	146.0

Table IV.C3.5 Fetal abnormalities in rabbit embryofetal development study

Group	:	1	2	3	4	5
Treatment	:	Control		ucb 34714		
Dosage (mg/kg/day)	:	0	30	60	120	240

Key	Finding	Type	Group 1		Group 2		Group 3		Group 4		Group 5	
Total number of foetuses examined			139		142		133		127		119	
Total number of litters examined			19		16		18		17		17	
Head												
A	entire: multiple cranio-facial abnormality	major	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
B	entire: acephaly	major	0	(0.0)	1	(0.8)	0	(0.0)	0	(0.0)	0	(0.0)
C	interparietal region: meningocele	major	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Abdomen												
D	abdomen: gastroschisis	major	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
1	abdomen: distended	minor	0	(0.0)	2	(1.5)	0	(0.0)	1	(0.6)	0	(0.0)
2	abdomen: thin walled	minor	0	(0.0)	1	(0.8)	0	(0.0)	1	(0.6)	0	(0.0)
Body												
3	entire: runted foetus	minor	0	(0.0)	0	(0.0)	2	(1.4)	0	(0.0)	5*	(4.3)
Forelimb												
4	forepaw- uni- or bilateral: abnormal flexure	minor	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(1.3)
E	forepaw- uni- or bilateral: arthrogryposis	major	0	(0.0)	2	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)
Head												
5	eye- uni- or bilateral: misshapen	minor	1	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Oral cavity												
F	palate: malformed	major	1	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Thoracic cavity											
6	subclavian artery- right: retro-oesophageal	minor	0	(0.0)	0	(0.0)	2	(1.4)	1	(2.0)	0	(0.0)
a	common carotid artery- uni- or bilateral: arising from innominate artery	variant	8	(7.2)	11	(8.0)	16	(11.8)	9	(7.0)	6	(4.7)
G	aortic arch: interrupted	major	0	(0.0)	1	(0.8)	0	(0.0)	1	(0.8)	0	(0.0)
H	aortic arch: right sided	major	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
I	aortic arch: enlarged	major	0	(0.0)	1	(1.0)	1	(0.7)	0	(0.0)	1	(0.7)
J	aortic arch: constricted	major	0	(0.0)	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
b	aortic arch: additional blood vessel	variant	1	(0.6)	0	(0.0)	2	(1.4)	1	(0.7)	1	(1.5)
K	pulmonary arch: enlarged	major	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)	0	(0.0)
L	aortic and pulmonary arch: pulmonary valvular atresia	major	1	(0.5)	4	(2.7)	1	(1.1)	1	(0.6)	3	(1.9)
M	aortic and pulmonary arch: persistent truncus arteriosus	major	1	(0.5)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
7	heart - entire: dextrocardia	minor	0	(0.0)	1	(0.8)	0	(0.0)	0	(0.0)	0	(0.0)
N	atrium- uni- or bilateral: enlarged	major	0	(0.0)	1	(0.7)	0	(0.0)	1	(0.6)	0	(0.0)
O	atrium- uni- or bilateral: reduced in size	major	0	(0.0)	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
P	ventricle- uni- or bilateral: enlarged	major	1	(0.5)	1	(0.8)	0	(0.0)	0	(0.0)	0	(0.0)
8	ventricle- uni- or bilateral: misshapen	minor	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)	0	(0.0)
Q	intraventricular septum: incomplete	major	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
9	pericardial sac: fluid filled	minor	0	(0.0)	1	(0.8)	0	(0.0)	0	(0.0)	0	(0.0)
10	both lungs: reduced in size	minor	0	(0.0)	1	(1.0)	0	(0.0)	1	(0.6)	0	(0.0)
11	post caval lung lobe: absent	minor	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
Abdominal cavity											
R	abdomen: incomplete closure of muscular layer	major	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)
12	abdomen: fluid filled	minor	0	(0.0)	1	(0.8)	0	(0.0)	0	(0.0)	0	(0.0)
13	liver- one or more lobe: clear raised areas on surface	minor	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)
14	gall bladder: bilobed	minor	0	(0.0)	1	(0.8)	1	(0.8)	0	(0.0)	1	(0.7)
S	kidney- uni- or bilateral: hydronephrosis	major	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
15	ureter- uni- or bilateral: dilated	minor	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
T	testis- uni- or bilateral: undescended	major	1	(0.6)	1	(1.0)	0	(0.0)	0	(0.0)	2	(2.1)
16	uterus- horns - both: elongated	minor	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)
17	ovary- uni- or bilateral: cystic	minor	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)	1	(0.7)
Brain											
U	one or more lobe: anencephaly	major	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)
V	one or more lobe: hydrocephaly	major	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)
W	one or more lobe: undifferentiated	major	1	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
19	lateral ventricle: enlarged	minor	1	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Head											
18	eye- uni- or bilateral: intra-orbital haemorrhage	minor	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)	0	(0.0)
Brain											
19	lateral ventricle: enlarged	minor	0	(0.0)	1	(1.3)	0	(0.0)	0	(0.0)	2	(3.9)

Skull

X	premaxilla- uni- or bilateral: absent	major	1	(1.1)	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)
Y	nasal- bilateral: absent	major	1	(1.1)	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)
Z	orbital cavity- uni- or bilateral: absent	major	1	(1.1)	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)
20	fontanelle- posterior: increased in size	minor	1	(1.1)	0	(0.0)	1	(1.9)	0	(0.0)	0	(0.0)
21	fontanelle- anterior: increased in size	minor	1	(1.1)	1	(1.3)	1	(1.9)	0	(0.0)	1	(1.5)
AA	frontal- uni- or bilateral: absent	major	1	(1.1)	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)
22	frontal- uni- or bilateral: incomplete ossification	minor	0	(0.0)	1	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
BB	frontal- uni- or bilateral: malformed	major	1	(1.1)	0	(0.0)	2	(3.2)	0	(0.0)	0	(0.0)
23	one or more: fissure/plaque of bone integral to normal structure of bone	minor	1	(1.1)	2	(2.5)	0	(0.0)	0	(0.0)	0	(0.0)
24	parietal- uni- or bilateral: incomplete ossification	minor	2	(2.4)	3	(3.8)	3	(4.2)	1	(1.2)	2	(2.8)
CC	parietal- uni- or bilateral: absent	major	1	(1.1)	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)
DD	parietal- uni- or bilateral: malformed	major	0	(0.0)	0	(0.0)	2	(3.2)	0	(0.0)	0	(0.0)
EE	interparietal: absent	major	1	(1.1)	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)
25	interparietal: incomplete ossification	minor	0	(0.0)	0	(0.0)	1	(1.9)	1	(2.0)	0	(0.0)
FF	interparietal: bifid	major	1	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
GG	occipital: absent	major	1	(1.1)	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)
HH	zygomatic arch- uni- or bilateral: absent	major	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)
II	zygomatic arch- uni- or bilateral: malformed	major	1	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
JJ	squamosal- uni- or bilateral: malformed	major	0	(0.0)	1	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
KK	squamosal- uni- or bilateral: absent	major	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)
26	zygomatic arch and maxilla- uni- or bilateral: partial fusion	minor	3	(3.4)	1	(1.6)	3	(4.2)	2	(2.5)	1	(1.2)
LL	maxilla- uni- or bilateral: absent	major	1	(1.1)	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)
c	maxilla- uni- or bilateral: incomplete ossification	variant	25	(28.6)	7	(9.1)	16	(19.3)	15	(19.1)	13	(19.3)
d	hyoid: incomplete ossification	variant	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	3	(3.8)
27	hyoid: cornua bent	minor	3	(7.6)	7	(9.7)	5	(7.4)	2	(2.6)	2	(3.9)
28	palatine: incomplete ossification	minor	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(0.8)
MM	palatine: malformed	major	1	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
NN	auditory malleus- uni- or bilateral: malformed	major	0	(0.0)	1	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)

Vertebra													
29	number of presacral vertebrae: 27	minor	6	(4.1)	13	(9.1)	22***	(14.5)	26***	(19.7)	31***	(22.9)	
Cervical vertebra													
30	one or more centra: additional ossification centre	minor	0	(0.0)	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)	
31	one or more centra: misshapen	minor	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	
32	one or more centra: bipartite ossification	minor	0	(0.0)	1	(1.0)	0	(0.0)	1	(0.7)	0	(0.0)	
33	one or more centra: asymmetrically ossified	minor	0	(0.0)	1	(1.0)	1	(0.7)	1	(0.7)	2	(1.9)	
34	one or more centra: hemicentric	minor	1	(0.5)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)	
35	one or more centra: offset	minor	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)	0	(0.0)	
36	one or more centra: fused	minor	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)	
37	one or more centra: not ossified	minor	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	
38	one or more centra: incomplete ossification	minor	0	(0.0)	1	(1.0)	1	(0.7)	2	(1.1)	2	(0.9)	
39	one or more neural arch: misaligned	minor	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)	
OO	one or more neural arch: absent	major	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)	
40	ventral tubercle: bipartite ossification	minor	0	(0.0)	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)	
Thoracic vertebra													
e	number of vertebra: 13	variant	49	(37.7)	70*	(53.0)	76***	(56.9)	60*	(46.7)	75***	(65.7)	
41	one or more centra: bilobed ossification	minor	2	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	2	(1.3)	
42	one or more centra: bipartite ossification	minor	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)	
43	one or more centra: asymmetrically ossified	minor	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.0)	
PP	one or more centra: absent	major	0	(0.0)	1	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)	
QQ	one or more neural arch: absent	major	0	(0.0)	1	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)	
44	one or more neural arch: misaligned	minor	0	(0.0)	1	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)	
Cervical, thoracic, lumbar, sacral or caudal vertebra													
RR	one or more: scoliosis	major	0	(0.0)	1	(0.7)	0	(0.0)	1	(0.7)	0	(0.0)	
Lumbar vertebra													
f	number of vertebra: 6	variant	45	(34.8)	57	(43.8)	57*	(44.0)	37	(29.4)	45	(43.5)	
45	number of vertebra: 8	minor	2	(1.3)	0	(0.0)	3	(1.6)	3	(2.4)	1	(0.7)	
Sacral vertebra													
SS	one or more neural arch: bifid	major	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	
46	one or more neural arch: misaligned	minor	0	(0.0)	3	(2.0)	1	(0.6)	0	(0.0)	1	(1.5)	

Caudal vertebra												
g	number of centra: <=14	variant	7	(3.8)	19*	(12.6)	13	(8.8)	14	(10.4)	14*	(11.9)
h	number of neural arches: <=6	variant	2	(3.2)	2	(1.6)	2	(1.6)	2	(1.5)	0	(0.0)
Rib												
47	rib- uni- or bilateral: cervical	minor	4	(2.4)	4	(2.5)	1	(0.7)	0	(0.0)	0	(0.0)
TT	one or more: fused	major	0	(0.0)	2	(2.3)	0	(0.0)	0	(0.0)	1	(0.7)
48	one or more: wavy	minor	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)
49	one or more: bulbous	minor	0	(0.0)	1	(0.6)	1	(0.6)	1	(0.5)	2	(2.6)
50	one or more: misshapen	minor	3	(1.9)	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)
i	13th- uni- or bilateral: extra	variant	49	(37.7)	70*	(53.0)	76***	(56.9)	60*	(46.7)	75***	(65.7)
j	13th- uni- or bilateral: vestigial	variant	12	(6.7)	13	(9.9)	7	(4.7)	15	(11.8)	13	(14.5)
k	13th- uni- or bilateral: floating	variant	9	(5.0)	9	(6.3)	8	(5.2)	13	(10.7)	12	(12.8)
51	one or more: discontinuous	minor	0	(0.0)	1	(0.7)	1	(0.7)	0	(0.0)	1	(0.5)
Pectoral girdle												
52	spine- uni- or bilateral: misshapen	minor	0	(0.0)	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Sternum												
53	additional centre- one or more: ossified	minor	1	(0.6)	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
54	1st sternebra: incomplete ossification	minor	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)
UU	one or more: bifid	major	1	(0.5)	1	(0.8)	0	(0.0)	0	(0.0)	0	(0.0)
55	2nd sternebra: incomplete ossification	minor	0	(0.0)	1	(0.7)	0	(0.0)	1	(0.7)	1	(1.0)
56	one or more: fused	minor	1	(0.6)	0	(0.0)	2	(1.4)	1	(2.0)	2	(1.1)
VV	one or more: fused	major	0	(0.0)	1	(0.7)	1	(0.7)	1	(0.7)	0	(0.0)
57	4th sternebra: incomplete ossification	minor	0	(0.0)	1	(1.0)	0	(0.0)	2	(2.6)	0	(0.0)
58	one or more: mis-shapen or misaligned	minor	8	(6.2)	6	(4.4)	3	(2.3)	5	(5.2)	6	(3.3)
m	5th sternebra: not ossified	variant	24	(16.9)	24	(17.8)	24	(16.8)	18	(15.7)	8	(7.3)
n	5th sternebra: incomplete ossification	variant	31	(21.7)	32	(22.2)	20	(13.6)	23	(17.3)	8	(7.2)
59	one or more: misplaced	minor	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
o	6th sternebra: not ossified	variant	7	(3.8)	6	(4.3)	14	(8.7)	5	(3.1)	3	(2.3)
p	6th sternebra: incomplete ossification	variant	20	(12.4)	19	(12.6)	16	(11.4)	11	(7.3)	17	(12.5)
Pelvic girdle												
60	entire: asymmetric insertion	minor	2	(1.3)	6	(4.6)	5	(3.9)	5	(4.7)	4	(4.8)
61	pubis- uni- or bilateral: not ossified	minor	0	(0.0)	0	(0.0)	2	(1.4)	0	(0.0)	3	(2.4)
62	pubis- uni- or bilateral: incomplete ossification	minor	4	(3.0)	8	(5.3)	3	(1.6)	1	(0.7)	6	(4.1)

Forelimb															
q	epiphyses: not ossified	variant	20	(15.0)	54***	(38.1)	26	(20.5)	18	(12.8)	47***	(33.
r	proximal or distal epiphyses of humerus only: not ossified	variant	60	(40.8)	58	(41.3)	49	(36.3)	58	(44.6)	35	(29.8)
WW	radius- uni- or bilateral: short	major	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
XX	radius- uni- or bilateral: malformed	major	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
YY	pollex- uni- or bilateral: absent	major	0	(0.0)	1	(0.8)	1	(0.9)	0	(0.0)	1	(0.7)
63	one or more metacarpal: not ossified	minor	2	(1.5)	16***	(10.4)	5	(3.1)	2	(2.5)	15***	(10.9)
64	one or more metacarpal: incomplete ossification	minor	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)
65	one or more phalange: not ossified	minor	1	(0.5)	2	(1.4)	2	(1.4)	0	(0.0)	10**	(7.5)
s	one or more phalange: incomplete ossification	variant	30	(26.7)	56***	(38.7)	41	(29.5)	40*	(29.0)	62***	(48.3)
66	one or more claw: absent	minor	0	(0.0)	1	(0.8)	0	(0.0)	0	(0.0)	0	(0.0)
Hindlimb												
t	epiphyses: not ossified	variant	51	(34.4)	72*	(52.7)	39	(27.1)	38	(26.7)	56	(40.6)
u	proximal epiphyses of tibia or distal epiphyses of femur only: not ossified	variant	53	(37.6)	47	(31.3)	63	(50.0)	57	(44.4)	49	(45.2)
67	astragalus- uni- or bilateral: not ossified	minor	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	5*	(3.4)
68	one or more phalange: not ossified	minor	0	(0.0)	0	(0.0)	2	(1.4)	0	(0.0)	1	(0.5)
v	one or more phalange: incomplete ossification	variant	6	(4.0)	23***	(17.1)	11	(7.8)	8	(5.6)	26***	(18.0)
69	one or more claw: absent	minor	0	(0.0)	1	(0.8)	0	(0.0)	0	(0.0)	0	(0.0)

Statistically analysed *=<0.05 **=p<0.01 ***=p<0.001

c. Conclusions

Treatment of pregnant rabbits with BRV (oral doses of 30, 60, 120, or 240 mg/kg/day, given BID, 6 hr apart) throughout the period of organogenesis (GDs 6-19) produced maternal toxicity and adverse effects on development (increased postimplantation loss, decreased fetal BW, and increased incidence of runted fetuses) at the HD. Increased incidences of skeletal variations were seen at all doses, but their toxicological significance is unclear. Based on the presence of maternal toxicity and postimplantation loss at the HD, the study can be considered adequate for assessing effects on embryofetal development in the rabbit.

