# Population pharmacokinetics of the new antiepileptic drug Brivaracetam

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## INTRODUCTION

Brivaracetam (BRV) ((2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl] butanamide) is a new drug under clinical development for the treatment of epilepsy and neuropathic pain. The aim of this analysis was to describe the population pharmacokinetic profile of BRV in healthy and epileptic adults, and to assess the effect of demographic covariates and concomitant use of AEDs.

## METHODS

### Study design

This was a retrospective population analysis based on 12 clinical studies conducted in young healthy, renally impaired, elderly volunteers and in epileptic patients populations.

**Table 1. Description of studies included in the analysis**

| Study # | Study type and duration | Number of subjects and population[a] | Daily doses (mg) | Samples/ subject/period | AEDs (max)[b] |
|---|---|---|---|---|---|
| **N01066** | MTD, SD | 27 HV | 10-1400 | 12-14 | - |
| **N01075** | Food interaction, SD | 8 HV | 150 | 14 | - |
| **N01068** | Mass balance, SD | 6 HV | 150 | 19 | - |
| **N01067** | MTD, MD (2w) | 36 HV | 200-800 | 32 | - |
| **N01080** | OC DDI (3w) | 24 HV | 400 | 18 | - |
| **N01081** | CBZ DDI (10 days) | 14 HV | 200-400 | 12 | 1 |
| **N01082** | PHT DDI (10 days) | 20 HV | 400 | 3 | 1 |
| **N01079** | POC 1, MD (3 days) | 24 HV | 400-800 | 11 | - |
| **N01118** | Elderly subjects, MD (10 days) | 15 EV | 200-400 | 26 | - |
| **N01109** | Renally impairment, SD | 18 (9 SRI+9 HV) | 200 | 15 | - |
| **N01069** | POC 2, SD | 19 EP | 10-80 | 9-12 | Any |
| **N01133** | CBZ DDI, MD (4w) | 9 EP | 100-400 | 5 | 1 |

[a] HV: young healthy subjects; EV: elderly healthy subjects; SRI: subjects with severe renal impairment; EP: subjects with epilepsy
[b] Maximum number of concomitant AEDs as specified in the protocol

### Data analysis

- Database consisted of demographic information and concentration-time records from single and repeated oral *b.i.d.* administration studies (3 days to 4 weeks) in young and elderly healthy subjects, subjects with severe renal impairment, and epileptic patients.
- In total, 4277 plasma concentration measurements from 203 subjects were used.
- Population PK analysis was performed by non-linear mixed effects modeling using NONMEM Version V, with double precision and first order conditional estimation (FOCE).
- The structural model was a 1-compartment, open model with first order absorption and elimination rates (Subroutine ADVAN 2 TRANS2), using the parameters:
  - KA: absorption rate constant
  - CL/F: apparent total body clearance
  - V/F: apparent volume of distribution
- Inter-individual variability (IIV) was modeled on each PK parameter
- Residual variability was modeled by a proportional error model
- Modeling was performed on log-transformed concentrations
- Investigated covariates :
  - Food on KA
  - Age, weight, BSA, gender, ethnicity, CLcr, concomitant AEDs, dose, duration of treatment, health status on CL/F
  - Age, weight, BSA, gender, ethnicity, dose and duration of treatment on V/F
- Simulations in different subject sub-populations were undertaken to evaluate the clinical significance of covariates significantly affecting the PK parameters

## RESULTS

### Subjects

- Population demographic characteristics are summarized in **Table 2**.
  - Subjects with epilepsy were chronically treated with 1-3 concomitant AEDs, classified as neutral, inducer or inhibitor

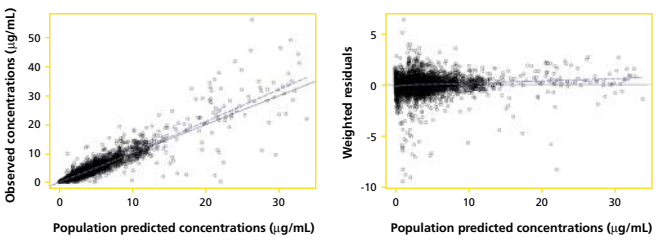
**Table 2. Demographic characteristics**

| Continuous Covariates (median [range]) | | Categorical Covariates (N) | |
|---|---|---|---|
| **Weight (kg)** | 73 (44.2-124) | Males/Females | 142/61 |
| **Age (years)** | 28.4 (18.3-78.8) | Healthy/epileptic | 175/28 |
| **BSA ($m^2$)** | 1.88 (1.37-2.43) | AEDs : none/neutral | 165/4 |
| **CLcr (mL/min)** | 104.1 (12.9-169.6) | AEDs: inducer | 23 |
| | | AEDs: inhibitor | 11 |

