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Evaluation of brivaracetam efficacy as monotherapy in adult patients with focal seizures

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ABSTRACT

Brivaracetam is a selective, high-affinity ligand for synaptic vesicle protein 2A, recently approved as adjunctive therapy in the treatment of focal (partial-onset) seizures in patients 16 years of age and older with epilepsy. The goal of the present analysis was to determine if the dose-response of brivaracetam as monotherapy would fall within the range associated with brivaracetam efficacy as adjunctive therapy.

An existing brivaracetam population pharmacokinetic model consisting of first-order absorption, single compartment distribution, and first-order elimination components was extended by estimating the clearance changes due to co-administration of 12 widely prescribed AEDs. Data for the population pharmacokinetic analysis originated from three Phase III add-on trials and two terminated Phase III monotherapy trials.

An existing population model of daily seizure rate versus brivaracetam daily average concentration was applied to the data from the three add-on trials. Simulations allowed the assessment of the combined impact of covariate effects on both the pharmacokinetics and the pharmacodynamics of brivaracetam, and indicated that in the absence of other AEDs, only marginal changes in the overall dose-response relationship would be expected. This suggests that brivaracetam can be used as monotherapy without dose modifications.

1. Introduction

Seventy million people have epilepsy, with 34–76 per 100,000 developing the condition every year (Brodie et al., 2012).

For many years a significant proportion of patients with epilepsy have been treated with polytherapy since initial monotherapy did not result in all patients being seizure free. The widespread use of polytherapy is sustained by the nature of developing new AEDs where newer agents are studied 'on top' of existing therapy to avoid the unethical situation of a patient with epilepsy being without effective therapy, and thus newer AEDs are usually approved as adjunctive therapy (St. Louis, 2009).

In recent years the advantages of AED monotherapy have been described; they include easier dosage optimization for a given single agent, lower treatment costs, simpler dosing schedules (expected to improve adherence), reduced likelihood of adverse events, decreased risk of drug–drug interactions and, possibly, lower medication costs (St Louis, 2009; Wechsler et al., 2014). If a patient is to be weaned onto monotherapy for a particular AED from a polytherapy situation, then it is critical to understand what dosage modifications may be needed for the intended monotherapy agent as the remaining polytherapy agents are withdrawn. Whether or not a separate monotherapy indication is warranted for AEDs has been discussed by Mintzer et al. (2015) who concluded that the regulatory requirement for separate monotherapy and adjunctive therapy indications in epilepsy were unnecessarily restrictive. The same authors recommended that regulatory agencies should approve AEDs for the treatment of specific seizure types or epilepsy syndromes, irrespective of concomitant drug use.

Brivaracetam (UCB34714) is a selective, high-affinity synaptic vesicle protein 2A (SV2A) ligand (Klitgaard et al., 2016) that was recently approved as adjunctive therapy in the treatment of focal (partial-onset) seizures in patients 16 years of age and older with epilepsy (French et al., 2010a; Van Paesschen et al., 2013; Biton et al., 2014; Ryvlin et al., 2014; Klein et al., 2015). Brivaracetam is rapidly and highly absorbed and peak plasma concentrations are generally reached within 1 h after dosing in fasting healthy volunteers (Stockis et al., 2016). The disposition of brivaracetam is characterized by linear pharmacokinetics over a large range of doses (10–600 mg) (Sargentini-Maier et al., 2007). Brivaracetam is eliminated primarily by metabolism, which is partially cytochrome P450 dependent. The three main metabolites are not

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Table 1
Summary of study designs.