4. ucb 34714: Oral (gavage) pre- and postnatal development study in the Wistar rat (Study # NCD1330, report dated 6/29/07, conducted by (b) (4) GLP)

a. Methods

Female (mated) Wistar rats (Crl:WI (Han); 25/group + 6/group TK) were administered 0 (1% methylcellulose 400 cps vehicle), 150, 300, or 600 mg/kg/day BRV (dosed BID, 10 hr apart; lot #E04-83162) by oral gavage (5 mL/kg) from GD 6 through PND 20. Dams were observed for viability, clinical signs, premature deliveries, and deaths. BWs and food consumption were recorded during the dosing period. All females were allowed to deliver and rear their offspring to PND 21. On PND 10, blood samples for determination of plasma drug concentration were collected from the first 3 females/grp at 1 and 4.5 hrs after the first daily dose and blood samples were also collected from 4 pups/sex/litter at 4.5 hrs and pooled by sex and litter. Blood samples were collected from another 3 dams/grp at 10 (just prior to administration of the second daily dose), 11, 14.5, and 24 hrs after the first daily dose and blood samples were collected from 4 pups/sex/litter at 24 hrs. Clinical observations and BWs were assessed in pups at appropriate intervals. Each pup was evaluated for pre-weaning developmental landmarks (pinna detachment, surface righting, incisor eruption, eye opening, and auditory reflex) and 2/sex/litter were randomly selected for post-weaning developmental landmarks. From these, 1/sex/litter were randomly assigned to 1 of 2 subsets. Subset A was selected for acoustic startle response on PND 20 and 60, locomotor activity on PND 21 and 61, and learning and memory (Biel maze) beginning on PND 62. The remaining 1/sex/litter were assigned to Subset B for evaluation of learning and memory assessment beginning on PND 22. Pups selected for assessment of developmental landmarks and additional pups from each litter were assigned to a maturational phase, including reproductive functional assessment. F1 females were allowed to deliver and rear their pups to PND 10 when F2 pups were examined externally. F1 males were necropsied following necropsy of the last F1 female.

Dose selection: Doses were based on the results of the 4-week oral toxicity study and embryofetal development study, in which rats were dosed twice daily, 6 hours apart. In the 4-week study, the HD of 1500 mg/kg/day was not tolerated, and animals were euthanized by week 2. At 1000 mg/kg/day, 3 males were euthanized by day 11. Both of these doses induced hepatic toxicity (lipofuscin, bile and porphyrin pigment deposits, bile duct hyperplasia, and peribiliary inflammation). The NOAEL in this (4-week) study was considered to be 300 mg/kg/day. In the rat embryofetal study, there was little maternal toxicity (clinical signs consisting of salivation and partially closed eyes, no effect on BW gain) at the HD of 600 mg/kg/day (given BID, 6 hr apart) and no clear effects on development. It was thought by the sponsor that administering the daily doses 10 hrs apart (versus 6 hrs in the previous studies) would ensure sufficiently sustained exposure.

b. Results

i. Effects on the dam and litter parameters

There were no maternal deaths or drug-related clinical signs. BW was not affected by drug dosing during gestation or lactation. Gestation lengths, pregnancy rates (100, 96, 96, and 100% in C, LD, MD, and HD groups, respectively), and parturition were unaffected by treatment. There were no drug-related macroscopic findings. Numbers of implantation sites were similar among groups. TK parameters during lactation are shown in **Table IV.C4.1**. The mean number of pups born, live litter size, percentage of males per litter at birth were unaffected by drug (**Table IV.C4.2**).

Table IV.C4.1 TK values of ucb 34714 and its metabolites during lactation

Parameter (Unit) [(a)]	Dose (mg/kg/day)		
	150	300	600
C_{max} (µg/mL)			
ucb 34714	38.0	57.0	74.9
$AUC_{(0\text{-}24\ h)}$ (µg eq*h/mL)			
ucb 34714 (µg·h/mL)	278	377	964
ucb 42145	5.30	6.16	20.5
ucb-100406-1	78.7	132	342

[(a)]: Day 10 of lactation = 26 days of treatment.

Table IV.C4.2 Delivery observations

GROUP :	1	2	3	4
NUMBER BORN				
MEAN	12.4	12.0	11.6	12.2
S.D.	2.45	2.00	2.55	3.04
N	25	24	23	25
SEX AT BIRTH (% MALES PER LITTER)				
MEAN	51.4	52.0	41.7	49.5
S.D.	10.57	14.97	13.34	16.43
N	25	24	23	25
LIVE LITTER SIZE (PND 0)				
MEAN	12.3	11.9	11.5	12.0
S.D.	2.54	1.91	2.56	2.92
N	25	24	23	25

1- 0 MG/KG/DAY 2- 150 MG/KG/DAY 3- 300 MG/KG/DAY 4- 600 MG/KG/DAY

ii. Offspring evaluations

Survival – Postnatal survival was unaffected by treatment (**Table IV.C4.3**). The numbers of F1 pups found dead, euthanized in extremis, and/or missing were similar among groups. At the HD, 11/4 pups/litters were noted as being small, generally on PND 10 and 14. This finding was considered drug-related because of lower BW gains in this group.

Table IV.C4.3 Summary of postnatal survival (% per litter)

GROUP :	1	2	3	4
PND 14 TO PND 21				
MEAN	100.0	100.0	100.0	100.0
S.D.	0.00	0.00	0.00	0.00
N	25	24	23	24
BIRTH TO PND 4 (PRE-SELECTION)				
MEAN	93.8	96.4	93.8	92.9
S.D.	15.53	6.70	6.13	20.23
N	25	24	23	25
PND 4 (POST-SELECTION) TO PND 21				
MEAN	99.0	99.5	99.5	97.4
S.D.	5.00	2.55	2.61	10.41
N	25	24	23	24

1- 0 MG/KG/DAY 2- 150 MG/KG/DAY 3- 300 MG/KG/DAY 4- 600 MG/KG/DAY

Body Weight - Pup BW gain was decreased at the HD (SS between PND 10-17) and a small deficit (5%, NS) was seen at weaning in this group (**Table IV.C4.4**). This deficit persisted into the postweaning period in both sexes.

Table IV.C4.4 Offspring bodyweight

(LITTER AS EXPERIMENTAL UNIT)

GROUP:	0 MG/KG/DAY	150 MG/KG/DAY	300 MG/KG/DAY	600 MG/KG/DAY
PND 21				
MALES				
MEAN	42.0	42.5	44.1	40.8
S.D.	3.97	4.45	4.19	5.40
N	25	24	23	24
FEMALES				
MEAN	40.6	40.8	43.2	38.9
S.D.	4.80	4.32	3.61	5.65
N	25	24	23	24

PND = POSTNATAL DAY

MALES

GROUP:	0 MG/KG/DAY	150 MG/KG/DAY	300 MG/KG/DAY	600 MG/KG/DAY
DAY 133				
MEAN	421.	416.	429.	396.*
% CHANGE		-1.2	1.9	-5.9
S.D.	37.6	34.8	33.2	34.0
N	25	25	25	25

FEMALES

GROUP:	0 MG/KG/DAY	150 MG/KG/DAY	300 MG/KG/DAY	600 MG/KG/DAY
PND 63				
MEAN	187.	182.	188.	175.**
% CHANGE		-2.7	0.5	-6.4
S.D.	14.9	14.0	11.1	14.5
N	25	24	23	24
PND 70				
MEAN	195.	190.	197.	184.*
% CHANGE		-2.6	1.0	-5.6
S.D.	14.9	13.4	12.1	14.0
N	25	24	23	24
PND 77				
MEAN	204.	194.	208.	194.
% CHANGE		-4.9	2.0	-4.9
S.D.	15.9	19.9	14.4	16.9
N	25	25	25	25
PND 84				
MEAN	212.	204.	217.	202.
% CHANGE		-3.8	2.4	-4.7
S.D.	17.7	16.4	16.1	17.7
N	25	25	25	25

* = Significantly different from the control group at 0.05 using Dunnett's test
** = Significantly different from the control group at 0.01 using Dunnett's test

Developmental Landmarks - There were no clear effects of treatment on pre-weaning sensory function parameters (pinna detachment, surface righting, incisor eruption, eye opening, and auditory reflex). While the age of attainment of balanopreputial separation was not different among groups, age of attainment of vaginal patency was delayed by ~2 day at the HD compared to C (**Table IV.C4.5**). This delay could be secondary to the BW reductions, based on the effect sizes seen.

Table IV.C4.5. Vaginal opening in female offspring

GROUP:	0 MG/KG/DAY	150 MG/KG/DAY	300 MG/KG/DAY	600 MG/KG/DAY
VAGINAL PATENCY (PND)				
MEAN	32.4	32.8	33.1	34.1**
S.D.	1.17	1.79	1.63	2.74
N	25	24	23	24
BODY WEIGHT (GRAMS)				
MEAN	91.4	92.7	98.0	93.1
S.D.	10.06	10.96	8.63	10.04
N	25	24	23	24

** - Significantly different from the control group at 0.01 using Dunnett's test

Offspring Behavior - An apparent effect on auditory startle (decreased Vmax and Vave) was seen in HD males and females at PND 20 and in males at PND 60, although SS was not reached (**Table IV.C4.6**). Decreased locomotor activity (SS) was seen in HD females on PND 61 (**Table IV.C4.7**). There were apparent drug-related differences in learning and memory, based on performance in the Biel maze, although none reached SS. On PND 62, HD males and females took longer to learn the more difficult B path and made more errors (**Table IV.C4.8**). HD females also performed more poorly in the memory phase of the test (**Table IV.C4.9**).

Table IV.C4.6 Summary of auditory startle response data

GROUP:	0 MG/KG/DAY	150 MG/KG/DAY	300 MG/KG/DAY	600 MG/KG/DAY
		MALES		
PND 20				
Vave (Millivolts)				
ALL TRIALS				
MEAN	27.7	30.1	28.3	23.7
S.D.	8.73	9.98	11.07	8.71
PND 60				
Vave (Millivolts)				
ALL TRIALS				
MEAN	38.7	38.4	50.4	29.7
S.D.	21.64	27.81	33.05	16.60
NUMBER OF ANIMALS TESTED				
N	20	20	20	20
None significantly different from control group				
		FEMALES		
PND 20				
Vave (Millivolts)				
ALL TRIALS				
MEAN	24.5	25.4	28.6	22.1
S.D.	13.20	10.50	11.50	4.94
PND 60				
Vave (Millivolts)				
ALL TRIALS				
MEAN	27.4	22.5	24.0	25.2
S.D.	23.45	21.73	22.13	23.78
NUMBER OF ANIMALS TESTED				
N	18	20	20	20
None significantly different from control group				

Table IV.C4.7 Summary of motor activity counts

Period	Sex	Variable	Group	Statistic	Minutes 0-15	16-30	31-45	46-60	Overall	Cumulative
JTD061	F	TOTAL	1	Mean	977.84	465.95	367.16	287.68	524.66	2098.63
				S.D.	224.460	163.315	218.233	257.564	NA	718.499
				N	19	19	19	19	19	19
				LSMean	977.84	465.95	367.16	287.68	524.66	NA
			2	Mean	943.95	439.10	372.40	256.30	502.94	2011.75
				S.D.	198.258	218.092	200.221	206.002	NA	634.937
				N	20	20	20	20	20	20
				LSMean	943.95	439.10	372.40	256.30	502.94	NA
				Linear Trend p-value#	NT	NT	NT	NT	NT	NA
			3	Mean	1003.50	482.35	267.65	152.35	476.46	1905.85
				S.D.	184.823	216.601	195.809	130.297	NA	431.481
				N	20	20	20	20	20	20
				LSMean	1003.50	482.35	267.65	152.35	476.46	NA
				Linear Trend p-value#	NT	NT	NT	NT	0.283	NA
			4	Mean	869.45	377.25	263.25	239.45	437.35	1749.40
				S.D.	133.520	150.647	198.576	187.189	NA	436.885
				N	20	20	20	20	20	20
				LSMean	869.45	377.25	263.25	239.45	437.35	NA
				Linear Trend p-value#	NT	NT	NT	NT	0.044*	NA
			ALL	Trt F-test p-value++					0.241	
			INTN	Trt*Time p-value++					0.203	
				LinTrt*Time p-value#					0.721	
				Covariance Structure					AR1	

: Level of Significance tested = .05. ++ : Level of Significance tested = .01.
* : Statistically Significant. NT : Not tested. NA : Not applicable.

Table IV.C4.8 Summary of Biel maze swim trials

							Trial						
Period	Sex	Path	Type	Variable	Group	Statistic	5	6	7	8	9	10	Overall
PND62	M	B	LEARNING	ESCTIME	1	Mean	159.06	97.987	79.994	62.194	49.365	33.924	80.420
						S.D.	34.414	60.6904	64.5171	56.8693	39.9433	39.4277	NA
						N	20	20	20	20	20	20	20
						LSMean	159.06	97.987	79.993	62.194	49.365	33.924	80.420
					2	Mean	151.37	94.958	94.972	62.829	50.242	37.533	81.984
						S.D.	43.689	58.8839	65.5446	56.7856	34.6741	24.7842	NA
						N	20	20	20	20	20	20	20
						LSMean	151.37	94.958	94.971	62.828	50.242	37.533	81.984
						Linear Trend p-value#	NT	NT	NT	NT	NT	NT	NT
					3	Mean	147.69	106.59	103.39	56.423	40.889	31.607	81.098
						S.D.	47.804	63.265	47.762	52.1122	33.3985	18.8177	NA
						N	20	20	20	20	20	20	20
						LSMean	147.69	106.59	103.39	56.422	40.889	31.607	81.098
						Linear Trend p-value#	NT	NT	NT	NT	NT	NT	NT
					4	Mean	138.40	126.46	109.36	69.056	76.989	43.329	93.931
						S.D.	55.606	53.078	68.053	57.9669	64.9751	43.0618	NA
						N	20	20	20	20	20	20	20
						LSMean	138.40	126.46	109.36	69.056	76.989	43.328	93.931
						Linear Trend p-value#	NT	NT	NT	NT	NT	NT	0.164
					ALL	Trt F-test p-value++							0.382
					INTN	Trt*Trial p-value++							0.376
						LinTrt*Trial p-value#							0.051
						Covariance Structure							AR1
PND62	M	B	LEARNING	ERRORS	1	Mean	28.900	17.600	13.000	9.6000	8.6500	4.7500	13.750
						S.D.	8.1815	11.7043	11.4294	9.95463	8.07384	8.33430	NA
						N	20	20	20	20	20	20	20
						LSMean	28.900	17.600	13.000	9.6000	8.6500	4.7500	13.750
					2	Mean	27.000	17.200	16.900	9.3500	7.8500	5.8500	14.025
						S.D.	7.4763	13.1453	12.6445	8.99868	7.84236	5.38297	NA
						N	20	20	20	20	20	20	20
						LSMean	27.000	17.200	16.900	9.3500	7.8500	5.8500	14.025
						Pairwise p-value++	NA	NA	NA	NA	NA	NA	NA
						Linear Trend p-value#	NT	NT	NT	NT	NT	NT	NT
					3	Mean	28.150	19.850	19.950	10.050	7.3500	5.3500	15.117
						S.D.	11.1699	12.2529	11.5050	11.4454	7.98864	4.72702	NA
						N	20	20	20	20	20	20	20
						LSMean	28.150	19.850	19.950	10.050	7.3500	5.3500	15.117
						Pairwise p-value++	NA	NA	NA	NA	NA	NA	NA
						Linear Trend p-value#	NT	NT	NT	NT	NT	NT	NT
					4	Mean	25.750	21.350	19.550	9.7000	10.150	7.1500	15.608
						S.D.	11.7019	9.1839	13.0565	9.80923	10.7276	8.96352	NA
						N	20	20	20	20	20	20	20
						LSMean	25.750	21.350	19.550	9.7000	10.150	7.1500	15.608
						Pairwise p-value++	NA	NA	NA	NA	NA	NA	NA
						Linear Trend p-value#	NT	NT	NT	NT	NT	NT	0.206
					ALL	Trt F-test p-value++							0.636
					INTN	Trt*Trial p-value++							0.822
						LinTrt*Trial p-value#							0.229
						Covariance Structure							AR1