### Population pharmacokinetics

- Goodness of fit plots demonstrated the even distribution of predicted and observed values and the adequacy of the proportional model for residual variability (**Figure 1**).
- Covariates including CLcr, ethnicity, dose, duration of therapy and health status showed no significant effect on BRV pharmacokinetics.
- The influential covariates identified were age, weight, concomitant inducer AEDs and gender on CL/F; weight and gender on V/F; food intake on KA

**Figure 1: Goodness of fit plots of the final model**




- The final model was expressed as follows:
  - KA ($h^{-1}$) = 4.05 (fasted intake) or 0.979 (intake with food)
  - CL/F (L/h) = [3.84 + 0.0345 * (WT-73) - 0.0146 * (AGE-28.4) - 0.000856 * (AGE-28.4) * (WT-73)] * (1+AAEDC * 0.261) * (1 -0.182 * SEX)
    (WT=weight in kg; AGE= age in years; AAEDC=1 for concomitant inducer AEDs and 0 for all other concomitant AEDs categories; SEX=0 for male and 1 for female subjects)
  - V/F (L) = [40.1 + 0.345 * (WT-73)] * (1-0.128 * SEX)
    (WT= weight in kg; SEX=0 for male subjects and 1 for female subjects)
- The parameter estimates from the final PK model are listed in **Table 3**.
- Structural parameters of the population PK model (KA, CL/F, V/F) were estimated with good precision (<23% RSE); inter-individual variability for CL/F (15 %) and V/F (9 %) was low (**Table 3**)
- The inter-subject variability in CL/F and V/F was reduced from 23% and 14% in the base model, to 15% and 9% respectively when all the statistically significant covariates were incorporated in the final model.

**Table 3. PK parameter Estimates of the Final Model**

| Parameter | Estimate [95% CI] | Inter-Individual Variability % |
|---|---|---|
| **KA fasting conditions, $h^{-1}$**<br>**KA fed conditions, $h^{-1}$** | 4.05 [2.24-5.86]<br>0.979 [0.756-1.20] | 80.2 |
| **CL/F typical value, L/h**<br>• Weight factor<br>• Age factor<br>• Age/weight correlation factor<br>• Inducer AEDs factor<br>• Gender factor | 3.84 [3.72-3.96]<br>0.0345 [0.0238-0.0452]<br>-0.0146 [-0.0195- -0.00972]<br>-0.000856 [-0.00122- -0.000493]<br>0.261 [0.188-0.334]<br>-0.182 [-0.239- -0.125] | 15.1 |
| **V/F typical value, L**<br>• Weight factor<br>• Gender factor | 40.1 [38.9-41.3]<br>0.345 [0.246-0.444]<br>-0.128 [-0.174 - -0.0817] | 8.55 |
| **Residual variability (%CV)** | 25.9 | |

### Effect of Covariates

- Post-hoc estimates of KA under fasted and fed conditions are shown in **Figure 2**
- Post-hoc estimates of CL/F versus age (males not under concomitant AEDs), bodyweight (males not under concomitant AEDs), gender and concomitant inducer AEDs are shown in **Figure 3**
- Post-hoc estimates of V/F versus bodyweight (male subjects) and gender are shown in **Figure 4**