Study number/clinicaltrials.gov identifier	Type	Patient number: total/ active population[1]	Treatment regimen
N01252/NCT00490035	Phase III add-on therapy	400/300	8 weeks baseline assessment, 12 weeks of 20, 50, or 100 mg/day BRV in twice daily (bid) administration without up-titration, 2 weeks down-titration
N01253/NCT00464269	Phase III add-on therapy	400/300	8 weeks baseline assessment, 12 weeks of 5, 20, or 50 mg/day BRV bid without up-titration, 1 week down-titration
N01358/NCT01261325	Phase III add-on therapy	720/480	8 weeks baseline assessment, 12 weeks of 100 or 200 mg/day BRV bid without up-titration, 4 weeks down-titration
N01276/NCT00698581	Phase III monotherapy	120/120	8 weeks baseline assessment, 1 week BRV add-on, 8 weeks baseline AED down-titration, 8 weeks BRV monotherapy, 6 weeks BRV down-titration and re-conversion to previous therapy. BRV dosed at 50 and 100 mg/day bid during conversion and monotherapy
N01306/NCT00699283	Phase III monotherapy	120/120	8 weeks baseline assessment, 1 week BRV add-on, 8 weeks baseline down-titration, 8 weeks BRV monotherapy, 6 weeks BRV down-titration and re-conversion to previous therapy. BRV dosed at 50 and 100 mg/day bid during conversion and monotherapy

Bid: twice daily, BRV: brivaracetam.
[1] Total population = brivaracetam + placebo as planned in protocol; active population = planned in protocol for randomization to brivaracetam.

pharmacologically active. Only a small fraction (up to 10%) of the dose is excreted as parent compound in the urine (Sargentini-Maier et al., 2008). The potential for interference with brivaracetam metabolism through inhibition of cytochrome P450 mediated metabolism is low (Stockis et al., 2014); this is supported by the results from a population pharmacokinetic analysis where it was found that co-administration of brivaracetam with carbamazepine, phenytoin, and phenobarbital decreased brivaracetam exposure by 26%, 21%, and 19% (Schoemaker et al., 2016).

The objective of the present analyses was to describe the population pharmacokinetics and pharmacodynamics (effect on seizure frequency) of brivaracetam in different adjunctive treatment settings and in monotherapy, and to use these results to guide the selection of brivaracetam doses in monotherapy. The data originated from three Phase III add-on trials and two terminated Phase III conversion to monotherapy trials in refractory adult patients with focal seizures. The current analysis included extending an existing brivaracetam population pharmacokinetic model (Schoemaker et al., 2016) so it could quantify the effect of AED co-administration on the clearance of brivaracetam. Subsequently, a previously published brivaracetam exposure-response model that described the adjunctive brivaracetam exposure-response in refractory adult patients with focal seizures (Schoemaker et al., 2016) was updated to incorporate the effects on response of co-administration of common AEDs. The updated exposure-response model was then used to quantify and simulate the effect of AED co-administration. The overall aim of the analyses was to provide dosing suggestions for brivaracetam use as monotherapy.

2. Materials and methods

The studies were conducted in accordance with the International Council on Harmonization notes for Guidance on Good Clinical Practice and the Declaration of Helsinki. The study protocols were approved by institutional review boards at all study sites, and written informed consent was obtained from all patients before enrolment.

2.1. Data

The brivaracetam plasma concentration and demographic data from three Phase III add-on trials N01252 (NCT00490035) (Ryvlin et al., 2014), N01253 (NCT00464269) (Biton et al., 2014) and N01358 (NCT01261325) (Klein et al., 2015) were combined with data from two Phase III conversion to monotherapy trials N01276 (NCT00698581) and N01306 (NCT00699283) (Mula, 2016).