PND62	F	B	LEARNING ESCTIME	1	Mean	134.90	87.966	106.51	58.838	51.174	38.728	79.687
					S.D.	53.525	47.3476	57.648	54.8061	49.4716	45.9090	NA
					N	19	19	19	19	19	19	19
					LSMean	134.90	87.966	106.51	58.838	51.174	38.728	79.687
				2	Mean	123.73	77.219	65.483	71.572	66.717	40.328	74.378
					S.D.	56.762	55.3905	54.3976	43.5849	52.6832	29.8573	NA
					N	20	20	19	20	20	20	20
					LSMean	123.73	77.219	65.976	71.572	66.717	40.328	74.257
					Linear Trend p-value#	NT	NT	NT	NT	NT	NT	NT
				3	Mean	146.21	103.99	63.819	43.182	67.958	34.093	76.542
					S.D.	54.864	65.350	45.7131	23.1689	52.1372	27.1507	NA
					N	20	20	20	20	20	20	20
					LSMean	146.21	103.99	63.819	43.182	67.958	34.093	76.542
					Linear Trend p-value#	NT	NT	NT	NT	NT	NT	NT
				4	Mean	127.55	112.81	91.146	74.350	64.419	54.157	87.405
					S.D.	57.864	57.152	60.9571	61.0028	48.4127	47.9501	NA
					N	20	20	20	20	20	20	20
					LSMean	127.55	112.81	91.146	74.350	64.419	54.157	87.405
					Linear Trend p-value#	NT	NT	NT	NT	NT	NT	0.444
				ALL	Trt F-test p-value++							0.606
				INTN	Trt*Trial p-value++							0.019
					LinTrt*Trial p-value#							0.267
					Covariance Structure							CS
PND62	F	B	LEARNING ERRORS	1	Mean	24.053	15.895	20.263	10.000	8.1579	6.1053	14.079
					S.D.	10.5329	7.6150	10.2786	9.9833	9.58739	9.28496	NA
					N	19	19	19	19	19	19	19
					LSMean	24.053	15.895	20.263	10.0000	8.1579	6.1053	14.079
				2	Mean	22.400	14.550	13.450	13.350	10.700	6.7500	13.533
					S.D.	10.4549	10.8214	12.5718	9.3487	7.6578	5.50478	NA
					N	20	20	20	20	20	20	20
					LSMean	22.400	14.550	13.450	13.350	10.700	6.7500	13.533
					Pairwise p-value++	NA	NA	NA	NA	NA	NA	NA
					Linear Trend p-value#	NT	NT	NT	NT	NT	NT	NT
				3	Mean	28.850	19.750	11.300	6.8500	10.350	4.9500	13.675
					S.D.	11.8111	12.9650	8.3420	5.07081	8.0999	4.83926	NA
					N	20	20	20	20	20	20	20
					LSMean	28.850	19.750	11.300	6.8500	10.350	4.9500	13.675
					Pairwise p-value++	NA	NA	NA	NA	NA	NA	NA
					Linear Trend p-value#	NT	NT	NT	NT	NT	NT	NT
				4	Mean	26.800	21.650	17.550	15.300	13.100	10.400	17.467
					S.D.	12.8087	11.3475	12.7547	15.0791	13.8560	10.0546	NA
					N	20	20	20	20	20	20	20
					LSMean	26.800	21.650	17.550	15.300	13.100	10.400	17.467
					Pairwise p-value++	NA	NA	NA	NA	NA	NA	NA
					Linear Trend p-value#	NT	NT	NT	NT	NT	NT	0.090
				ALL	Trt F-test p-value++							0.124
				INTN	Trt*Trial p-value++							0.046
					LinTrt*Trial p-value#							0.236
					Covariance Structure							CS

: Level of Significance tested = .05.
* : Statistically Significant.
++ : Level of Significance tested = .01.
NT : Not tested. NA : Not applicable.

Period	Sex	Path	Type	Variable	Group	Statistic	Trial 11	Trial 12	Overall
PND62	F	A	MEMORY	ESCTIME	1	Mean	102.14	65.384	83.761
						S.D.	63.616	55.3752	NA
						N	19	19	19
						LSMean	102.14	65.384	83.761
					2	Mean	79.557	65.275	72.416
						S.D.	55.4331	49.7840	NA
						N	20	20	20
						LSMean	79.557	65.275	72.416
						Linear Trend p-value#	NT	NT	NT
					3	Mean	77.262	61.066	69.164
						S.D.	49.4561	35.9493	NA
						N	20	20	20
						LSMean	77.262	61.066	69.164
						Linear Trend p-value#	NT	NT	NT
					4	Mean	112.89	92.191	102.54
						S.D.	57.690	54.3594	NA
						N	20	20	20
						LSMean	112.89	92.191	102.54
						Linear Trend p-value#	NT	NT	0.226
					ALL	Trt F-test p-value++			0.069
					INTN	Trt*Trial p-value++			0.675
						LinTrt*Trial p-value#			0.468
						Covariance Structure			CS
PND62	F	A	MEMORY	ERRORS	1	Mean	21.000	11.474	16.237
						S.D.	15.7692	10.5376	NA
						N	19	19	19
						LSMean	21.000	11.474	16.237
					2	Mean	16.100	12.750	14.425
						S.D.	12.5232	9.8669	NA
						N	20	20	20
						LSMean	16.100	12.750	14.425
						Linear Trend p-value#	NT	NT	NT
					3	Mean	15.300	13.350	14.325
						S.D.	10.3319	10.6290	NA
						N	20	20	20
						LSMean	15.300	13.350	14.325
						Linear Trend p-value#	NT	NT	NT
					4	Mean	24.300	20.200	22.250
						S.D.	13.9966	12.5009	NA
						N	20	20	20
						LSMean	24.300	20.200	22.250
						Linear Trend p-value#	NT	NT	0.055
					ALL	Trt F-test p-value++			0.023
					INTN	Trt*Trial p-value++			0.489
						LinTrt*Trial p-value#			0.282
						Covariance Structure			CS

: Level of Significance tested = .05.
* : Statistically Significant.
++ : Level of Significance tested = .01.
NT : Not tested. NA : Not applicable.

Offspring Reproductive Performance - No clear effects of treatment on F1 reproductive performance were observed; mating and fertility indices were similar among groups. The mean numbers of days between pairing and coitus were increased at the MD and HD (3.7 days) compared to C (2.6 days), primarily due to 2 females in each of these groups with a period of extended diestrus (11-14 days) during the mating period. However, all 4 of these females had been cycling normally prior to being paired with a male, and all had evidence of mating and produced litters. The number of F2 pups born, live litter size, percentage of males per litter at birth, and postnatal survival up to PND 10 were unaffected by treatment.

Offspring Necropsy Observations - All necropsy findings were considered unrelated to treatment.

c. Conclusions

Treatment of female rats with oral doses of 0, 150, 300, or 600 mg/kg BRV (dosed BID, 10 hr apart) from GD 7 through PND 20 produced no appreciable maternal toxicity or effects on litter parameters. A slight decrease in pup BW gain during lactation was seen at the HD in both sexes, which persisted into the postweaning period, and there was a delay in attainment of vaginal patency in HD females. There was some evidence of long-term neurobehavioral effects at the HD, i.e., decreased auditory startle reactivity, decreased locomotor activity, and impaired Biel maze learning and memory in animals test as adults. However, SS was only reached for overall motor activity in females. Based on the lack of maternal toxicity at the HD, dose selection for this study was again questionable, so the study may not have fully characterized the developmental effects of the drug. Therefore, it is recommended that the study be repeated if a repeat rat embryofetal development study (or dose range-finding study) shows that significantly higher doses can be administered to pregnant rats.

D. JUVENILE ANIMAL TOXICOLOGY

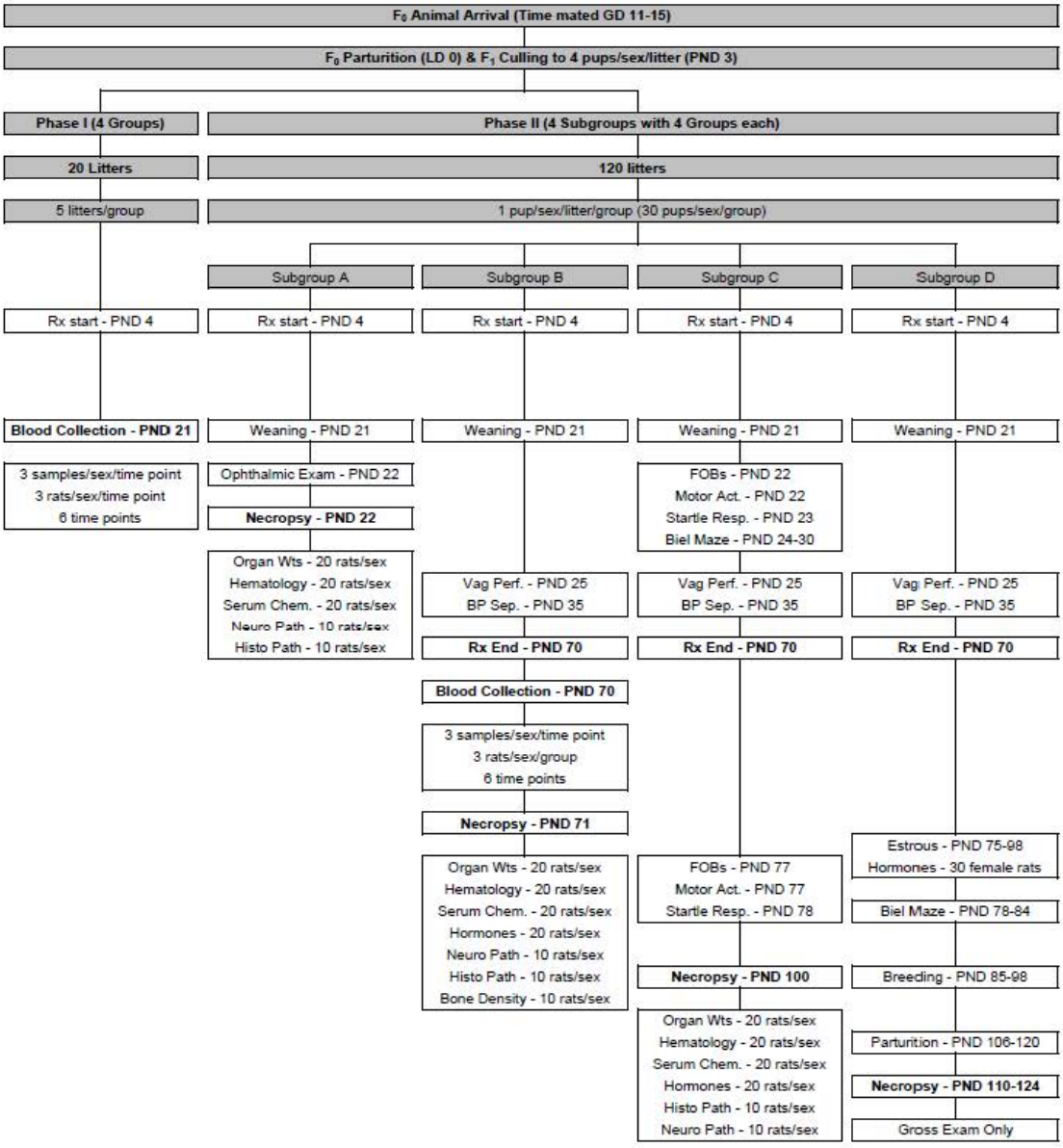
1. ucb 34714: Nine week oral (gavage) toxicity study in juvenile Wistar rats (Report No. NCD 167 1, dated 8/9/10, conducted by (b) (4) GLP)

a. Methods

Young rats (Crl:WI(Han); 4/sex/litter from 35 litters/group, whole litter design) were given 0 (1% w/v methylcellulose 400 cps vehicle), 150, 300, or 600 mg/kg/day BRV (dosed BID, 10 hr apart; lot #CB14000006) by gavage (5 mL/kg/dose) either from PND 7 to 21 (pups from 5 litters/group assigned to Phase I [TK phase] and from 30 litters/group to Phase II [main study phase], subgroup A) or PND 4 to 70 (pups from 30 litters/group assigned to Phase II, subgroups B, C, and D). Within each group, animals assigned to the main study (Phase II) were subdivided into 4 subgroups (A, B, C, and D), with 1 pup/sex/litter assigned to each subgroup (total of 30 rats/sex/group/subgroup) prior to the start of dosing (**Figure IV.D1.1**). Pups were observed for mortality, clinical observations, body weights, and food consumption. Indicators of physical development (balanopreputial separation and vaginal patency) were evaluated in 3 pups/sex/litter (Phase II, subgroups B, C and D). On PND 22, ophthalmology examinations were conducted in all subgroup A animals and 20 subgroup A animals/sex/group were assigned to blood sampling for hematology and serum chemistry, macroscopic examinations, organ weights, and histopathological examinations on PND 22. The remaining 10 subgroup A animals/sex/group were assigned to neurohistopathological examinations (brain weight and size measurements, macroscopic and microscopic examinations) on PND 22. Subgroup B animals (20/sex/group) were assigned to blood sampling for TK on the last day of dose administration (PND 70), hematology, serum chemistry and hormone assessment, macroscopic examinations, organ weights, and histopathological examinations on PND 71. Ten of these same subgroup B animals/sex/group were selected for bone densitometry assessments on PND 71. The remaining 10 subgroup B animals/sex/group were assigned to neurohistopathological examinations on PND 71. All subgroup C animals were assigned to neurobehavioral testing (FOB, locomotor assessment, acoustic startle response, and learning and memory assessment in Biel maze) during and/or after the treatment period. Subgroup C animals (20/sex/grp) were also assigned to blood sampling for hematology, serum chemistry and hormone assessment, macroscopic examinations, organ weights, histopathological examinations or neurohistopathology (10/sex/grp) following a 30-day recovery period (PND 100). Subgroup D animals were assigned to neurobehavioral testing (learning and memory assessment) after the end of the treatment period, blood sampling for hormone assessment prior to breeding, assessment of reproductive potential, and macroscopic examinations. For TK analyses of BRV and its major metabolites, the 5 litters assigned to Phase I and 1 pup/sex/litter (N=9 pups/group) assigned to Phase II, subgroup B were used for blood collection on PNDs 21 and 70, respectively. Blood samples were collected from 3 rats/sex/group/time point at 1, 4.5, 10, 11, 14.5, and 24 hrs after dose administration on PND 21 and 70.

Dose selection was based on 2 dose range-finding studies in juvenile Wistar rats conducted at (b) (4) in which oral (gavage) doses of 150, 300, or 600 mg/kg/day (given BID, 10 hours apart) were administered from PND 4 to either PND 28 or PND 21. Increased mortality (2, 1, 8 and 11 males and 0, 2, 4 and 12 females in 24 day study and 0, 0, 3, and 7 males and 0, 3, 1 and 5 females in 17 day study in C, LD, MD, and HD groups, respectively), clinical signs (hypothermia, rales, and clear and red material around the nose), and transient decreases in BW gain were observed, primarily at the HD.

Figure IV.D1.1.



b. Results

i. Mortality, clinical signs

A drug-related increase in mortality was seen at the HD, with most deaths occurring between PNDs 11 and 21 (**Table IV.D1.1**). Pale, cool bodies, gasping, labored respiration, rales, hypoactivity, slightly drooping or completely shut eyelids and/or rocking, lurching or swaying while ambulating were noted for 12 males and 7 females in the HD group that were later found dead. These clinical findings were generally seen on the day prior to and/or on the day of death. In addition, 1 HD female was euthanized on PND 45 following observations of pale or cool body and labored respiration for up to 4 consecutive days, hypoactivity, red material around the mouth, and rales. Drug-related occurrences of rales were noted for 48 and 51 surviving HD males and females, respectively. This finding was noted approximately twice as frequently in the females as in the males and was observed during PND 10-55. Despite the high rate of mortality at the HD, N's were adequate for evaluation of developmental toxicity (~20/sex/grp for behavioral and reproductive testing).

Table IV.D1.1 Mortality in juvenile rats

	Males				Females			
Dosage (mg/kg/day):	0	150	300	600	0	150	300	600
Interval								
PND 4-10	6	1	0	7	5	1	3	9
PND 11-21	2	4	5	16	4	0	7	27
PND 22-133	1	2	3	5	1	1	2	5
PND 4-133	9	7	8	28	10	2	12	41

ii. Body weight

BW gain was decreased in HD males (SS) and females (NS) during the preweaning period (**Table IV.D1.2**) and during the first 4 weeks of the postweaning period in HD males (SS), without effects on food consumption. These resulted in decreased (SS) BWs during PND 10-60 in males and PND 12-14 in females. There were no group differences in BWs at the end of the treatment period.

