Population Pharmacokinetics of Brivaracetam in Patients With Partial Epilepsy

Brigitte Lacroix,* Philipp von Rosenstiel, and Maria Laura Sargentini-Maier***

***UCB Pharma SA, Braine-l'Alleud, Belgium; **UCB, Inc., Smyrna, Georgia, USA**

RATIONALE

- Brivaracetam (BRV) is a novel SV2A ligand currently under Phase III of development for epilepsy.
- BRV has a 10-fold higher affinity for SV2A than levetiracetam and also has inhibitory activity at neuronal voltage-dependent sodium channels.
- BRV is completely absorbed, is weakly bound to plasma proteins, has a plasma half-life of approximately 8 hours, is extensively metabolized through several non-CYP– and CYP-dependent pathways, and is eliminated renally (Sargentini-Maier *et al*, 2007).
- In this study, we collected sparse plasma samples for BRV determination in 2 double-blind, placebo-controlled, phase 2 trials of BRV as add-on treatment of partial onset seizures with the following aims:
  - to build a population pharmacokinetics (PK) model in adult patients with epilepsy;
  - to identify potential demographic covariates;
  - to identify potential drug-drug interaction covariates.

METHODS

- Adult patients with refractory partial onset seizures received adjunctive BRV b.i.d. for 7 to 10 weeks in 2 double-blind, placebo-controlled, parallel-group, dose-ranging studies. The dose levels were placebo, BRV 5, BRV 20, and BRV 50 mg/day (study N01114) and placebo, BRV 50, and BRV 150 mg/day (study N01193) in 2 intakes. There were approximately 50 patients per group.
- Two plasma samples per visit were obtained on 2 to 4 occasions between weeks 3 and 10.
- BRV concentration-time data were modeled by nonlinear mixed-effect modeling using NONMEM with first order conditional estimation method (FOCE).
- A 1-compartment model with first-order absorption and elimination was used, parameterized as a function of absorption rate constant (K_A), clearance (CL), and distribution volume (V).
- Body weight (BW) was included in the base model as an allometric factor of CL and V:

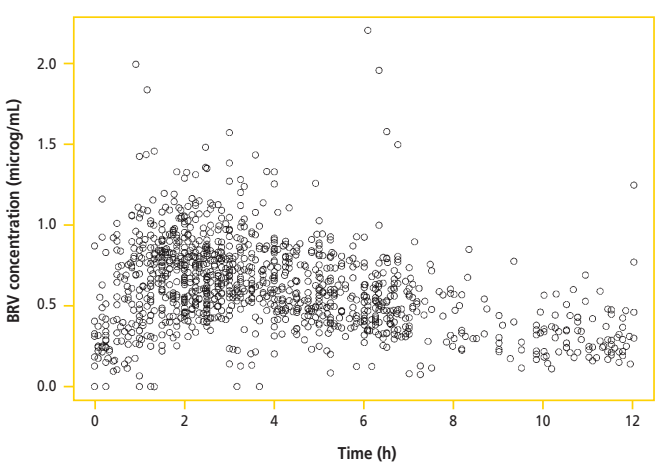
$$CL = \theta_1 \cdot \left(\frac{BW}{median\ BW}\right)^{0.75} \qquad V = \theta_2 \cdot \left(\frac{BW}{median\ BW}\right)^{1}$$

- Age, sex, race, concomitant antiepileptic drugs (AEDs), and creatinine clearance (CL_{cr}) were examined as possible covariates to explain interindividual variabilities (IIV) in PK parameters of BRV.
- Concomitant AED treatments were classified as neutral (no hepatic enzyme–inhibiting/inducing properties), *inducer* (hepatic inducer alone or in combination with neutral), *inhibitor* (hepatic inhibitor alone or in combination with neutral), or *mixed* (combination of inhibitor and inducer).

RESULTS

- 1150 concentration-time measurements and dosing records were available within 12 hours postdose in 254 patients (**Figure 1**).

Figure 1. BRV Concentration-Time Observations (µg/mL, normalized to 25 mg/intake)



- Patients were taking 1 or 2 concomitant AEDs (39 neutral, 98 inducer, 77 inhibitor, and 40 mixed).
- Demographic characteristics:
  - Males: 50%
  - Caucasians: 67% , Indian Asians 16%, Hispanics 11%, Blacks 3%, Others 3%
- Mean BW (range): 70 kg (24-129 kg)
- Mean age (range): 34 years (16-65 years)
- Mean CL_{cr} (range): 122 mL/min (39-253 mL/min)
- BRV plasma concentrations were adequately described by the 1-compartment model, without lag time. The residual variability was low (20.0%) (**Table 1**).
- The population mean for V was 36 L or 0.51 L/kg.
- IIVs are shown in **Table 1**.