The design of the three add-on-trials has been summarized by Ben-Menachem et al. (2016). The two conversion to monotherapy trials N01276 and N01306 were double-blind, therapeutic confirmatory, randomized, multi-center, parallel-group, historical-controlled conversion to monotherapy studies to evaluate the efficacy and safety of brivaracetam in patients (aged from 16 to 75 years) with focal seizures with or without secondary generalization. The primary objective of these studies was to evaluate the efficacy of brivaracetam in conversion to monotherapy at doses of 50 and 100 mg/day (administered in two equal doses per day) when compared to a historical control group (French et al., 2010b). The trial consisted of a baseline period of 8 weeks during which time patients remained on a stable dose of 1–2 AEDs. After successful completion of the baseline period patients were randomized to either brivaracetam 50 mg/day or brivaracetam 100 mg/day in a 3:1 ratio. After randomization, patients remained on their current dose of baseline AED in parallel to the randomized dose of brivaracetam for one week to assure that brivaracetam had reached steady-state before starting tapering of the baseline AED. The subsequent 16-week evaluation period consisted of 8 weeks baseline AED down-titration followed by 8 weeks brivaracetam monotherapy. Finally, a 6-week reconversion period or inclusion into a long-term follow-up study was foreseen. Criteria were set to allow early discontinuation. Two blood samples with at least a 15-min interval were to be collected at two visits.

A summary of the design of the five studies included in the present analyses is given in Table 1.

The population pharmacokinetic data set contained 4928 brivaracetam concentrations from 1101 patients; among these, 453 concentrations in 141 patients came from the two conversion to monotherapy trials, of which 122 concentrations came from 64 patients achieving monotherapy. Focal seizure count data were available from 1549 patients in the three add-on trials (including 318 on placebo) who contributed 217,524 daily seizure counts.

2.2. Software and hardware

The analyses were performed using NONMEM Version 7.2.0 (Beal et al., 1989–2009) software, supplemented with the PsN toolkit (Lindbom et al., 2005), and were further processed using 64 bit R Version 3.1.2 software (R Development Core Team, 2014). Pharmacokinetic data were analyzed using First Order Conditional Estimation with the Interaction option; seizure count data were analyzed using the Laplacian estimation method. Simulations were performed using R and NONMEM.

2.3. Population pharmacokinetic model

The previously published population pharmacokinetic model

(Schoemaker et al., 2016) found that brivaracetam was well described using a one-compartment model with first-order absorption. Clearance (CL) and volume (V) were influenced by body weight using an allometric relationship, and CL was influenced by concomitant hepatic enzyme-inducing AEDs. This model was applied to the current data set, and the following concomitant drugs were tested for their potential effect on CL:

- CBZ carbamazepine
- PHT phenytoin
- PB phenobarbital or primidone
- VPA valproate
- LTG lamotrigine
- LEV levetiracetam
- OXC oxcarbazepine
- TPM topiramate
- BENZC benzodiazepines chronically prescribed for the indication 'epilepsy'
- LCM lacosamide
- PGN pregabalin
- ZNS zonisamide

All drug effects on CL were simultaneously estimated, and no further covariates were assessed.

The updated brivaracetam population pharmacokinetic model with concomitant drug effects was used to generate daily average concentration (C_{av}) estimates for use in the exposure-response modeling. The generated daily C_{av} estimates reflected a given patient's actual dosing history, and as such could change from day to day. For patients with no brivaracetam concentrations (n = 130), C_{av} was obtained using the typical population pharmacokinetic model parameters and those patients' specific covariate influences.

2.4. Concentration-daily seizure rate frequency model

The present exposure-response analysis was restricted to the Phase III add-on trials only. If effects were found of concomitant AEDs on the concentration-effect relationship of brivaracetam, monotherapy efficacy predictions can be obtained by removing these effects from the model. The current model assumes constant concomitant AED therapy, and temporal changes in brivaracetam concentrations is the only factor to describe temporal changes in seizure frequencies. Applying the model to the monotherapy study data would require concentration-effect models and concentration-time profiles of the different AEDs, and models to describe the combined effect of brivaracetam and these AEDs. These models and concentration-time profiles were not available, and would require a far more complex model than the data could support. Therefore daily seizure counts for the monotherapy trials were not included in the analysis.