Table IV.D1.2 Body Weight Gain in Juvenile Rats

Males

GROUP:	0 MG/KG/DAY	MALES 150 MG/KG/DAY	300 MG/KG/DAY	600 MG/KG/DAY
PND 4- 21 (PRE-WEANING TREATMENT PERIOD)				
MEAN	28.2	28.8	29.2	25.6*
S.D.	3.38	3.64	3.98	4.57
S.E.	0.57	0.62	0.67	0.77
N	35	35	35	35
PND 21- 70 (POST-WEANING TREATMENT PERIOD)				
MEAN	259.0	252.7	246.4	249.6
S.D.	19.49	21.77	13.19	16.84
S.E.	3.56	4.04	2.41	3.13
N	30	29	30	29
PND 4- 70 (ENTIRE TREATMENT PERIOD)				
MEAN	286.4	280.9	275.7	274.3
S.D.	20.52	24.12	16.38	18.34
S.E.	3.75	4.48	2.99	3.40
N	30	29	30	29
PND 70- 84 (PREMATING RECOVERY PERIOD)				
MEAN	38.8	38.3	35.4	36.8
S.D.	9.23	5.81	5.81	6.43
S.E.	1.68	1.08	1.08	1.24
N	30	29	29	27
PND 70- 98 (ENTIRE RECOVERY PERIOD - PHASE II, SUBGROUP C)				
MEAN	65.9	67.1	60.8	65.9
S.D.	15.65	9.63	8.75	11.30
S.E.	2.86	1.79	1.62	2.17
N	30	29	29	27
PND 70- 126 (ENTIRE RECOVERY PERIOD - PHASE II, SUBGROUP D)				
MEAN	98.7	105.7	95.9	106.4
S.D.	15.80	19.47	15.76	17.36
S.E.	3.04	3.75	3.09	3.98
N	27	27	26	19

Females

PND 4- 21 (PRE-WEANING TREATMENT PERIOD)				
MEAN	27.6	28.0	28.9	26.4
S.D.	3.26	2.98	3.53	4.03
S.E.	0.55	0.50	0.60	0.68
N	35	35	35	35
PND 21- 70 (POST-WEANING TREATMENT PERIOD)				
MEAN	160.8	159.3	154.6	160.8
S.D.	11.89	11.64	7.89	16.86
S.E.	2.17	2.16	1.44	3.24
N	30	29	30	27
PND 4- 70 (ENTIRE TREATMENT PERIOD)				
MEAN	187.9	187.5	184.0	187.2
S.D.	12.29	13.03	9.09	17.77
S.E.	2.24	2.42	1.66	3.42
N	30	29	30	27
PND 70- 84 (PREMATING RECOVERY PERIOD)				
MEAN	15.6	13.5	12.6	12.9
S.D.	5.09	4.97	3.58	5.95
S.E.	0.93	0.92	0.65	1.17
N	30	29	30	26
PND 70- 98 (ENTIRE RECOVERY PERIOD)				
MEAN	27.9	26.5	25.6	24.5
S.D.	5.46	6.02	6.60	6.01
S.E.	1.03	1.14	1.27	1.31
N	28	28	27	21

* = Significantly different from the control group at 0.05 using Dunnett's test
MEAN DIFFERENCES CALCULATED FROM INDIVIDUAL DIFFERENCES

iii. Developmental Landmarks and FOB

Attainment of balanopreputial separation was delayed in HD males (47.8 vs 46.2 days in C, SS). This was attributed to decreased BWs in this group during the postweaning treatment period (BW in HD males 8.6% below C on PND 46). There was no effect on attainment of vaginal patency in females. Grip strength, assessed in the FOB, was decreased in treated animals at all doses, although the effect was not D-R (**Table IV.D1.3**).

Table IV.D1.3 FOB in juvenile rats

Males

GROUP:			1	2	3	4
NUMBER TESTED:			28	27	27	22
HINDLIMB EXTENSOR STRENGTH HINDLIMB RESISTANCE PRESENT			28	27	27	22
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE:	MEAN	937.2	836.0++	851.8+	845.3+
		S.D.	140.24	103.37	121.37	124.60
	HIND:	MEAN	386.4	326.1+	340.4	350.3
		S.D.	76.12	62.87	76.21	84.24
ROTAROD PERFORMANCE (seconds)	:	MEAN	78.3	55.8	69.0	81.9
		S.D.	43.73	45.31	44.40	38.50
HINDLIMB FOOTSPLAY (mm)	:	MEAN	85.9	78.6	85.3	85.1
		S.D.	11.62	13.51	14.00	14.46

Females

GROUP:			1	2	3	4
NUMBER TESTED:			28	28	27	21
HINDLIMB EXTENSOR STRENGTH HINDLIMB RESISTANCE PRESENT			28	28	27	21
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE:	MEAN	783.0	697.9+	764.9	716.4
		S.D.	106.83	121.05	102.25	137.25
	HIND:	MEAN	291.4	288.3	305.8	290.3
		S.D.	90.55	44.13	71.39	75.54
ROTAROD PERFORMANCE (seconds)	:	MEAN	70.0	61.6	72.7	87.4
		S.D.	44.40	44.65	45.09	40.51
HINDLIMB FOOTSPLAY (mm)	:	MEAN	73.4	73.1	76.1	78.1
		S.D.	13.75	11.52	14.01	8.26

1- 0 MG/KG/DAY 2- 150 MG/KG/DAY 3- 300 MG/KG/DAY 4- 600 MG/KG/DAY
+ = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING DUNNETT'S TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

iv. Clinical Pathology, Ophthalmological Examinations

There were no notable changes in hematological parameters. Several small changes in serum chemistry parameters on PND 22 and 71 (↓chloride, ↑calcium, ↑cholesterol) were considered T-R (**Table IV.D1.4**). These changes were no longer seen after the recovery period. Ophthalmological examinations did not reveal any T-R effects.

Table IV.D1.4 T-R changes in serum chemistry values

	Males				Females			
Dosage (mg/kg/day):	0	150	300	600	0	150	300	600
Interval/Parameter								
PND 22/ Chloride (mEq/L)	108	107	107	106**	109	108	107*	107**
PND 71/ Calcium (mg/dL)	10.4	10.6	10.6	10.9**	10.4	10.6*	10.7**	10.9**
PND 22/ Cholesterol (mg/dL)	87	86	82	93	77	87	85	96**
PND 71/ Cholesterol (mg/dL)	52	58	59	56	46	55	54	69**

* = Significantly different from the control group at $p<0.05$
** = Significantly different from the control group at $p<0.01$

v. Developmental Neurotoxicity Testing

Locomotor activity appeared to be decreased in treated animals on both PNDs 22 and 77 (**Table IV.D1.5**), but was only SS in HD males during the first subinterval (0-15 minutes) on PND 22 (total counts decreased 23%).

On PND 78, auditory startle responsiveness was increased in treated animals. For Vmax, the differences were evident in each trial block and when all trials were combined for both sexes at the HD, reaching SS during the first 4 trial blocks (1-10, 11-20, 21-30 and 31-40) and for all trials combined for HD females (**Table IV.D1.6**).

In the Biel water maze, conducted starting on PND 24, a deficit in the memory component was seen in HD females (increased escape times and errors, **Table IV.D1.7**). In the Biel maze conducted starting on PND 78, there were no clearly T-R differences in learning and memory performance.

Table IV.D1.5 Open field performance in juvenile rats

Period	Sex	Variable	Minutes	Statistic	Dosage Level (mg/kg/day) 0	150	300	600	Statistical Model
PND022	M	TOTAL	0-15	Mean	349	343	346	270	
				% Difference Control	NA	-1.6	-0.9	-22.6	
				S.D.	119.6	148.7	120.5	138.7	
				S.E.	22.6	28.6	22.8	27.7	
				Linear Trend p-value#		NT	0.922	0.021*	
			16-30	Mean	121	149	159	121	
				% Difference Control	NA	22.9	31.2	0.1	
				S.D.	98.0	114.2	129.3	108.0	
				S.E.	18.5	22.0	24.4	21.6	
				Linear Trend p-value#		NT	NT	0.919	
			31-45	Mean	101	108	118	110	
				S.D.	108.4	97.0	124.7	105.0	
				S.E.	20.5	18.7	23.6	21.0	
				Linear Trend p-value#		NT	NT	0.712	
			46-60	Mean	69	94	96	110	
				S.D.	78.2	94.4	136.1	100.3	
				S.E.	14.8	18.2	25.7	20.1	
				Linear Trend p-value#		NT	NT	0.227	
			Overall	Mean	160	174	179	153	
				Linear Trend p-value#		NT	NT	0.835	
			Cumulative	Mean	640	694	718	611	
				% Difference Control	NA	8.4	12.1	-4.6	
				S.D.	300.5	326.7	395.8	358.8	
				S.E.	56.8	62.9	74.8	71.8	
				N	28	27	28	25	
				Trt F-test p-value++					0.682
				Trt*Time p-value++					0.163
				LinTrt*Time p-value#					0.017*
				Covariance Structure					AR1

PND077	M	TOTAL	0-15	Mean	853	813	836	790	
				% Difference Control	NA	-4.6	-1.9	-7.4	
				S.D.	222.3	187.0	223.8	174.6	
				S.E.	42.0	36.0	43.1	37.2	
				Linear Trend p-value#		NT	NT	NT	
			16-30	Mean	491	476	466	473	
				% Difference Control	NA	-3.1	-5.1	-3.7	
				S.D.	189.2	154.5	211.4	199.6	
				S.E.	35.8	29.7	40.7	42.5	
				Linear Trend p-value#		NT	NT	NT	
			31-45	Mean	265	243	215	247	
				S.D.	217.7	183.0	224.8	219.3	
				S.E.	41.1	35.2	43.3	46.8	
				Linear Trend p-value#		NT	NT	NT	
			46-60	Mean	125	100	93	104	
				S.D.	182.8	118.0	147.2	148.8	
				S.E.	34.5	22.7	28.3	31.7	
				Linear Trend p-value#		NT	NT	NT	
			Overall	Mean	434	408	402	403	
				Linear Trend p-value#		NT	NT	0.394	
			Cumulative	Mean	1734	1633	1610	1614	
				% Difference Control	NA	-5.8	-7.2	-6.9	
				S.D.	565.6	363.0	567.3	484.3	
				S.E.	106.9	69.9	109.2	103.2	
				N	28	27	27	22	
				Trt F-test p-value++					0.775
				Trt*Time p-value++					0.996
				LinTrt*Time p-value#					0.956
				Covariance Structure					AR1
PND022	F	TOTAL	0-15	Mean	314	304	265	282	
				% Difference Control	NA	-3.4	-15.6	-10.3	
				S.D.	112.0	106.9	114.7	132.3	
				S.E.	21.2	20.2	22.1	28.2	
				Linear Trend p-value#		NT	NT	NT	
			16-30	Mean	130	99	61	136	
				% Difference Control	NA	-23.9	-52.9	4.6	
				S.D.	106.8	94.8	84.5	86.4	
				S.E.	20.2	17.9	16.3	18.4	
				Linear Trend p-value#		NT	NT	NT	
			31-45	Mean	74	74	38	66	
				S.D.	121.9	68.6	63.6	91.0	
				S.E.	23.0	13.0	12.2	19.4	
				Linear Trend p-value#		NT	NT	NT	
			46-60	Mean	77	65	64	66	
				S.D.	121.1	82.4	85.2	69.8	
				S.E.	22.9	15.6	16.4	14.9	
				Linear Trend p-value#		NT	NT	NT	
			Overall	Mean	149	135	107	138	
				Linear Trend p-value#		NT	NT	0.359	
			Cumulative	Mean	596	542	428	551	
				% Difference Control	NA	-9.1	-28.1	-7.5	
				S.D.	321.3	258.0	239.6	291.9	
				S.E.	60.7	48.8	46.1	62.2	
				N	28	28	27	22	
				Trt F-test p-value++					0.208
				Trt*Time p-value++					0.240
				LinTrt*Time p-value#					0.539
				Covariance Structure					AR1

PND077	F	TOTAL	0-15	Mean	786	720	774	713
				% Difference Control	NA	-8.4	-1.5	-9.3
				S.D.	140.6	130.4	191.4	157.8
				S.E.	26.6	24.6	36.8	34.4
				Linear Trend p-value#		NT	NT	NT
			16-30	Mean	427	346	405	369
				% Difference Control	NA	-18.8	-5.1	-13.5
				S.D.	161.9	147.3	110.8	141.5
				S.E.	30.6	27.8	21.3	30.9
				Linear Trend p-value#		NT	NT	NT
			31-45	Mean	309	216	229	279
				S.D.	150.9	133.7	192.6	201.7
				S.E.	28.5	25.3	37.1	44.0
				Linear Trend p-value#		NT	NT	NT
			46-60	Mean	193	92	161	149
				S.D.	147.4	107.6	193.5	163.9
				S.E.	27.9	20.3	37.2	35.8
				Linear Trend p-value#		NT	NT	NT
			Overall	Mean	429	344	392	378
				Linear Trend p-value#		NT	NT	0.240
			Cumulative	Mean	1714	1375	1568	1511
				% Difference Control	NA	-19.8	-8.5	-11.9
				S.D.	376.3	315.0	422.6	453.6
				S.E.	71.1	59.5	81.3	99.0
				N	28	28	27	21
				Trt F-test p-value++				0.014
				Trt*Time p-value++				0.843
				LinTrt*Time p-value#				0.956
				Covariance Structure				AR1

: Level of Significance tested = .05.
++ : Level of Significance tested = .01.
* : Statistically Significant.
NT : Not tested. NA : Not applicable.

Table IV.D1.6 Startle response in juvenile rats

Period	Variable	Sex	Blocks	Statistic	Dosage Level (mg/kg/day) 0	150	300	600	Statistical Model
PND078	VMAX	M	1-10	Mean	653.9	649.0	694.0	839.8	
				% Difference Control	NA	-0.8	6.1	28.4	
				S.D.	328.80	361.53	541.94	395.56	
				S.E.	62.14	69.58	104.30	84.33	
				Linear Trend p-value#		NT	NT	NT	
			11-20	Mean	543.9	626.1	494.3	706.9	
				% Difference Control	NA	15.1	-9.1	30.0	
				S.D.	362.16	398.44	378.12	468.60	
				S.E.	68.44	76.68	72.77	99.90	
				Linear Trend p-value#		NT	NT	NT	
			21-30	Mean	469.8	519.7	436.3	586.6	
				% Difference Control	NA	10.6	-7.1	24.9	
				S.D.	327.27	352.25	304.77	446.22	
				S.E.	61.85	67.79	58.65	95.14	
				Linear Trend p-value#		NT	NT	NT	
			31-40	Mean	387.4	434.0	439.4	498.7	
				% Difference Control	NA	12.0	13.4	28.8	
				S.D.	266.99	318.83	345.40	342.51	
				S.E.	50.46	61.36	66.47	73.02	
				Linear Trend p-value#		NT	NT	NT	
			41-50	Mean	357.9	443.9	389.9	511.2	
				% Difference Control	NA	24.0	8.9	42.8	
				S.D.	277.29	365.46	253.07	349.16	
				S.E.	52.40	70.33	48.70	74.44	
				Linear Trend p-value#		NT	NT	NT	
PND078	VMAX	M	Overall	Mean	482.6	534.5	490.8	628.6	
				N	28	27	27	22	
				Linear Trend p-value#		NT	NT	0.165	
				Trt F-test p-value++					0.364
				Trt*Trial p-value++					0.469
				LinTrt*Trial p-value#					0.765
				Covariance Structure					AR1

PND078	VMAX	F	1-10	Mean	298.4	384.2	467.2	544.7	
				% Difference Control	NA	28.8	56.6	82.6	
				S.D.	190.67	241.06	193.39	250.39	
				S.E.	36.03	45.56	37.22	54.64	
				Linear Trend p-value#		0.180	0.009*	<.001*	
			11-20	Mean	280.0	309.1	438.1	464.8	
				% Difference Control	NA	10.4	56.5	66.0	
				S.D.	227.16	185.85	280.25	221.91	
				S.E.	42.93	35.12	53.93	48.42	
				Linear Trend p-value#		0.649	0.015*	0.002*	
			21-30	Mean	284.6	273.8	355.3	442.2	
				% Difference Control	NA	-3.8	24.9	55.4	
				S.D.	275.53	204.95	231.17	206.19	
				S.E.	52.07	38.73	44.49	44.99	
				Linear Trend p-value#		NT	0.274	0.011*	
			31-40	Mean	289.2	257.0	335.8	476.8	
				% Difference Control	NA	-11.1	16.1	64.9	
				S.D.	296.55	216.63	211.18	268.79	
				S.E.	56.04	40.94	40.64	58.66	
				Linear Trend p-value#		NT	0.471	0.003*	
			41-50	Mean	300.3	285.7	323.4	375.3	
				% Difference Control	NA	-4.9	7.7	25.0	
				S.D.	333.87	216.56	225.22	231.72	
				S.E.	63.09	40.93	43.34	50.57	
				Linear Trend p-value#		NT	NT	0.227	
PND078	VMAX	F	Overall	Mean	290.5	302.0	384.0	460.8	
				N	28	28	27	21	
				Linear Trend p-value#		NT	0.090	0.001*	
				Trt F-test p-value++					0.013
				Trt*Trial p-value++					0.088
				LinTrt*Trial p-value#					0.035*
				Covariance Structure					AR1

: Level of Significance tested = .05.
* : Statistically Significant.
++ : Level of Significance tested = .01.
NT : Not tested. NA : Not applicable.