Table 1. PK Parameters of BRV From the Final Model

Parameter	Estimate	% RSE*
K_A	0.902 h^{-1}	14.1
CL	3.63 L/h	2.6
Multiplicative Effect of Inducer on CL	1.42	3.7
V	35.9 L	7.0
IIV (K_A)†	78.2%	27.0
IIV (CL)	24.0%	19.0
IIV (V)	38.7%	35.3
Residual Variability	20.0%	12.7

* Relative standard error of parameter estimate.

† IIV on parameter.

- Race (**Figure 2**), age, sex, and CL_{cr} did not influence BRV PK.
- Concomitant intake of enzyme inducing AEDs was a significant covariate for CL (**Figure 3**), resulting in a reduction of IIV from 31% to 24%.
- The population mean of CL was estimated to be 61 mL/min (3.63 L/h) in absence of enzyme inducing AEDs and 86 mL/min (3.63×1.42 = 5.15 L/h) in presence of enzyme inducing AEDs.

Figure 2. BRV Clearance by Race

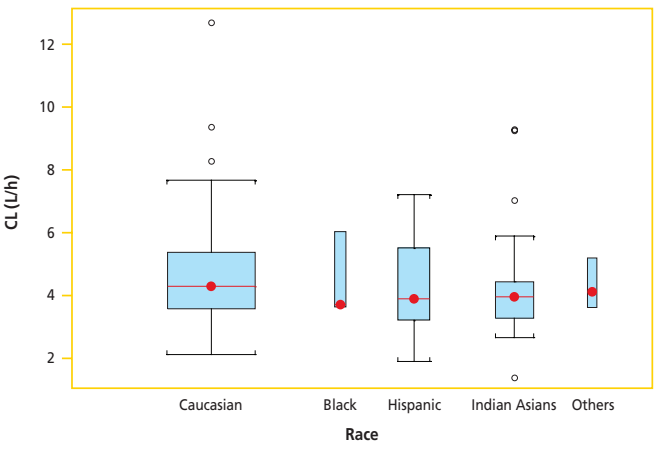
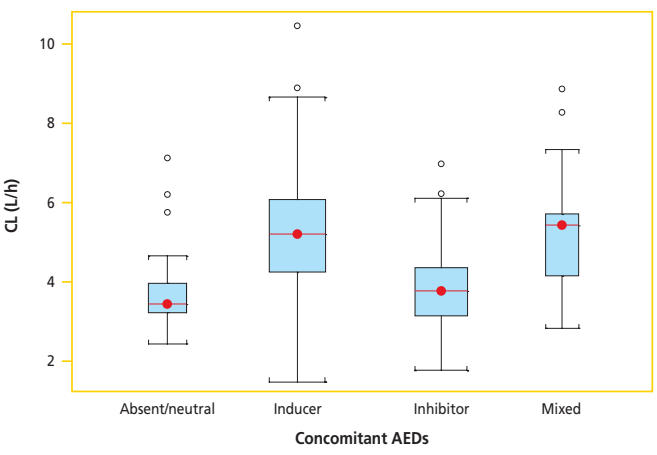


Figure 3. BRV Clearance by Concomitant AED Class



- Steady state C_{max}, C_{min}, and area under the curve ($AUC_{0\text{-}12\ h}$) were simulated for 1000 subjects with the default covariate values (BW 70 kg, no inducer AEDs) and for subjects taking inducer AEDs or with BW of 50 kg or 100 kg. The median values and 90% prediction intervals (PIs) are shown in **Table 2**, together with ratios to the reference population.
- Predicted exposures were similar to those determined in formal PK studies in healthy subjects (Rolan *et al*, 2004).
- BWs of 50 or 100 kg resulted in exposure changes of ± 25% compared with a 70-kg individual receiving the same dose of 25 mg b.i.d. (**Table 2**, **Figure 4**).

Table 2: Comparison of $AUC_{0\text{-}12\ h}$, C_{max}, and C_{min} Following BRV Dose*

Patient Profile	$AUC_{0\text{-}12\ h}$ (µg·h/mL)			C_{max} (µg/mL)			C_{min} (µg/mL)		
	Median	90% PI	Ratio	Median	90% PI	Ratio	Median	90% PI	Ratio
Typical†	6.90	4.7-10.4	1	0.81	0.54-1.18	1	0.34	0.13-0.66	1
Patient Taking Inducer AED	4.77	3.2-7.2	0.69	0.62	0.42-0.94	0.77	0.19	0.05-0.40	0.56
Patient With BW = 50 kg	8.71	6.0-13.1	1.26	1.04	0.70-1.52	1.28	0.41	0.13-0.80	1.21
Patient With BW = 100 kg	5.23	3.5-7.6	0.76	0.59	0.40-0.85	0.73	0.27	0.11-0.48	0.79

* BRV dose: 25 mg b.i.d.