The C_{av}-daily seizure count relationship was estimated based on the model structure described previously (Schoemaker et al., 2016). Since daily C_{av} was used as a measure for exposure, this allowed an independent assessment of the concomitant AED effects on pharmacokinetics (by changing the daily exposure to brivaracetam), as well as on the exposure-response relationship (by changing the efficacy of brivaracetam in the presence of concomitant AEDs).

Count models were used to describe daily seizures where seizure rates were a function of both placebo and drug, and the occurrence of seizures on the previous day (a 'Markovian aspect'). During model development it became apparent that a fraction of the patients were following a daily seizure pattern very similar to those receiving placebo, while another fraction of patients was associated with much larger and dose-dependent decreases from baseline. This concept was implemented by assuming two populations, the first where a concentration-dependent decrease in seizure frequency was added onto the placebo distribution, and the second with a placebo-like response, governed only by the placebo model-parameter. NONMEM estimated the probability for a patient to end up in one of the two populations (P1). The first population was denoted as the 'mixture-model responder population' and the second as the 'mixture-model placebo-like population' (Schoemaker et al., 2016).

A visual predictive check (VPC, Karlsson and Holford, 2008) was performed to investigate if model simulations of daily seizure counts corresponded to observed trial outcomes for the entire population, split by administered dose. Seizure counts were simulated 500 times using the trial structure, dose and covariate data from the patients in the data set.

The potential influence on the pharmacodynamic effect of brivaracetam of the individual concomitant AEDs, was investigated on the EC_{50} of the concentration-effect relationship, and on the parameter describing the probability of being in the 'mixture-model responder population'. For benzodiazepines, only those chronically administered for epilepsy treatment were investigated, since these drugs are frequently prescribed as rescue medication, and may therefore be confounded with cases of potentially high seizure frequency.

2.5. Monotherapy dose simulations

The obtained pharmacokinetic and exposure-response (C_{av}-daily seizure count) models were used to simulate the effects on pharmacokinetics and on change in seizure counts under the full concomitant AED therapy profile, and under the situation corresponding to monotherapy where the estimated AED effects were removed from the model.

For the pharmacokinetic simulations, all patients included in the analysis were taken with their concomitant AED covariates. These were combined with fixed weight steps of 10 kg, ranging from 40 to 130 kg, and pharmacokinetic parameters were subsequently sampled from the distributions described by the NONMEM parameter estimates for the final pharmacokinetic model. C_{av} was calculated for a 100 mg/day steady-state dose, both by assuming the presence of the full concomitant AED profile, and by removing the AED effects, corresponding to the monotherapy situation.

For the daily seizure count simulations, all patients in the analysis were taken with their concomitant AED and baseline weight covariates. Pharmacokinetic parameters were subsequently sampled from the distributions described by the NONMEM parameter estimates for the final pharmacokinetic model, and C_{av} was calculated for steady-state doses of 0, 25, 50, 100, 150 and 200 mg/day, both by assuming the presence of the full concomitant AED profile, and by removing the AED effects (corresponding to the monotherapy situation). These C_{av} values were then combined with a trial structure consisting of 8 weeks of daily seizure count assessments at baseline followed by 12 weeks' treatment, and the simulated C_{av} values were assumed to drive the effect, again both by assuming the presence of the full concomitant AED profile, and by removing the AED effects on the pharmacodynamics, corresponding to the monotherapy situation. Mean seizure frequencies were calculated for each simulated patient and dose combination for the entire baseline and treatment periods, for both adjunctive therapy and for monotherapy.

3. Results and discussion

3.1. Population pharmacokinetic model

Graphical analyses of output from the brivaracetam population pharmacokinetic model confirmed that the one-compartment model with first-order absorption was appropriate for describing the available brivaracetam pharmacokinetic data.

Estimating the influence on CL of AED co-administration using all AEDs simultaneously, resulted in a significant decrease in the NONMEM objective function (OFV) of 371.56 points ($p < 0.0001$), indicating the presence of pronounced AED co-administration effects.