Table IV.D1.7 Biel maze performance

Period	Sex	Path	Type	Variable	Trial	Statistic	Dosage Level (mg/kg/day) 0	150	300	600	Statistical Model
PND24	F	A	MEMORY	ESCTIME	11	Mean	83.82	78.00	90.31	118.68	
						% Difference Control	NA	-6.9	7.7	41.6	
						S.D.	56.588	42.897	62.336	56.526	
						S.E.	10.694	8.107	11.997	12.051	
						Linear Trend p-value#		NT	0.647	0.014*	
					12	Mean	79.45	87.08	51.99	78.42	
						% Difference Control	NA	9.6	-34.6	-1.3	
						S.D.	48.826	45.884	47.653	57.810	
						S.E.	9.227	8.671	9.171	12.325	
						Linear Trend p-value#		NT	NT	0.419	
					Overall	Mean	81.63	82.54	71.15	98.55	
						N	28	28	27	22	
						Linear Trend p-value#		NT	NT	0.274	
						Trt F-test p-value++					0.132
						Trt*Trial p-value++					0.019
						LinTrt*Trial p-value#					0.012*
						Covariance Structure					CS
PND24	F	A	MEMORY	ERRORS	11	Mean	21	19	23	29	
						% Difference Control	NA	-9.0	7.3	35.1	
						S.D.	16.4	10.7	18.1	16.5	
						S.E.	3.1	2.0	3.5	3.5	
						Linear Trend p-value#		NT	0.683	0.044*	
					12	Mean	19	20	12	17	
						% Difference Control	NA	6.4	-38.4	-11.0	
						S.D.	13.4	11.1	12.2	14.1	
						S.E.	2.5	2.1	2.3	3.0	
						Linear Trend p-value#		NT	NT	0.251	
					Overall	Mean	20	20	17	23	
						N	28	28	27	22	
						Linear Trend p-value#		NT	NT	0.566	
						Trt F-test p-value++					0.375
						Trt*Trial p-value++					0.026
						LinTrt*Trial p-value#					0.014*
						Covariance Structure					CS

: Level of Significance tested = .05.
* : Statistically Significant.
++ : Level of Significance tested = .01.
NT : Not tested. NA : Not applicable.

vi. Reproductive Performance

Estrous cycle lengths were not affected by treatment, but male and female fertility indices were decreased and pre-coital interval increased at the HD (**Table IV.D1.8**). Three of 19 HD females with evidence of mating were not pregnant and 1 pregnant HD female had total litter loss. There were no T-R effects on gestation or parturition.

Table IV.D1.8 Reproductive performance

DOSE GROUP :	1		2		3		4	
	NO.	%	NO.	%	NO.	%	NO.	%
MALE MATING INDEX	27/27	100.0	27/27	100.0	26/26	100.0	19/19	100.0
FEMALE MATING INDEX	28/28	100.0	27/27	100.0	26/26	100.0	19/19	100.0
MALE FERTILITY INDEX	26/27	96.3	27/27	100.0	26/26	100.0	16/19	84.2
FEMALE FERTILITY INDEX	27/28	96.4	27/27	100.0	26/26	100.0	16/19	84.2
MALE COPULATION INDEX	26/27	96.3	27/27	100.0	26/26	100.0	16/19	84.2
FEMALE CONCEPTION INDEX	27/28	96.4	27/27	100.0	26/26	100.0	16/19	84.2
MEAN PRE-COITAL INTERVALS (DAYS)	2.5	NA	2.6	NA	2.8	NA	3.4	NA
S.D.	1.14	NA	1.45	NA	1.11	NA	2.91	NA
S.E.	0.22		0.28		0.22		0.67	
N	28		27		26		19	

$$\text{MALE (FEMALE) MATING INDEX (\%)} = \frac{\text{NO. OF MALES (FEMALES) WITH EVIDENCE OF MATING (OR CONFIRMED PREGNANCY)}}{\text{TOTAL NO. OF MALES (FEMALES) USED FOR MATING}} \times 100$$

$$\text{MALE FERTILITY INDEX (\%)} = \frac{\text{NO. OF MALES SIRING A LITTER}}{\text{TOTAL NO. OF MALES USED FOR MATING}} \times 100$$

$$\text{MALE COPULATION INDEX (\%)} = \frac{\text{NO. OF MALES SIRING A LITTER}}{\text{NO. OF MALES WITH EVIDENCE OF MATING (OR FEMALES CONFIRMED PREGNANT)}} \times 100$$

$$\text{FEMALE FERTILITY INDEX (\%)} = \frac{\text{NO. OF FEMALES WITH CONFIRMED PREGNANCY}}{\text{TOTAL NO. OF FEMALES USED FOR MATING}} \times 100$$

$$\text{FEMALE CONCEPTION INDEX (\%)} = \frac{\text{NO. OF FEMALES WITH CONFIRMED PREGNANCY}}{\text{NO. OF FEMALES WITH EVIDENCE OF MATING (OR CONFIRMED PREGNANCY)}} \times 100$$

1- 0 MG/KG/DAY 2- 150 MG/KG/DAY 3- 300 MG/KG/DAY 4- 600 MG/KG/DAY
PRE-COITAL INTERVALS NOT SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP USING DUNNETT'S TEST
MATING, FERTILITY, COPULATION AND CONCEPTION INDICES NOT SIGNIFICANTLY DIFFERENT USING CHI-SQUARE TEST
NA = NOT APPLICABLE

vii. Pathology

D-R decreases in absolute and/or relative brain wts and brain size were found at all doses in treated males and females at the end of the treatment period (PND 71) in both the groups not selected for special neurohistopathology and the groups selected for neurohistopathology (**Table IV.D1.9A**). These deficits persisted to the end recovery period (PND 100) in both sexes (**Table IV.D1.9B**) The neurohistopathological examination (C and HD) did not reveal any apparent T-R morphological lesions in the brain. In addition, treated rats necropsied on PND 71 had increased liver wts and increased incidences of centrilobular hepatocyte hypertrophy at the MD and HD in both sexes. Small decreases (3-6%, NS) in bone mineral content and density in the lumbar vertebrae were seen in treated MD and HD males (**Table IV.D1.10A**). There were also decreases in total femur length (-5%, SS) and distal femur bone area (-7%, SS) in HD males (**Table IV.D1.10B**). The effect on femur length was attributed to 1 small animal (no. 50281-02) that was considered an outlier (femur length 29.8 mm compared to the group mean (including this animal) of 32.86 mm and final BW of 154 g compared to group mean of 254 g).

Table IV.D1.9A Brain weights

Males not selected for neurohistopathology PND 71

GROUP:	0 MG/KG/DAY	MALES 150 MG/KG/DAY	300 MG/KG/DAY	600 MG/KG/DAY
BRAIN (G)				
MEAN	1.84	1.72**	1.72**	1.63**
% DIFFERENCE		-6.5	-6.5	-11.4
S.D.	0.072	0.106	0.089	0.083
S.E.	0.017	0.026	0.021	0.021
N	18	17	19	16
BRAIN (G/100 G FINAL BODY WEIGHT)				
MEAN	0.684	0.673	0.669	0.654
S.D.	0.0431	0.0618	0.0420	0.0975
S.E.	0.0102	0.0150	0.0096	0.0244
N	18	17	19	16

Females not selected for neurohistopathology PND 71

BRAIN (G)				
MEAN	1.71	1.65	1.64	1.54**
% DIFFERENCE		-3.5	-4.1	-9.9
S.D.	0.094	0.095	0.062	0.061
S.E.	0.024	0.021	0.015	0.019
N	16	20	18	10
BRAIN (G/100 G FINAL BODY WEIGHT)				
MEAN	0.986	0.942	0.931	0.882**
S.D.	0.0617	0.0795	0.0581	0.0610
S.E.	0.0154	0.0178	0.0137	0.0193
N	16	20	18	10

** = Significantly different from the control group at 0.01 using Dunnett's test

Males selected for neurohistopathology PND 71

GROUP:	0 MG/KG/DAY	MALES 150 MG/KG/DAY	300 MG/KG/DAY	600 MG/KG/DAY
FINAL BODY WT (G)				
MEAN	286.	295.	286.	277.
% DIFFERENCE		3.1	0.0	-3.1
S.D.	25.5	23.9	24.8	20.0
S.E.	8.1	7.6	7.8	6.3
N	10	10	10	10
BRAIN (G)				
MEAN	1.90	1.85	1.83	1.73**
% DIFFERENCE		-2.6	-3.7	-8.9
S.D.	0.118	0.062	0.083	0.103
S.E.	0.037	0.020	0.026	0.032
N	10	10	10	10
BRAIN (G/100 G FINAL BODY WEIGHT)				
MEAN	0.667	0.631	0.645	0.626
S.D.	0.0530	0.0441	0.0491	0.0311
S.E.	0.0168	0.0139	0.0155	0.0098
N	10	10	10	10
BRAIN LENGTH (MM)				
MEAN	19.1	19.1	19.0	18.9
S.D.	0.40	0.34	0.20	0.47
S.E.	0.13	0.11	0.06	0.15
N	10	10	10	10
BRAIN WIDTH (MM)				
MEAN	15.0	14.8	14.7*	14.5**
S.D.	0.32	0.18	0.31	0.34
S.E.	0.10	0.06	0.10	0.11
N	10	10	10	10

Females selected for neurohistopatholgy PND 71

FINAL BODY WT (G)				
MEAN	197.	192.	191.	195.
% DIFFERENCE		-2.5	-3.0	-1.0
S.D.	19.1	18.0	21.5	19.4
S.E.	6.1	5.7	6.8	6.5
N	10	10	10	9
BRAIN (G)				
MEAN	1.78	1.75	1.73	1.70
% DIFFERENCE		-1.7	-2.8	-4.5
S.D.	0.061	0.051	0.096	0.085
S.E.	0.019	0.016	0.030	0.028
N	10	10	10	9
BRAIN (G/100 G FINAL BODY WEIGHT)				
MEAN	0.910	0.918	0.908	0.876
S.D.	0.0762	0.0828	0.0582	0.0614
S.E.	0.0241	0.0262	0.0184	0.0205
N	10	10	10	9
BRAIN LENGTH (MM)				
MEAN	18.6	18.7	18.6	18.6
S.D.	0.36	0.21	0.39	0.36
S.E.	0.11	0.07	0.12	0.12
N	10	10	10	9
BRAIN WIDTH (MM)				
MEAN	14.5	14.4	14.3	14.3
S.D.	0.27	0.26	0.39	0.27
S.E.	0.08	0.08	0.12	0.09
N	10	10	10	9

* = Significantly different from the control group at 0.05 using Dunnett's test
** = Significantly different from the control group at 0.01 using Dunnett's test

Table IV.D1.9B

Males selected for neurohistopathology PND 100

	MALES			
GROUP:	0 MG/KG/DAY	150 MG/KG/DAY	300 MG/KG/DAY	600 MG/KG/DAY
FINAL BODY WT (G)				
MEAN	371.	379.	349.	364.
% DIFFERENCE		2.2	-5.9	-1.9
S.D.	49.3	54.3	25.6	26.9
S.E.	15.6	17.2	8.1	8.5
N	10	10	10	10
BRAIN (G)				
MEAN	2.02	1.95	1.87*	1.89*
% DIFFERENCE		-3.5	-7.4	-6.4
S.D.	0.147	0.123	0.093	0.092
S.E.	0.046	0.039	0.029	0.029
N	10	10	10	10
BRAIN (G/100 G FINAL BODY WEIGHT)				
MEAN	0.555	0.521	0.539	0.520
S.D.	0.0945	0.0452	0.0386	0.0366
S.E.	0.0299	0.0143	0.0122	0.0116
N	10	10	10	10
BRAIN LENGTH (MM)				
MEAN	19.9	19.9	19.4	19.7
S.D.	0.53	0.47	0.47	0.48
S.E.	0.17	0.15	0.15	0.15
N	10	10	10	10
BRAIN WIDTH (MM)				
MEAN	15.4	15.1	14.7**	14.9**
S.D.	0.34	0.30	0.32	0.45
S.E.	0.11	0.10	0.10	0.14
N	10	10	10	10
BRAIN WIDTH (MM)				
MEAN	15.4	15.1	14.7**	14.9**
S.D.	0.34	0.30	0.32	0.45
S.E.	0.11	0.10	0.10	0.14
N	10	10	10	10

Females selected for neurohistopathology PND 100

FINAL BODY WT (G)				
MEAN	230.	216.	219.	223.
% DIFFERENCE		-6.1	-4.8	-3.0
S.D.	15.3	16.1	20.5	20.2
S.E.	4.8	5.1	6.5	6.4
N	10	10	10	10
BRAIN (G)				
MEAN	1.88	1.82	1.80	1.69**
% DIFFERENCE		-3.2	-4.3	-10.1
S.D.	0.066	0.073	0.106	0.088
S.E.	0.021	0.023	0.034	0.028
N	10	10	10	10
BRAIN (G/100 G FINAL BODY WEIGHT)				
MEAN	0.823	0.847	0.831	0.761
S.D.	0.0751	0.0520	0.0785	0.0382
S.E.	0.0237	0.0164	0.0248	0.0121
N	10	10	10	10
BRAIN LENGTH (MM)				
MEAN	19.2	18.9	18.9	18.6**
S.D.	0.28	0.36	0.51	0.41
S.E.	0.09	0.11	0.16	0.13
N	10	10	10	10
BRAIN WIDTH (MM)				
MEAN	14.9	14.7	14.6	14.3**
S.D.	0.22	0.29	0.48	0.31
S.E.	0.07	0.09	0.15	0.10
N	10	10	10	10

** - Significantly different from the control group at 0.01 using Dunnett's test

Table IV.D1.10A DXA scans at the L3-L4 lumbar vertebral column

Treatment Group	Sex	Data	Bone Mineral Content	Bone Area	Bone Mineral Density
			g	cm^2	g/cm^2
1	F	mean	0.152	0.958	0.159
vehicle		SD	0.016	0.095	0.009
			n.a.	n.a.	n.a.
2	F	mean	0.165	1.007	0.164
150 mg/kg/day		SD	0.014	0.066	0.008
ucb 34714			n.s.	n.s.	n.s.
3	F	mean	0.162	1.008	0.161
300 mg/kg/day		SD	0.015	0.078	0.013
ucb 34714			n.s.	n.s.	n.s.
4	F	mean	0.155	0.957	0.162
600 mg/kg/day		SD	0.011	0.055	0.008
ucb 34714			n.s.	n.s.	n.s.
1	M	mean	0.192	1.051	0.182
vehicle		SD	0.014	0.063	0.006
			n.a.	n.a.	n.a.
2	M	mean	0.193	1.068	0.181
150 mg/kg/day		SD	0.020	0.070	0.012
ucb 34714			n.s.	n.s.	n.s.
3	M	mean	0.187	1.069	0.176
300 mg/kg/day		SD	0.008	0.052	0.008
ucb 34714			n.s.	n.s.	n.s.
4	M	mean	0.180	1.016	0.177
600 mg/kg/day		SD	0.021	0.071	0.016
ucb 34714			n.s.	n.s.	n.s.

Table IV.D1.10B DXA scan results at the femur

			Distal Femur			Midshaft Femur		
Treatment Group	Sex	Data	Bone Mineral Content	Bone Area	Bone Mineral Density	Bone Mineral Content	Bone Area	Bone Mineral Density
			g	cm^2	g/cm^2	g	cm^2	g/cm^2
1	F	mean	0.074	0.406	0.183	0.087	0.600	0.145
vehicle	F	SD	0.007	0.021	0.013	0.007	0.035	0.010
	F		n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
2	F	mean	0.079	0.415	0.189	0.093	0.619	0.151
150 mg/kg/day	F	SD	0.005	0.018	0.008	0.007	0.029	0.010
ucb 34714	F		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
3	F	mean	0.078	0.422	0.186	0.093	0.636	0.146
300 mg/kg/day	F	SD	0.006	0.017	0.008	0.007	0.032	0.006
ucb 34714	F		n.s.	n.s.	n.s.	n.s.	**a**	n.s.
4	F	mean	0.078	0.410	0.190	0.092	0.617	0.149
600 mg/kg/day	F	SD	0.005	0.011	0.011	0.006	0.025	0.007
ucb 34714	F		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
1	M	mean	0.094	0.512	0.184	0.121	0.777	0.155
vehicle	M	SD	0.006	0.021	0.009	0.009	0.041	0.009
	M		n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
2	M	mean	0.092	0.499	0.184	0.118	0.763	0.155
150 mg/kg/day	M	SD	0.007	0.028	0.007	0.009	0.051	0.003
ucb 34714	M		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
3	M	mean	0.089	0.490	0.182	0.114	0.734	0.155
300 mg/kg/day	M	SD	0.007	0.025	0.006	0.009	0.047	0.004
ucb 34714	M		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
4	M	mean	0.089	0.475	0.187	0.113	0.726	0.155
600 mg/kg/day	M	SD	0.013	0.036	0.016	0.013	0.056	0.009
ucb 34714	M		n.s.	**a**	n.s.	n.s.	n.s.	n.s.

viii. Plasma drug levels

TK data for BRV and its metabolites are shown in **Table IV.D1.11**. Peak levels for parent were seen at 1 hour and both Cmax and AUC values generally increased less than dose-proportionally, which was more marked in males than females and on PND 21 than on PND 70.

