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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