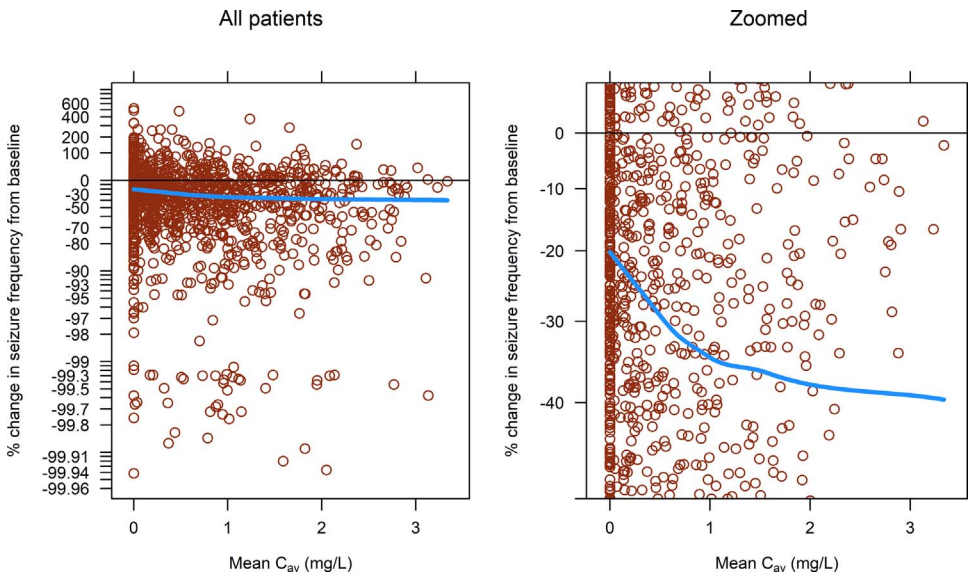

Fig. 1. Seizure frequency change from baseline versus mean individual brivaracetam daily average plasma concentration (C_{av}) during treatment. Left: all patients; right: y-axis zoomed in. Black horizontal line: no change from baseline; blue line: LOESS smoothing.

The largest influence on brivaracetam CL was estimated for co-administration of the enzyme inducers carbamazepine, phenytoin, and phenobarbital or primidone, with percentage change in exposure with 90% confidence intervals of −27.1% (−29.4%/−24.7%), −23.8% (−27.7%/−19.6%), and −20.1% (−24.0%/−16.0%) respectively. These values are very similar to what has been published previously (Schoemaker et al., 2016). Since enzyme-inducing AED co-administration is widespread (50.5% of the population in this data set), monotherapy was estimated to lead to a 22.6% higher population C_{av} for a 70 kg patient when compared with the add-on trial results.

The fold changes in C_{av} associated with AED co-administration estimated for all AED and drug class covariates were summarized in a forest plot. As the forest plot was very similar to the one previously generated (Schoemaker et al., 2016), it is only provided in the online Supplement as Fig. S1. The relatively low increase in median C_{av} for a patient receiving brivaracetam monotherapy compared with the add-on trial results is entirely in keeping with what would be expected given that only 20% of brivaracetam is metabolized via the cytochrome P450 enzyme system (Sargentini-Maier et al., 2008).

3.2. Concentration-daily seizure rate frequency model

Inspection of the graphs generated to guide the choice for the shape of the relationship between C_{av} and seizure rate (Fig. 1) revealed both the large variability in response between patients (left panel) and the potential shape of the exposure-response curve using a locally weighted scatterplot smoothing (LOESS) through the data (right panel). An E_{max}-type relationship seemed most appropriate.