Table IV.D1.11 TK parameters for SPM 927 (lacosamide) in juvenile rats

Parameter	Compound	Dose (mg/kg/day)								
		150			300			600		
(unit)		M	F	M&F	M	F	M&F	M	F	M&F
PND 21										
C_{max}	ucb 34714	31.5	25.0	28.2	33.4	44.4	38.9	45.9	42.0	41.0
(µg/mL)										
AUC(0-24 h)	ucb 34714	119	120	120	164	172	168	246	196	226
(µg eq*h/mL)	ucb 42145	4.15	4.79	4.47	6.28	6.54	6.41	8.99	6.46	7.91
	ucb-100406-1	77.2	82.9	80.1	166	139	153	304	210	263
	ucb-107092-1	1.20	1.39	1.30	2.36	2.17	2.26	4.37	3.22	3.88
PND 70										
C_{max}	ucb 34714	29.4	37.9	33.7	44.2	61.6	52.9	59.0	127	93.0
(µg/mL)										
AUC(0-24 h)	ucb 34714	164	239	202	253	493	373	309	855	583
(µg eq*h/mL)	ucb 42145	4.48	6.24	5.36	6.85	13.3	10.1	7.72	20.1	13.9
	ucb-100406-1	75.1	70.7	72.9	150	147	149	249	246	247
	ucb-107092-1	0.850	0.769	0.810	1.58	1.82	1.70	2.84	2.64	2.74

c. Conclusions

Administration of BRV to young rats for 10 weeks beginning on PND 4 at doses of 150, 300, or 600 mg/kg/day increased mortality, transiently decreased BW gain, delayed male sexual maturation, produced short and long-term neurobehavioral changes (altered locomotor activity and auditory startle responsiveness), and impaired reproductive performance at the HD and produced persistent decreases in brain weight and size at all doses.

2. ucb 34714: 9-Month Oral (Gavage) Toxicity Study in Juvenile Beagle Dogs with a 2-Month Recovery Period (Report no. NCD1863, dated 8/11/10, conducted by (b) (4), GLP)

a. Methods

Juvenile Beagle dogs (9-11/sex/group + 6-9/sex/grp TK from 46 pregnant females) were given BRV (batch #s CB14000015 and CB14000037) at oral (gavage) doses of 0 (1% w/v methylcellulose 400 cps), 15, 30, or 100 mg/kg/day (administered BID, 10 hr apart, 5 mL/kg/day) from PND 4 through PND 276. Observations consisted of clinical signs, body weight, food and water consumption, developmental landmarks (eye opening and teeth eruption), neurobehavioral functions (FOB), ophthalmology, ECG, hematology, clinical chemistry (including serum thyroid and reproductive hormone analysis), urinalysis, bone parameters (biomarkers, densitometry and strength, femur length), and macroscopic and microscopic pathology (including detailed central and peripheral nervous system histopathology). Plasma samples for TK analysis were obtained on PND 4 and PNDs 31 and 276 at 1, 4.5, 10 (prior to the second daily dose), 11, 14.5, and 24 h after the first daily dose.

Dose selection was based on the results of dose range-finding study in juvenile dogs (15, 50 and 100 mg/kg/day dosed orally BID from PND 4 through PND 31) in which decreased BW gain, decreased bone indices (bone mineral content, area and density in the femur and bone mineral content and density in the lumbar vertebrae), increased liver weights and hepatocellular hypertrophy, and decreased thymus weights and thymic atrophy were seen at the MD and HD.

b. Results

i. Mortality and Clinical signs

There were no early deaths or T-R clinical signs.

ii. Growth and development

There were no T-R effects on BW or developmental landmarks.

iii. Electrocardiographic examinations

There were no T-R changes in ECGs performed during PNDs 193-199, during the last week of dosing (PNDs 270-276) and during the last week of recovery (PNDs 327-331).

iv. Clinical Pathology, Ophthalmological Examination

There were no apparent T-R effects on hematology, reproductive hormone level, urinalysis, or ophthalmological evaluations. Clinical chemistry changes consistent with those seen in general toxicity studies in adult dogs were seen, primarily at the HD (**Table IV.D2.1**). T-R increases (SS at HD) in ALP, ALT, AST, GGT, and bile acids and decreases (SS at HD) in albumin, A/G ratio, and cholesterol were seen in both sexes at PND 114, 202, and/or 277. T4 values were decreased (SS on PND 277) in HD females (**Table IV.D2.2)**. Increases (SS on PND 277) in serum bone specific alkaline phosphatase (BSAP) were seen in HD males and females (**Table IV.D2.3**). There were no clear changes in the other two bone biomarkers (osteocalcin and cross-linked C telopeptide of type 1 collagen).

ALP, AST, GGT, A/G, T4, and BSAP values appeared to return to normal after the recovery period, while only partial recovery was seen for ALT (males), bile acids (females), cholesterol, and albumin.

Table IV.D2.1 Clinical chemistry findings in juvenile dogs

Total daily dose (mg/kg/day)[a]:	0 (Control)		15		30		100	
Number of animals (Toxicology phase)	**M:9**	**F:11**	**M:9**	**F:10**	**M:10**	**F:10**	**M:10**	**F:9**
Serum chemistry[b]								
Aspartate aminotransferase (U/L)								
PND 32	21	22	-4.8	4.5	-4.8	4.5	4.8	4.5
PND 114	32	34	-12.5	5.9	-6.3	11.8	12.5	8.8
PND 202	33	31	-6.1	3.2	-6.1	16.1	30.3*	32.3*
PND 277	30	30	6.7	3.3	0.0	0.0	53.3**	33.3**
PND 333	32	28	15.6	7.1	-6.3	42.9	18.8	14.3
Gamma glutamyltransferase (U/L)								
PND 32	2.2	2.7	18.2	-14.8	-13.6	-11.1	27.3	0.0
PND 114	0.7	1.0	57.1	-10.0	14.3	-10.0	171.4	0.0
PND 202	2.3	2.4	30.4	-4.2	-8.7	-29.2	160.9**	50.0
PND 277	1.0	1.0	80.0	40.0	0.0	40.0	450.0**	310.0**
PND 333	2.7	0.9	22.2	111.1	-70.4	322.2	-14.8	66.7
Cholesterol (mg/dL)								
PND 32	286	280	-6.6	-5.7	-14.0	-18.9	-6.6	-12.5
PND 114	149	131	-1.3	-4.6	2.0	-0.8	-19.5*	-10.7
PND 202	155	142	-4.5	-6.3	-1.3	-7.7	-20.0*	-19.7**
PND 277	148	145	-3.4	0.7	-2.0	-2.8	-18.9**	-15.9
PND 333	162	156	-20.4	13.5	-17.9	-7.1	-27.8	-14.7
Bile acids (µmol/L)								
PND 32	4.1	4.9	4.9	40.8	12.2	49.0	97.6	55.1
PND 114	4.4	2.1	-31.8	-47.6	-75.0	-23.8	-45.5	-33.3
PND 202	1.9	3.9	-10.5	-41.0	47.4	-56.4	110.5	2.6
PND 277	0.8	2.5	125.0	-40.0	75.0	-52.0	487.5**	56.0
PND 333	1.5	2.4	40.0	50.0	420.0	-25.0	80.0	-25.0
Albumin (g/dL)								
PND 32	3.1	3.1	3.2	6.5*	0.0	0.0	-3.2	-3.2
PND 114	3.3	3.3	-3.0	-3.0	-3.0	-3.0	-6.1**	-6.1
PND 202	3.5	3.5	-2.9	0.0	-2.9	0.0	-5.7	-5.7*
PND 277	3.5	3.6	0.0	-2.8	-2.9	-5.6	-5.7**	-8.3**
PND 333	3.6	3.5	2.8	2.9	-2.8	2.9	-2.8	-2.9
Albumin/Globulin ratio								
PND 32	2.47	2.3	8.5	20.0	3.2	10.0	-3.6	4.8
PND 114	1.75	1.82	-1.7	-6.6	1.7	-6.0	-10.9*	-9.3
PND 202	1.63	1.89	4.9	-2.1	-2.5	-5.3	-3.1	-9.5
PND 277	1.65	1.99	0.6	-6.0	-6.1	-12.6	-6.1	-11.1
PND 333	1.47	1.89	15.6	-3.7	12.9	-2.6	29.3	9.0
Alkaline phosphatase (U/L)								
PND 32	173	158	2.9	0.6	-5.2	10.1	-11.6	6.3
PND 114	207	207	-3.4	-12.6	-9.2	2.4	9.2	13.0
PND 202	120	119	-5.0	-9.2	-5.0	5.0	92.5**	83.2**
PND 277	70	66	-5.7	-7.6	-1.4	19.7	150.0**	142.4**
PND 333	61	40	-23.0	0.0	-19.7	77.5	14.8	40.0
Alanine aminotransferase (U/L)								
PND 32	27	27	-3.7	-7.4	3.7	7.4	7.4	11.1
PND 114	39	41	0.0	2.4	2.6	19.5	197.4**	100.0**
PND 202	45	46	6.7	0.0	-4.4	10.9	500.0**	308.7**
PND 277	51	46	0.0	0.0	-11.8	10.9	494.1**	341.3**
PND 333	47	42	14.9	14.3	6.4	31.0	89.4**	11.9

(a) Total daily dosage split into 2 equal subdoses given approximately 10 hours apart (b) For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences); M=Male; F=Female; -=No noteworthy findings; * P<0.05 and ** P<0.01 when compared to the control group using Dunnett's test.

Table IV.D2.2 Thyroid hormone levels in juvenile dogs

ANALYSIS	GROUP:	FEMALES 0 MG/KG/DAY	15 MG/KG/DAY	30 MG/KG/DAY	100 MG/KG/DAY
TOTAL T4 (uG/dL)					
DAY 32	MEAN	4.81	4.66	4.71	4.21
	% DIFFERENCE		-3.1	-2.1	-12.5
	S.D.	0.912	0.684	0.689	0.722
	S.E.	0.304	0.242	0.218	0.241
	N	9	8	10	9
DAY 114	MEAN	1.96	1.83	1.95	1.44
	% DIFFERENCE		-6.6	-0.5	-26.5
	S.D.	0.378	0.250	0.624	0.384
	S.E.	0.126	0.083	0.197	0.128
	N	9	9	10	9
DAY 202	MEAN	1.79	1.33	1.72	1.52
	% DIFFERENCE		-25.7	-3.9	-15.1
	S.D.	0.499	0.434	0.551	0.849
	S.E.	0.166	0.145	0.174	0.283
	N	9	9	10	9
DAY 277	MEAN	1.62	1.59	1.70	0.95*
	% DIFFERENCE		-1.9	4.9	-41.4
	S.D.	0.412	0.457	0.585	0.511
	S.E.	0.137	0.152	0.185	0.170
	N	9	9	10	9

uG/dL = MICROGRAMS/DECILITER, mg/dL = MILLIGRAMS/DECILITER, umol/L = micromoles/Liter, ng/mL = NANOGRAMS/MILLILITER, ng/dL = NANOGRAMS/DECILITER, pg/mL = PICOGRAMS/MILLILITER

* = Significantly different from the control group at 0.05 using Dunnett's test

Table IV.D2.3 Serum bone biomarker analysis

Treatment Group	Data	PND 32			PND 114			PND 202			PND 277			PND 333		
		BSAP	OSCL	CTx	BSAP	OSCL	CTx	BSAP	OSCL	CTx	BSAP	OSCL	CTx	BSAP	OSCL	CTx
		U/L	ng/mL	ng/mL	U/L	ng/mL	ng/mL	U/L	ng/mL	ng/mL	U/L	ng/mL	ng/mL	U/L	ng/mL	ng/mL
1 Male	Mean	113.77	37.49	0.21	190.04	48.00	0.58	87.63	26.93	0.67	41.70	18.54	0.65	28.98	13.60	0.61
Vehicle Control	SD	20.45	9.39	0.02	36.58	12.09	0.14	28.10	8.45	0.05	14.45	6.15	0.10	4.34	0.37	0.04
0 mg/kg/day	n	9	9	9	9	9	9	9	9	9	9	9	9	3	3	3
Stat		n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
2 Male	Mean	121.46	34.64	0.17	171.75	46.45	0.54	86.19	29.09	0.68	36.98	17.08	0.58	22.66	16.98	0.79
ucb 34714	SD	19.02	5.26	0.03	20.05	13.05	0.06	23.41	4.01	0.08	11.11	4.16	0.10	3.50	8.45	0.13
15 mg/kg/day	n	7	7	7	9	9	9	9	9	9	9	9	9	3	3	3
Stat		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
3 Male	Mean	110.72	37.59	0.17	181.14	43.67	0.62	83.04	27.29	0.63	37.53	19.41	0.64	27.08	14.39	0.80
ucb 34714	SD	22.89	11.71	0.05	83.17	7.31	0.12	24.68	6.09	0.10	14.27	4.15	0.08	9.05	1.83	0.21
30 mg/kg/day	n	9	9	9	10	10	10	10	10	10	10	10	10	3	3	3
Stat		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
4 Male	Mean	100.55	32.50	0.18	153.82	44.51	0.54	120.10	28.79	0.60	62.67	18.68	0.59	32.16	13.37	0.69
ucb 34714	SD	30.90	8.96	0.05	66.70	14.65	0.11	44.29	6.93	0.07	22.37	5.41	0.09	14.08	0.71	0.13
100 mg/kg/day	n	10	10	10	10	10	10	10	10	10	10	10	10	3	3	3
Stat		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	*	n.s.	n.s.	n.s.	n.s.	n.s.

1 Female	Mean	102.57	33.50	0.18	189.57	50.42	0.54	89.51	25.49	0.62	36.85	15.10	0.58	21.50	12.85	0.61
Vehicle Control	SD	17.94	8.68	0.04	34.49	9.77	0.06	26.42	5.63	0.13	6.65	3.26	0.09	3.30	2.55	0.06
0 mg/kg/day	n	9	9	9	9	9	9	9	9	9	9	9	9	3	3	3
Stat		n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
2 Female	Mean	105.65	33.43	0.15	175.63	49.45	0.58	80.48	29.59	0.66	33.18	16.70	0.62	19.76	13.12	0.57
ucb 34714	SD	34.64	8.96	0.03	47.39	8.73	0.09	11.63	6.38	0.08	7.05	3.13	0.10	2.81	2.40	0.05
15 mg/kg/day	n	8	8	8	9	9	9	9	9	9	9	9	9	3	3	3
Stat		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
3 Female	Mean	113.74	34.72	0.18	175.37	51.16	0.53	91.54	29.27	0.61	42.92	18.19	0.59	32.36	15.68	0.60
ucb 34714	SD	25.03	11.31	0.06	53.30	13.83	0.08	16.78	7.86	0.12	12.74	2.99	0.14	9.40	1.86	0.04
30 mg/kg/day	n	10	10	10	10	10	10	10	10	10	10	10	10	3	3	3
Stat		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
4 Female	Mean	105.35	31.76	0.19	156.13	48.31	0.58	105.66	26.24	0.62	56.67	15.75	0.52	28.61	13.89	0.64
ucb 34714	SD	36.91	8.99	0.04	51.60	8.98	0.09	47.46	6.78	0.14	22.81	3.82	0.11	12.67	1.43	0.06
100 mg/kg/day	n	9	9	9	9	9	9	9	9	9	9	9	9	3	3	3
Stat		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	*	n.s.	n.s.	n.s.	n.s.	n.s.

n.a. = not applicable
n.s. = not significant
* $p < 0.05$ using a parametric one-way analysis of variance ANOVA when compared to Group 1 of the same sex

v. Developmental Neurotoxicity Testing

The FOB performed on PNDs 30, 112, 200, 275, and 332 (recovery) prior to first daily dosing did not reveal any T-R differences.

vi. Anatomic pathology

There were no T-R macroscopic findings, or microscopic changes in the central and PNS tissues (no apparent effect on brain wt or size). The clinical chemistry changes in HD animals correlated with brown pigment accumulation, centrilobular and periportal fibrosis, inflammation, bile duct hyperplasia, and hepatocellular hypertrophy and degeneration at the HD in both sexes (**Table IV.D2.4**). These findings were more severe in males than in females and were associated with higher liver weights and gallbladder concretions in males. Partial or full reversal was observed at the end of the recovery period, with the exception of the brown pigment accumulation and gallbladder concretion. Lower thymus weight in HD females was associated with a slight increase in severity but not in incidence of thymic atrophy.