† Typical patient: 70 kg, not taking an AED characterized as an inducer.

- Concomitant enzyme inducing AEDs were predicted to decrease the steady state AUC of BRV by approximately 30% (**Table 2**, **Figure 5**).
- An exposure-response modeling of phase 2 trial data showed that concomitant intake of enzyme inducing AEDs did not influence the effect of BRV on seizure frequency (Laveille, 2007).
- This finding suggests that the moderately lower BRV exposure in patients taking enzyme inducing AEDs is unlikely to be of clinical consequences.

Figure 4. The Effect of BW on BRV Concentration Over 24 Hours

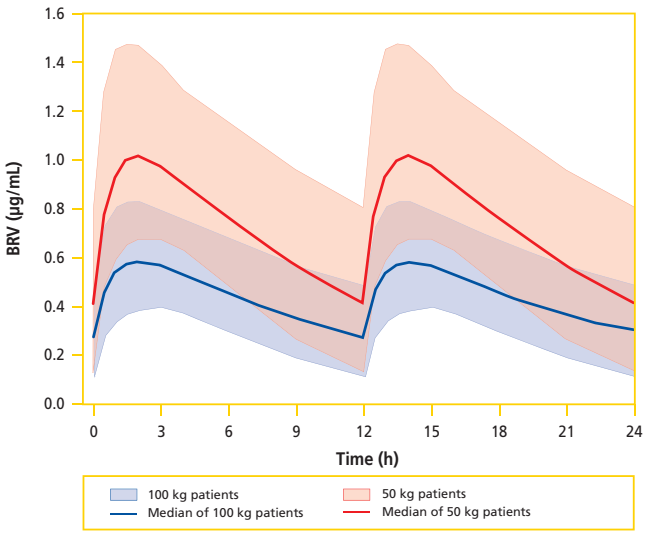
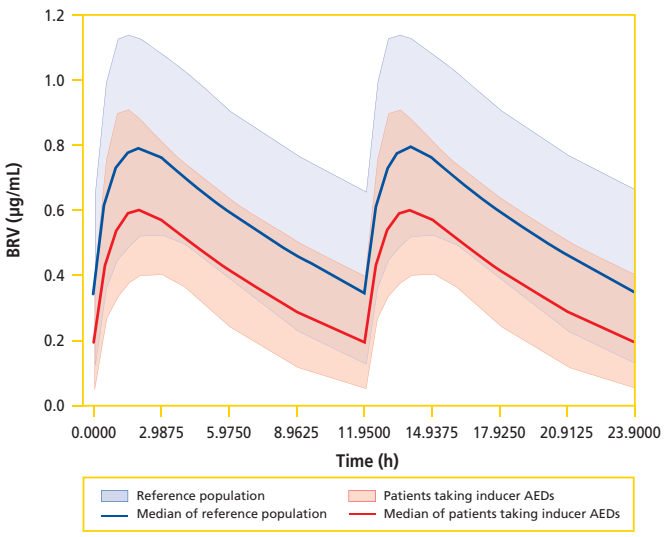


Figure 5. The Effect of Inducer AEDs on BRV Concentration Over 24 Hours



CONCLUSION

- Most of the IIV in BRV PK in an ethnically diverse population of patients was accounted for by differences in BW and concomitant use of enzyme inducing AEDs.
- Since the identified covariates had a moderate influence on PK parameters, BRV is deemed to have a highly predictable exposure in individual subjects.

References

- Laveille C, Lacroix B, Snoeck E, Sargentini-Maier ML, von Rosenstiel P, Stockis A. Dose- and exposure-response modeling of brivaracetam add-on treatment in patients with partial epilepsy [abstract]. Presented at: The American Epilepsy Society's 61st Annual Meeting; December 3, 2007; Philadelphia, Pa. Poster 3.217.
- Rolan P, Pigeolet E, Stockis A. ucb 34714: single and multiple rising dose safety, tolerability and pharmacokinetics in healthy subjects [abstract]. *Epilepsia*. 2004, **45**(Suppl 7): 314-315.
- Sargentini-Maier ML, Espie P, Coquette A, Stockis A. Pharmacokinetics and metabolism of 14C-brivaracetam, a novel SV2A ligand, in healthy subjects. *Drug Metab Dispos.* 2007 Oct 1; Epub ahead of print.