**Figure 2. Boxplot of post-hoc individual estimates of KA under fasted and fed conditions**

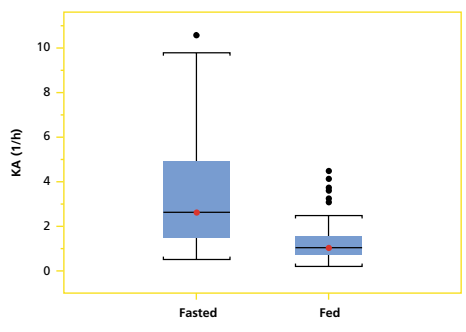



**Figure 3. Post-hoc individual estimates of CL/F *vs* age, bodyweight, gender and concomitant inducer AEDs**

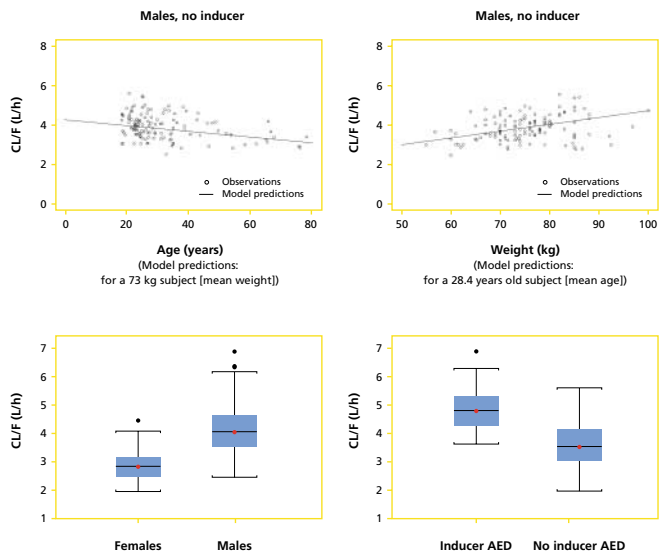
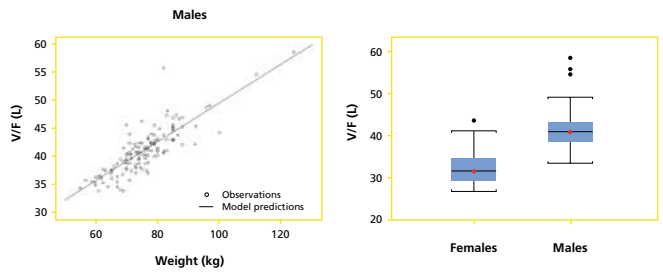



**Figure 4. Post-hoc estimates of V/F *vs* bodyweight and gender**




### Clinical relevance of statistically significant covariates

- $C_{max}$, $C_{min}$ and $AUC_T$ were simulated for extreme covariate values, with a 75 mg twice daily regimen, and compared to the reference population (**line 1, Table 4**).

**Table 4. Relative effect of extreme values of covariates on steady-state $C_{max}$, $C_{min}$ and $AUC_T$**

| Subjects (fed conditions ) sex-weight-age-AEDs | $C_{max}$ µg/mL | $C_{min}$ µg/mL | $AUC_T$ µg·h/mL | $C_{max}$ ratio | $C_{min}$ ratio | $AUC_T$ ratio |
|---|---|---|---|---|---|---|
| **Male-70 kg-30 years-no inducer AED** | 3.15 | 1.09 | 21.05 | - | - | - |
| **Male-70 kg-25 years-no inducer AED** | 3.14 | 1.06 | 20.98 | 0.997 | 0.972 | 0.997 |
| **Male-70 kg-75 years-no inducer AED** | 3.59 | 1.35 | 24.52 | 1.14 | 1.24 | 1.16 |
| **Male-50 kg-30 years-no inducer AED** | 3.90 | 1.33 | 26.00 | 1.24 | 1.22 | 1.24 |
| **Male-100 kg-30 years-no inducer AED** | 2.49 | 0.86 | 16.61 | 0.790 | 0.789 | 0.789 |
| **Male-70 kg-30 years-with inducer AED** | 2.65 | 0.76 | 16.70 | 0.841 | 0.697 | 0.793 |
| **Male-70 kg-30 years-no inducer AED*** | 3.59 | 0.985 | 21.34 | 1.14 | 0.904 | 1.01 |
| **Female-70 kg-30 years-no inducer AED** | 3.80 | 1.38 | 25.73 | 1.21 | 1.27 | 1.22 |

*Fasted conditions.

- Only weight, gender and concomitant inducer AEDs had a >20% effect on $C_{max}$ and/or $AUC_T$
- In the range of 50-100 kg bodyweight, $C_{max}$ and $AUC_T$ fluctuated by 43% around the mean value
- The limited effect of gender and concomitant inducer antiepileptic drugs (around 20%) are not considered as clinically significant, given the broad safety and tolerability profile of the compound.

## CONCLUSIONS

- A large part of the inter-individual variability in brivaracetam pharmacokinetics was accounted for by differences in weight, gender, age and concomitant enzyme-inducing AEDs.
- Since the identified covariates had a modest influence on PK parameters, brivaracetam is deemed to have a highly predictable exposure in individual subjects. No dose adjustment is required.
- The current model can be used to predict exposure in target populations in phase 2/3 studies.