Table IV.D2.4 Histopathology in juvenile dogs

Total daily dose (mg/kg/day)[a]:	0 (Control)		15		30		100	
Number of animals (Toxicology phase)	**M:9**	**F:11**	**M:9**	**F:10**	**M:10**	**F:10**	**M:10**	**F:9**
Histopathology (primary necropsy)[c]	6	6	6	6	7	7	7	6
Liver								
Pigment, brown	0	0	0	0	0	0	7	6
Minimal	-	-	-	-	-	-	0	2
Mild	-	-	-	-	-	-	7	4
Fibrosis	0	0	0	0	0	0	7	5
Minimal	-	-	-	-	-	-	3	4
Mild	-	-	-	-	-	-	3	1
Moderate	-	-	-	-	-	-	1	0
Inflammation	0	0	0	0	0	0	7	5
Minimal	-	-	-	-	-	-	4	5
Mild	-	-	-	-	-	-	3	0
Hyperplasia, bile duct	0	0	1	0	0	0	6	3
Minimal	-	-	1	-	-	-	3	3
Mild	-	-	0	-	-	-	2	0
Moderate	-	-	0	-	-	-	1	0
Hypertrophy, hepatocellular	0	0	0	0	0	0	4	2
Minimal	-	-	-	-	-	-	4	2
Degeneration, hepatocellular	0	0	0	0	0	0	7	6
Minimal	-	-	-	-	-	-	2	4
Mild	-	-	-	-	-	-	5	2
Gallbladder								
Concretion	0	0	0	0	0	0	2	0
Minimal	-	-	-	-	-	-	2	-
Histopathology (recovery necropsy)[c]	3	3	3	3	3	3	3	3
Liver								
Pigment, brown	0	0	0	0	0	0	3	3
Minimal	-	-	-	-	-	-	1	1
Mild	-	-	-	-	-	-	2	2
Fibrosis	0	0	1	0	0	0	1	2
Minimal	-	-	1	-	-	-	0	2
Mild	-	-	0	-	-	-	1	0
Inflammation	0	0	0	0	0	0	1	1
Minimal	-	-	-	-	-	-	1	1
Hyperplasia, bile duct	0	0	0	0	0	0	2	3
Minimal	-	-	-	-	-	-	1	3
Mild	-	-	-	-	-	-	1	0
Degeneration, hepatocellular	0	0	0	0	0	0	3	3
Minimal	-	-	-	-	-	-	2	3
Mild	-	-	-	-	-	-	1	0
Gallbladder								
Concretion	0	0	0	0	0	0	1	0
Minimal	-	-	-	-	-	-	1	-

(a) Total daily dosage split into 2 equal subdoses given approximately 10 hours apart; (c) Number of animals examined; M=Male; F=Female; -=No noteworthy findings.

vii. Bone parameters

Although DXA bone parameters (bone mineral content, area, and density) appeared to be decreased in recovery group HD males in association with decreased femur length, there were no SS differences compared to C (**Table IV.D2.5**). L5 Lumbar vertebral body extrinsic (maximum load, stiffness and energy) and intrinsic (ultimate strength, elastic modulus and toughness) strength parameters evaluated at the end of treatment and after the recovery period were not affected by treatment.

Table IV.D2.5. Bone parameters in juvenile dogs

Treatment Group	Data	Terminal				Recovery			
		Bone Mineral Content	Bone Area	Bone Mineral Density	Femur Length	Bone Mineral Content	Bone Area	Bone Mineral Density	Femur Length
		g	cm^2	g/cm^2	cm	g	cm^2	g/cm^2	cm
1 Male	Mean	11.955	22.938	0.519	12.83	12.424	23.645	0.527	13.27
Vehicle Control	SD	2.189	3.229	0.036	0.74	0.757	0.993	0.042	0.38
0 mg/kg/day	n	6	6	6	6	3	3	3	3
Stat		n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
2 Male	Mean	12.720	24.178	0.523	13.22	13.238	24.370	0.543	13.20
ucb 34714	SD	2.449	2.341	0.059	0.68	1.008	1.034	0.032	0.50
15 mg/kg/day	n	6	6	6	6	3	3	3	3
Stat		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
3 Male	Mean	12.640	23.825	0.529	12.89	13.549	25.285	0.537	13.40
ucb 34714	SD	1.574	2.012	0.031	0.62	0.875	2.378	0.015	0.62
30 mg/kg/day	n	7	7	7	7	3	3	3	3
Stat		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
4 Male	Mean	12.119	23.463	0.514	12.71	11.223	21.649	0.517	12.40
ucb 34714	SD	1.832	2.105	0.034	0.75	2.141	1.763	0.055	0.30
100 mg/kg/day	n	7	7	7	7	3	3	3	3
Stat		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
1 Female	Mean	9.036	19.863	0.455	12.07	9.354	19.999	0.467	12.20
Vehicle Control	SD	0.479	1.040	0.030	0.68	0.915	2.019	0.031	0.82
0 mg/kg/day	n	6	6	6	6	3	3	3	3
Stat		n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
2 Female	Mean	9.295	20.762	0.447	12.35	10.108	22.012	0.460	12.70
ucb 34714	SD	1.186	2.044	0.030	0.80	1.885	2.618	0.036	0.53
15 mg/kg/day	n	6	6	6	6	3	3	3	3
Stat		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
3 Female	Mean	9.700	20.704	0.467	12.20	10.535	22.065	0.477	12.73
ucb 34714	SD	1.789	1.937	0.050	0.70	1.803	1.948	0.042	0.71
30 mg/kg/day	n	7	7	7	7	3	3	3	3
Stat		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
4 Female	Mean	8.521	19.006	0.445	11.77	10.171	20.881	0.483	12.00
ucb 34714	SD	1.495	2.259	0.030	0.68	1.217	1.913	0.015	0.52
100 mg/kg/day	n	6	6	6	6	3	3	3	3
Stat		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

n.a. = not applicable n.s. = not significant

viii. Toxicokinetics

TK data summarized in **Table IV.D2.6** show approximately dose-proportional increases in parent and no sex differences.

Table IV.D2.6. PK parameters in juvenile dogs

Parameter (unit)	Compound	Dose Level* 15 mg/kg/day	30 mg/kg/day	100 mg/kg/day
PND 4[(a)]				
C_{max} (µg/mL)	ucb 34714	6.49 ± 1.39	13.6 ± 1.9	48.7 ± 23.4
AUC(0-24 h) (µg eq*h/mL)	ucb 34714	85.3 ± 15.4	190 ± 18	612 ± 148
PND 31				
C_{max} (µg/mL)	ucb 34714	4.84 ± 0.89	10.2 ± 1.7	29.2 ± 6.9
AUC(0-24 h) (µg eq*h/mL)	ucb 34714	28.4 ± 4.2	63.5 ± 16.6	207 ± 45
PND 276[(b)]				
C_{max} (µg/mL)	ucb 34714	5.70 ± 0.91	12.1 ± 2.0	43.3 ± 4.7
AUC(0-24 h) (µg eq*h/mL)	ucb 34714	37.1 ± 7.3	78.1 ± 16.3	335 ± 56

* : split into two equal sub-doses 10 hours apart; [(a)] : first day of treatment; [(b)] : last day of treatment.

c. Conclusions

When BRV was given to young dogs for 9 months beginning on PND 4 at doses of 15, 30, or 100 mg/kg, there were no apparent effects on body weight or other growth parameters (including bone), neurological testing, ECG, ophthalmology, or brain pathology. Clinical chemistry and histopathology changes consistent with the liver toxicity seen in general toxicity studies in adult dogs were observed at comparable exposures, indicating an absence of age-related effects.

IV. SUMMARY AND EVALUATION

Pharmacology

Brivaracetam was predicted to be a broad spectrum anticonvulsant based on its potent binding to the synaptic vesicle protein 2A site and activity in a variety of animal models of epilepsy. Interestingly, BRV showed activity in the standard MES and PTZ seizure models, while LEV was inactive in these models. The pharmacologic activity of BRV seems to be associated primarily with the parent, since only 1 minor metabolite demonstrated weak anticonvulsant activity.

In CNS safety testing in rats, signs of CNS depression were seen at acute oral doses ≥100mg/kg. Oral doses of 1000 and 1500 mg/kg were associated with mortality. In in vivo CV safety studies, decreases in blood pressure, heart rate, and cardiac contractility and increases in QT and QTc were observed in anesthetized male dogs after an iv dose of 150 mg/kg (Cmax 308 ug/mL). In conscious dogs, decreased blood pressure and increased heart rate were seen in females at single oral doses ≥ 50 mg/kg (Cmax 61 µg/mL) and QTc prolongation was seen in females at 150 mg/kg (Cmax 174 µg/mL). However, no prolongation of QT or QTc was observed in the repeated-dose toxicity studies in the dog at oral doses of up to 94 mg/kg/day given BID (Cmax ~50 µg/mL) or in the monkey at doses of up to 900 mg/kg/day given BID (Cmax ~250 µg/mL). The CV effects observed in the dog at doses ≥50mg/kg were associated with peak plasma levels well above the Cmax (3.5 µg/mL) at the maximum intended clinical dose of 100 mg bid and CV effects have not been reported clinically. BRV produced a slight respiratory stimulant effect at a dose of 100 mg/kg po in rats (Cmax of 63.6 µg/mL).

ADME

Oral absorption was rapid and complete in rats, dogs, and humans, with an oral bioavailability of nearly 100%. A much lower bioavailability (<10%) in the cynomolgus monkey was attributed to high first-pass metabolism rather than to poor absorption. There were no sex differences in exposure in dogs and monkeys, but in rats exposure was higher in females than in males. The half-life was ~2 hours after oral or iv administration to rat and dog and ~ 8 hr in humans. Rapid, widespread distribution into tissues was observed in studies of radiolabeled BRV, with the volume of distribution approximately equivalent to total body water (0.6 L/kg). Plasma protein binding was low (≤20%) in all species including humans. Parent drug represented the most abundant circulating material in vivo for all species (including humans) except the cynomolgus monkey, which showed increased metabolic clearance compared to other species.

The major metabolic route involves the stereoselective hydroxylation of the propyl chain to produce ucb-100406-1, both in animals and humans. In rodents, monkeys, and humans, ucb-100406-1 was the only metabolite exceeding 10% of the total circulating material. In dog, major metabolites included both ucb-100406-1 and ucb-102993-1, a derivative resulting from the hydroxylation of the butyramide side-chain. The other identified metabolic routes involved the hydrolysis of the acetamide moiety to the acid derivative ucb 42145, which can be then be hydroxylated to ucb-107092-1, and the oxidation of ucb-100406-1 to the corresponding ketone ucb 47074. The other metabolites and/or the other metabolite isomers were present in much smaller amounts. No in vivo metabolites were specific to humans. Auto-induction of metabolism was suggested by the decreased exposure with repeated dosing in the animal studies, except in monkeys.

The clinical pharmacology reviewer, Michael Bewernitz, confirmed that the hydroxy metabolite (ucb-100406-1) was the only major circulating metabolite in humans (i.e., exceeding >10% of total drug-related material in circulation). In severely renally impaired patients, levels of metabolites increase dramatically. For ucb-100406-1 (hydroxy metabolite), the mean AUC in severe RI patients was 57.5 µg*h/mL at the MRHD (which represented an ~400% increase compared to the AUC in healthy patients); for ucb 42145 (carboxylic acid metabolite), the AUC in

severe RI patients was 11.4 µg*h/mL (~325% increase compared to healthy patients); and for ucb-107091-1 (hydroxy acid metabolite) the mean AUC in severe RI patients was 35.8 µg eq.h/mL (~21-fold greater). The animal studies provided adequate coverage for all but ucb-107091-1 (**Tables III.5-6**); therefore, additional studies were conducted in which the metabolite was directly administered (see below).

Clearance was predominantly by metabolism and excretion of metabolites in urine and feces. After IV and oral administration of 5 mg/kg [14C]-ucb 34714 in mouse, rat, hamster, dog, and cynomolgus monkey, 60%-80% of dose radioactivity was recovered in urine during the first 24 hours after dosing and 86%-98% by 168 hours after dosing.

General Toxicology

Chronic oral toxicity of BRV was assessed in dogs, rats, and monkeys. In the chronic oral toxicity study in Wistar rats (0, 100+50, 100+130, or 100+350 mg/kg/day by diet and gavage for 26 weeks), clinical chemistry changes (increased cholesterol, triglycerides and glucose), increased liver weights, and centrilobular hepatocellular hypertrophy were attributed to liver enzyme auto-induction. Other minor histopathology findings, including brown (presumably lipofuscin) pigment deposition in the liver, thyroid, and spleen, were also considered to be adaptive responses. Therefore, except for hyaline droplet nephropathy seen in males at all doses, none of the findings was considered adverse by the sponsor, reasonably so, and the HD can be considered the NOAEL. The Cmax and AUC0-24h values were 36.6 and 65.9 µg/mL and 257 and 464 µg.h/mL, for males and females, respectively, at week 26.

In the chronic oral toxicity study in the beagle dog (0, 15, 37.5, or 75 mg/kg/day given TID by gavage for 26 weeks), clinical chemistry changes (dose-related increases in ALT, SDH, ALK PHOS, 5'-ND, and GGT), increased liver weights, and hepatobiliary histopathological changes (brown pigment deposits in hepatocytes, Kupffer cells, and bile canaliculi, fibrosis and hyperplasia of oval cells/bile ducts, hepatocyte necrosis and inflammation, gallbladder concretions) were seen primarily at the MD and HD. Exposure (AUC (0-24h)) to parent drug at the LD, which was considered the NOAEL, was 34.7 µg.h/mL (sexes combined) at 26 weeks. This is lower than the human plasma exposure at the MRHD of 200 mg/day (**Table III.3**).

In the chronic oral toxicity study in cynomolgus monkey (0, 300, 600, or 900 mg/kg/day dosed BID by gavage for 39 weeks), transient CNS signs (reduced activity, clumsy movements, loss of balance) and increased triglyceride concentrations and ALT and GGT activities were seen at the MD and HD and increased liver weights, hepatocellular hypertrophy, and increased brown pigment (lipofuscin) deposition in the liver were seen at the HD. These changes can be considered indicative of an adaptive response of the liver and not adverse, so the HD (week 39 Cmax and AUC0-24h values at of 223 µg/mL and 2351 µg.h/mL, respectively (sexes combined)) was considered the NOAEL.

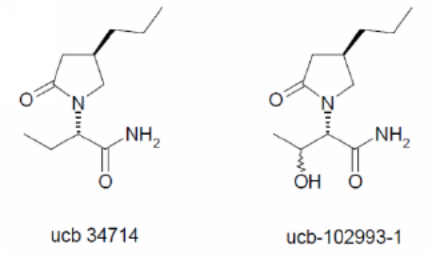
To support the safety of the iv formulation of BRV, for which bioequivalence to the oral dosage form was established clinically, 1-month continuous infusion studies were conducted in the rat and dog (see IND 103908 review dated 12/11/08 by Christopher Toscano). In the Wistar rat study (continuous iv infusion (4mL/kg/h) of 0, 200, 600, or 1000 mg/kg/day for 28 days), there were no T-R deaths, clinical signs, or BW effects, but increases (up to ~20%) in plasma creatinine concentrations were seen in males at the two highest doses (thought to reflect hyaline droplet nephropathy [HDN]), D-R increases in liver, kidney, and thyroid weights (up to 20-30%), centrilobular hepatocyte hypertrophy, and thyroid follicular cell hypertrophy were seen in all treated males and in MD and HD females, and HPN was seen in males at all doses. The NOAEL was <200mg/kg/day for males and 200 mg/kg/day for females. On Day 28, the AUC0-24h at this dose were 168 and 518 µg.h/mL for males and females, respectively, approximately 5-fold higher than those expected in humans receiving the proposed clinical dose. Metabolite 100406-1 was

detected at concentrations almost as high as the parent compound at the final day of dosing in males rats but was about 1/5 the parent exposure in females.

In the 1-month iv toxicity study in beagle dogs, BRV was tested at doses of 0, 30, 100, and 150/300/200 mg/kg/day for 28 days as continuous iv infusion (0.5mL/kg/h). The HD started at 150 mg/kg for 2 days but was raised to 300 mg/kg/ day and then lowered to 200 mg/kg on days 16-17 due to decrease in food intake. There was no T-R mortality, clinical signs, or total BW gain but findings included: decreased (~50%) reticulocytes at the HD; notable increases in ALT, AST, ALP activity (ALT up to 17-fold) and total bilirubin levels at the MD and HD; increased liver and decreased thymus weights; and histological findings of centrilobular hepatocellular hypertrophy, widespread deposition of protoporphyrin pigmentation in the liver (intra and extra- hepatocellular and Kupffer cell), increased hepatocellular apoptosis, inflammatory cell infiltration, and fibrosis (one animal) in the liver, accumulation of dark concretions in the gallbladder, thymic atrophy, and adrenal cortical cell hypertrophy, all primarily at the MD and HD in both sexes. Only partial recovery was seen, with hepatocellular apoptosis and inflammatory cell infiltration in the liver, dark concretions in the gallbladder, and increased ALT and ALP activities and total bilirubin remaining at the end of the 2-week recovery period. The day 28 exposure (AUC) to parent at the the LD, the NOAEL, was 58.4 µg.h/mL (males and females combined). Exposure to the major metabolite UCB-100406-1 was 20% greater than that of parent at the LD and 28 and 52% lower than parent at the MD and HD, respectively.