Development of the concentration-daily seizure rate model focused on detecting AED co-administration covariate effects, and started with the structural model without covariates (Schoemaker et al., 2016), which had utilized an E_{max}-type relationship for the 'mixture-model responder population'. When the potential effects of the background AED and log baseline seizure frequency on the probability of being in the 'mixture-model responder population' were estimated they revealed that log baseline seizure frequency, and levetiracetam and valproate co-administration all affected the probability of being in the 'mixture-model responder population'. None of the AED covariates was found to influence EC_{50} (estimated to be 0.548 mg/L), the population-typical average daily concentration associated with reaching 50% of the maximum effect. The parameter estimates of all parameters in the final concentration-daily seizure rate model were very similar to the ones previously generated (Schoemaker et al., 2016), and are therefore only provided in the online Supplement as Table S1.

The probabilities for being in the 'mixture-model responder population' as a function of log baseline seizure frequency were estimated to be 52.2% at 1 seizure/week, 27.1% at 0.32 seizures/day (median baseline seizure frequency), and 0.8% at 6 seizures/day. Levetiracetam co-administration was estimated to reduce the probability of being in the 'mixture-model responder population' at median baseline seizure frequency from 27.1% to 4.2%. Since levetiracetam and brivaracetam have a similar mode of action, the presence of levetiracetam likely precludes brivaracetam from inducing additional seizure reduction effects. Co-administration with valproate was associated with an estimated increase in the probability for being in the 'mixture-model responder population' from 27.1% to 39.1%. Whether this increase is due to a deviating sub-population of patients receiving valproate treatment, or due to an increased sensitivity to brivaracetam with the co-administration of valproate, is unclear.

Model evaluation for the final concentration-daily seizure rate count model was done using VPCs and is provided in the online Supplement. VPCs for the derived parameters of median percent change from baseline in seizure frequency, and fraction of ≥50% responders defined as patients experiencing at least 50% decrease from baseline in seizure frequency (online Supplement Fig. S2), and a VPC of seizure frequency change over time for the different doses (online Supplement Fig. S3) illustrated that the final model was able to simulate the various study outcome measures.

3.3. Monotherapy dose simulations

The 5th, 50th (median) and 95th percentiles of simulated brivaracetam C_{av} values for 100 mg/day brivaracetam adjunctive therapy and monotherapy were plotted against weight in Fig. 2, to depict the range of outcomes for the different weight classes Additionally, this figure illustrates the C_{av} estimates obtained for the individual patients receiving adjunctive therapy, and those receiving monotherapy. These results illustrate that observed individual patient values fall within the simulated concentration bands.

The median simulated C_{av} for a 70 kg patient increases by 22.6% for monotherapy compared with the concomitant AED therapy value, primarily due to the absence in the monotherapy population of enzyme-inducing AEDs.

The simulated brivaracetam effect on percent change in daily seizure rate by brivaracetam daily dose with and without full concomitant AED therapy is presented in Fig. 3, where the full concomitant AED therapy results (in gray) are provided as a reference behind the monotherapy results (in blue). The effect of removing AED co-