The more serious hepatotoxicity seen in dogs was attributed to a mechanism, thought to be unique to this species, involving the formation of a reactive metabolite with structural similarities to known porphyrogenic agents though oxidation of the butyramide side-chain. This putative reactive metabolite is thought to alkylate CYP and result in the formation of *N*-alkylprotoporphyrin IX (*N*-alkylPP), which leads to CYP inactivation. CYP inactivation, in turn, induces heme synthesis, accelerating the accumulation of porphyrin precursors, which ultimately produces the hepatocyte necrosis observed. Support for this mechanism came from metabolism data showing that the dog is the only species in which the β-hydroxylated product, ucb-102993-1, thought to be the precursor of the putative reactive species, exists as major circulating metabolite (≥10% total); non-linear PK seen in dogs after iv and oral dosing; a 2-week oral study (0, 100, 200, or 300 mg/kg/day given BID) in which liver enzyme analysis revealed induction of CYP3A and CYP2B and a depression of CYP1A and CYP4A; a 4-week oral study (6, 15, 37.5, or 94 mg/kg/day given BID) in which animals given ≥15 mg/kg/day had increased CYP concentration and induction of CYP2B and CYP3A (up to 2.9-fold), while suppression of enzyme activity was observed at 94 mg/kg/day for CYP1A, CYP2B, and CYP4A; and similar findings in a subsequent toxicological program performed with ucb-101747-1, a structurally-related SV2A ligand (**Figure IV.1**).

(b) (4)



(b) (4)

Figure IV.1 Chemical structures of BRV, UCB-101747-1, and β-oxidized metabolites

The sponsor provided an opinion paper on the dog liver findings and their clinical relevance. The authors of this paper concluded that the evidence from the dog studies of BRV as well as those performed with ucb-101747-1 supports this mechanism and that given the fact that similar effects were not seen in rats or monkeys at higher exposures and that human data showed no evidence of bioactivation (no measurable levels of ucb-102993-1 in human plasma or urine), CYP inactivation, nonlinear pharmacokinetics (as a result of auto-inhibition), or clinically relevant CYP induction, and no liver signal (in "over 2300 human subjects with epilepsy given BRV, some of them for up to 8 years, at doses up to 200 mg/day"), the data support "a lack of clinical relevance of the BRV-induced porphyria observed in dogs."

Because there was inadequate coverage for the minor metabolite ucb-107092-1 (found to be devoid of pharmacological activity) in subjects with severe renal impairment, the sponsor conducted stand-alone toxicity studies in which the metabolite was directly administered iv to rats for up to 3 months, as well as safety pharmacology, genotoxicity, and embryofetal development studies with the metabolite. This metabolite was devoid of pharmacological activity in seizure models and did not interact with any of the standard targets in in vitro binding assays. There was no indication of toxicity, including developmental toxicity (NOAEL was the highest dose tested), at exposures much higher (30-50X) than those in subjects with severe renal impairment. In a 13-week iv Wistar rat study (doses of 0, 500, 1000, or 2000 mg/kg/day administered by continuous iv infusion for 12 weeks), the only adverse effects were attributed to the procedure rather than the metabolite; dosing was stopped 1 week early because of bacterial contamination of cannulas. The NOAEL (2000 mg/kg/day) was associated with week 12 AUC values of 1220 µg.h/mL in males and 1818 µg.h/mL in females.

Genotoxicity and Carcinogenicity

Genotoxicity was investigated in a standard panel of studies (Ames bacterial mutation, mouse lymphoma *in vitro* mammalian cell mutation, Chinese hamster ovary *in vitro* chromosomal aberration, and an *in vivo* rat micronucleus assay; see IND 70205 review by Kathy Young date 5/11/06). BRV and its metabolite ucb-107092-1 were both negative in the Ames test. In the

mouse lymphoma assay, BRV produced a SS increase in mutant fraction at the highest concentration assessed (4800 µg/mL), a concentration considered to be at the limit of acceptable toxicity (10% RTG). No evidence of mutagenic activity was observed following treatment for 24 h without S9, and following treatment for 4 h with S9. It was concluded that a weak mutagenic response was seen at a toxic concentration in the absence of S9. In the CHO chromosomal aberration assay, there was an increase in structural aberrations in the presence of S9 at a cytotoxic (40% cell survival) concentration of BRV (3500 µg/mL), in the presence of S9 at 3000 µg/mL (54% cell survival), and in the absence of S9 following 6 h exposure at 4100µg/mL (44% cell survival). However, this assay was considered inconclusive because the response was not reproducible between duplicate cultures and between repeat tests. In the rat micronucleus test with BRV (Wistar rats dosed po BID, 6h apart, for 2 days at 0, 500, 1000, and 2000 mg/kg/day), the HD produced 2/20 deaths and 8/20 rats were sacrificed due to the severity of clinical signs (subdued behavior, rolling gait, prostration, labored breathing, hunched appearance, half closed eyes), but there were no increases in bone marrow MN-PCEs. The metabolite ucb-107092-1 was negative in the mouse lymphoma and rat micronucleus assays.

Two-year carcinogenicity studies of BRV were conducted in the mouse and rat (see statistical review dated 9/17/15 by Mohammad Atiar Rahman). In the mouse study (oral gavage and dietary administration of 0, 400, 550, and 700 mg/kg/day to CD1 mice for 2 years), there were no effects on survival or BW (non-D-R decreases in BW gain and final BW), but increased incidences (SS) of hepatocellular tumors were observed in males at the MD and HD and there was a (NS) trend for increased incidences of benign luteoma and Sertoli cell (ovary) tumors in treated females. In the sponsor's analysis, the incidence of hepatocellular adenoma or carcinoma showed a SS trend in males and the incidence of hepatocellular adenoma was SS greater than C at the MD and HD. The incidence of hepatocellular carcinoma was SS increased at the HD and also greater than C (no hepatocellular carcinomas) in MD and HD males, although within the historical control range. The FDA statistical reviewer found SS dose-response relationships in the incidences of hepatocellular adenoma, hepatocellular carcinoma, and combined hepatocellular adenoma and carcinoma in male mice. In female mice, the incidence of benign Sertoli cell tumor also showed a SS dose-response relationship. The pairwise comparisons showed SS increased incidences of hepatocellular adenoma and carcinoma at the HD and a SS increased combined incidence of hepatocellular adenoma and carcinoma at the MD and HD (see Exec-CAC minutes dated 9/4/15). The finding of enzyme inducing drug-related increases in liver tumors in mice is considered to be of limited clinical significance.

In the rat carcinogenicity study (oral (gavage and dietary) administration of 0, 150, 230, 450, or 700 mg/kg/day to Wistar rats for 2 years), there were no clear effects on survival or BW and, according to the sponsor, no T-R effects on the type, incidence, morphology, or time of appearance of tumors. However, in the sponsor's analysis, there was a SS trend for increased incidence of benign or malignant thymoma (an epithelial cell tumor) in females and a SS difference from C at the HD. In the FDA statistician's review, the analysis showed SS dose response relationships for the incidence of benign thymoma and combined incidences of benign and malignant thymoma in the thymus of female rats and the pairwise comparison showed SS increased incidences of benign thymoma and combined benign and malignant thymoma (same incidence as benign except one additional LD) in the thymus in HD females compared to C. The increased incidence of benign thymoma in female rats (22% at HD compared to 4% in C) was not considered toxicologically significant by the sponsor, who considered the C incidence unusually low (up to 9% in contemporaneous studies). In humans, thymoma is one of the most common neoplasms of the mediastinum and is often associated with disorders thought to have an autoimmune basis, such as myasthenia gravis (Murray et al, JNCI, 75:369-379, 1985). Non-neoplastic lesions in the liver, kidney, and thyroid were consistent with those observed in previous rat studies.

Reproductive and Developmental Toxicity

BRV was tested for effects on fertility and early embryonic development, embryofetal development, pre- and postnatal development, and in a postnatal development study in juvenile animals. In the rat fertility and early embryonic development study (oral gavage doses of 0, 100, 200, or 400 mg/kg/day (bid, 6h apart) administered to Wistar rats for 28 days (males) or 14 days (females) prior to throughout mating and until GD 6 (females) or at least 2 weeks post-mating (males)), there were only minor clinical signs of toxicity, slight effects on parental BW gain, and no apparent adverse effects on mating and fertility or on C-sectioning parameters (corpora lutea, implantations, and live embryos were actually D-D increased). Plasma TK data were not collected in this study. Because the HD was based on toxicity that was not dose-limiting in the 13-week study and did not produce the expected level of parental toxicity in this study, the adequacy of the assessment is questionable. Although no effects on reproductive organ weights or histopathology were noted in the general toxicity studies at somewhat higher doses, there is no indication that the testes were examined in a stage-aware manner. Although the results of the 4-week rat toxicity study (0, 100, 300, 1000, and 1500 mg/kg/day, administered BID by oral gavage 6 hr apart) in which the HD was not tolerated and some males were sacrificed moribund at the MHD, indicate that the HD selected for this study is close to the MTD, it would appear that there is an adequate dose gap between 400 and 1000 mg/kg/day (assuming linearity of exposure) to justify a recommendation that the study be repeated postmarketing in an attempt to reach the expected level of parental toxicity.

The same question about the adequacy of the HD applies to the rat embryofetal development study (oral (gavage) doses of 0, 150, 300, or 600 mg/kg/day administered BID, 6 hr apart, to pregnant Wistar rats on GDs 6-17) in which there was no significant maternal toxicity and no clear effects on development. Although the total incidences of major and minor fetal abnormalities were increased at the HD, the sponsor dismissed these findings due to their low incidence and sporadic occurrence. The maternal Cmax and AUC0-24h values at the MD and HD were 93 µg/mL and 1099 µg.h/mL (300 mg/kg/day) and 184 µg/mL and 1801 µg.h/mL (600 mg/kg/day), respectively. Again, an argument could be made based on the results of the 4-week rat toxicity study described above that the HD was close to MTD. In addition, there is a substantial exposure margin (32X) at the HD (see **Table III.3**). The results in this species suggest a low risk to human pregnancy; however, given what is known about species differences in sensitivity to developmental toxicants, it is recommended that an effort be made by the sponsor to reach a minimally maternally toxic dose in a repeat rat embryofetal development study conducted postmarketing.

In the rabbit embryofetal development study (oral gavage doses of 0, 30, 60, 120, or 240 mg/kg/day (BID, 6h apart) administered to pregnant NZW rabbits from G6-19), there was evidence of maternal toxicity and increased postimplantation loss and decreased fetal BW at the HD, indicating that dose selection was adequate. Increased incidences of fetal skeletal variations were also seen at all doses. The effect on variations appeared to be drug-related but was considered secondary to maternal toxicity by the sponsor. The specific skeletal variations increased by BRV (27 presacral vertebrae [PV], 13th rib) are common background findings in rabbits and the significance of their increased incidence is controversial. According to Stump et al. (Handbook of Developmental and Reproductive Toxicology, 3rd edition, CRC Press, Ron Hood ed., 2012, pp. 266-268), in an extensive discussion of these findings in rabbit embryofetal development studies, “In the absence of any other fetal effects (i.e., intrauterine growth retardation, major or minor malformations, fetal death, or functional impairment), an increased occurrence of 27 PV and/or 13th full rib is not sufficient evidence of developmental toxicity.” The maternal Cmax and AUC0-24h values at the MHD were 36 µg/mL and 198 µg.h/mL, respectively (10 and 3.5X human at MRD). The developmental effects of BRV in the rabbit appear similar to those observed with LEV, which is considered to present a low teratogenic risk to humans based on current epidemiological data (Hill et al., Expert Rev Neurother.10:943-959, 2010).

Because of the lack of exposure coverage in severely renally impaired patients, an iv rat embryofetal development study of the metabolite ucb-107092-1 was also conducted (0, 200, 500 or 1000 mg/kg/day administered to SD rats (not known why Wistar was not used) by continuous infusion from GDs 6 to 17). There were no effects on maternal survival, clinical signs, or BW and no T-R effects on development (post-implantation loss, live fetuses, fetal BW, or fetal morphology). Maternal exposure (AUC0-24h) at the HD was 810 µg.h/mL, which provides a safety margin of ~23X (see **Table III.6**).

The pre- and postnatal development study in rats (oral gavage doses of 0, 150, 300, or 600 mg/kg administered (BID, 6h apart) to Wistar rats from GD 7 through PND 20) used the same doses as the rat EFD, so the same criticism applies. There was no appreciable maternal toxicity or effects on litter parameters. A slight decrease in pup BW gain during lactation was seen at the HD in both sexes, which persisted into the postweaning period, and there was a (possibly related) delay in attainment of vaginal patency in HD females. There was some evidence of long-term neurobehavioral effects at the HD, i.e., decreased auditory startle reactivity, decreased locomotor activity, and impaired Biel maze learning and memory in animals test as adults. However, SS was only reached for overall motor activity in females on PND 61. Although maternal exposure to BRV at the HD (964µg.h/mL) was not as high as in the rat embryofetal development study, it provides a 17-fold safety margin (**Table III.3**). Based on the lack of maternal toxicity at the HD, dose selection for this study was again questionable, so the study may not have fully characterized the developmental effects of the drug. Therefore, it is recommended that the study be repeated if the repeat rat embryofetal development study shows that significantly higher doses can be administered to pregnant rats.

In the juvenile rat study (oral gavage dose of 0, 150, 300, or 600 mg/kg/day (BID, 10h apart) administered to Wistar rats from PND4 to 70), increased mortality (both sexes, primarily between PND11 and 21), transiently decreased BW gain, delayed male sexual maturation (attributed to the BW effect by the sponsor, which is plausible, given the effect sizes), short and long-term neurobehavioral changes (altered locomotor activity and auditory startle responsiveness), and impaired reproductive performance were seen at the HD and persistent decreases in brain weight (both sexes, absolute brain wts 10% below C on PND100) and size occurred at all doses (SS in MD and HD males on PND71). However, no microscopic alterations in brain were noted at either PND 22 or 71. The LD was associated with exposures of 120 µg.h/mL on PND21 in both sexes, and 164 µg.h/mL and 239 µg.h/mL on PND70 in males and females. The data suggest greater sensitivity to toxicity (mortality) and unique developmental effects of BRV in the juvenile rat compared to the adult.

The juvenile dog study (oral gavage doses of 0, 15, 30, or 100 mg/kg administered BID, 10 hr apart, to beagle dogs for 9 months beginning on PND 4), did not indicate any unique effects or increased sensitivity to effects seen in adults. The HD was based on bone findings (lower bone mineral content, bone area and bone mineral density in the femur, shorter femoral length and lower bone mineral content and density in the L3 to L5 lumbar vertebral column) seen in males given ≥50 mg/kg/day in the dose range-finding study in which the same doses were administered from PND4-31. In the definitive study, there were no apparent effects on body weight or other growth parameters (including bone, although some slight changes were observed), neurological testing, ECG, ophthalmology, or brain pathology. Clinical chemistry and histopathology changes consistent with the liver toxicity seen in general toxicity studies in adult dogs were observed at comparable exposures indicating an absence of age-related effects. At the MD, which was considered the NOAEL based on the liver effects, exposures (sexes combined) were 190, 63.5, and 78.1 µg.h/mL on PND 4, 31, or 276, respectively.

Excipients and Impurities

There are no novel excipients or excessive amounts of excipients that would present a toxicological concern in the tablet, oral solution, or injection formulations. With the exception of [redacted] the BRV [redacted] present as an [redacted] impurity, all other impurities are within the ICH specification limits. Because, in the course of the development, [redacted] was shown to be present at levels up to [redacted]%, while most batches used in nonclinical safety studies contained less than [redacted]%, the toxicity of [redacted] was assessed in general toxicity and genotoxicity studies.

In the 13-week rat oral toxicity study of [redacted] (reviewed under IND 70205 by Christopher Toscano, dated 1/31/14), effects were very similar to those seen with BRV in rats and included clinical signs, increased serum cholesterol and triglycerides, increased liver weights, centrilobular hepatocellular hypertrophy, lipofuscin pigment deposition, and male hyaline droplet nephropathy, all seen at the HD of 200mg/kg/day. The NOAEL was [redacted] mg/kg/day (AUC= [redacted] and [redacted] µg.h/mL in males and females, respectively), which is estimated to provide an [redacted] old margin over the predicted human exposure to [redacted] at the MRD of BRV, based on the similar TK profiles of [redacted] and BRV. The [redacted] ([redacted] was negative in the Ames and mouse lymphoma tests. These data support a specification limit for [redacted] of NMT [redacted]%.

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/s/

J EDWARD FISHER
11/20/2015

LOIS M FREED
12/02/2015