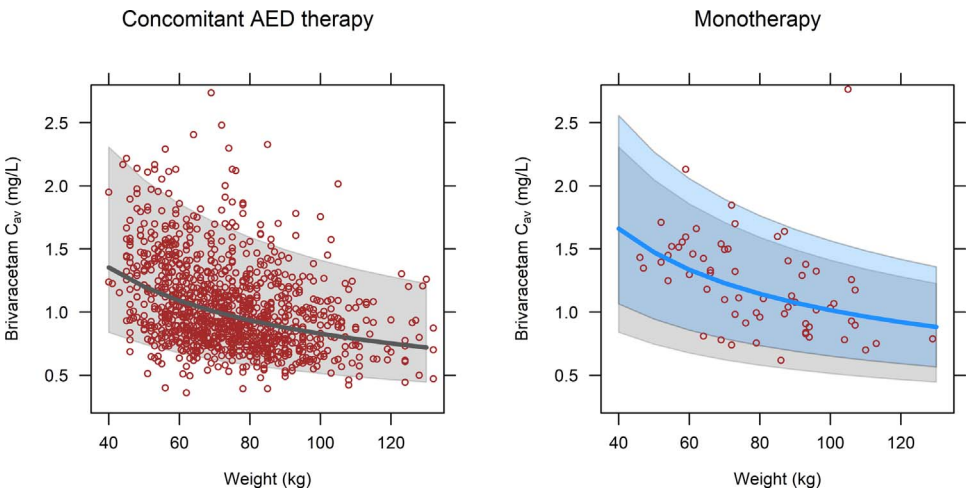

Fig. 2. Simulated daily average plasma concentration (C_{av}) for 100 mg/day brivaracetam add-on therapy (left) and monotherapy (right). Gray shaded area: 90% of simulated patients with observed concomitant AED profile. Blue shaded area (right): 90% of patients without concomitant AEDs. Solid lines: median simulated value. Brown markers are predicted patient C_{av} values using the individual estimates for brivaracetam add-on therapy patients (left) and monotherapy patients (right).

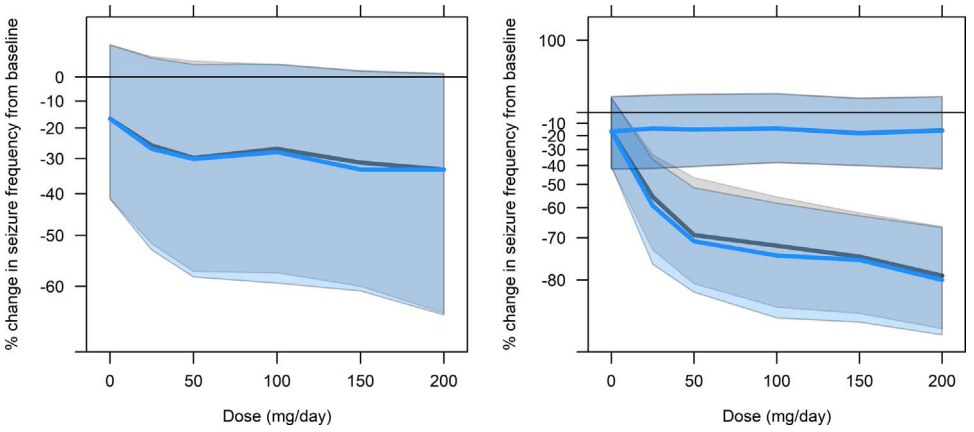

Fig. 3. Simulated median (interquartile range) brivaracetam effect on percent change from baseline in seizure frequency, by brivaracetam daily dose. The results for monotherapy are provided in blue with add-on therapy as an underlay in gray. The left panel shows the overall response of the simulated population, and the right panel shows the results split by mixture-model population. In the right panel, the horizontal lines and areas correspond to the mixture-model placebo-like population, and the lines and areas showing a clear dose-response correspond to the mixture-model responder population.

administration covariates is negligible because the reduction in Cav due to the absence of hepatic-enzyme inducing AEDs still leaves the responder patients close to their maximum effect. While the results across the entire population seem to suggest that maximal effects are reached at 50 mg/day, the results for the responder population show that doses up to 150–200 mg/day are still associated with an increased change from baseline.

4. Conclusion

Brivaracetam exposure as monotherapy was estimated from adjunctive therapy clinical trials and conversion to monotherapy trials. Strong enzyme inducers reduced brivaracetam exposure, but did not have a clinically relevant effect on predicted efficacy at the recommended dose range of 50–200 mg/day across the investigated population. Brivaracetam monotherapy was predicted to be equally effective compared with adjunctive therapy with the investigated AEDs. When converting from combination therapy to monotherapy, or when initiating brivaracetam monotherapy, the same recommended starting dose for add-on therapy can be used.

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Declaration of interest

Armel Stockis and Joseph D'Souza are employees of UCB Pharma; Rik Schoemaker and Janet R. Wade are engaged in contract research for UCB Pharma.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eplepsyres.2017.09.014.

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