The Preclinical Discovery and Development Of Brivaracetam For The Treatment Of Focal Epilepsy

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ABSTRACT

Introduction: Brivaracetam (BRV) is a new AED currently licensed for the adjunctive treatment of adult patients with focal epilepsies. It is a ligand of the ubiquitous synaptic vesicle glycoprotein 2A (SV2A).

Areas covered: This paper covers the preclinical and subsequent clinical development of BRV focusing on the discovery of the SV2A protein as the main target for levetiracetam

(LEV) and the main similarities and differences between LEV and BRV in terms of pharmacodynamic and pharmacokinetic properties. Phase II and Phase III studies are also presented and data from post-marketing phase IV studies are discussed.

Expert opinion: The preclinical development of BRV is quite unique and has raised several doubts on current methodologies adopted for AED development, reinforcing the need for new approaches. The preclinical and clinical profile suggest that BRV is potentially an ideal compound in the emergency setting given the rapid onset of action associated with being water soluble and, therefore, available in intravenous formulation. In addition, data from Phase III studies have already suggested that BRV may be effective not only in focal epilepsies but also in generalised syndromes. Further data from special populations such as children and women of child bearing age are urgently needed.

Key words: Brivaracetam, Levetiracetam, epilepsy, antiepileptic drugs, SV2A

Article Highlights:

- The discovery of the SV2A protein and the subsequent development of BRV have further confirmed the need for new and innovative preclinical models of epilepsy
- The preclinical and clinical profile of BRV suggest that it is probably the ideal AED to be used in an emergency setting but data on treatment of status epilepticus are currently just anecdotal
- Emerging data are suggesting that the overnight conversion from LEV to BRV is not only safe and well tolerated but may provide further benefits in terms of tolerability especially in patients with paradoxical sedation from LEV or behavioural adverse events.
- Data from preclinical and Phase III and IV studies are also suggesting that BRV may be effective also in primary generalised syndromes

- Data from special populations such as children and women of child baring age are urgently needed

1. INTRODUCTION

Epilepsy is one of the most common neurological conditions with incidence rates, in high-income countries, ranging between 40 and 70/100,000 persons/year [1]. Over 50 million people worldwide suffer from epilepsy with an overall health burden accounting for 0.5% of the total burden of diseases [2]. About two thirds of people with epilepsy become seizure free on current treatments but despite the introduction of several antiepileptic drugs (AEDs), one third of patients are still uncontrolled [3]. It is, therefore, evident that continuous research is needed in order to have new compounds.

Brivaracetam ((2S)-2-[(4R)-2-oxo-4-propylpyrrolidinyl] butanamide; UCB 34714; BRV), is a new AED currently licensed for the adjunctive treatment of focal epilepsies [4] (**Figure 1**). It is a ligand of the ubiquitous synaptic vesicle glycoprotein 2A (SV2A) [5]. The SV2 protein is a prototype protein present in the synaptic vesicles of neurons and endocrine cells [6,7], possess a 12-transmembrane-spanning structure and consists of three isoforms, SV2A, SV2B and SV2C. Among SV2 isoforms, SV2A is highly expressed in all brain areas including the cerebral cortex, hippocampus and cerebellum [6,8] but it is also expressed by neuroendocrine cells and neuromuscular junctions [9] and previous studies have suggested that SV2A regulates synaptic vesicle exocytosis and presynaptic neurotransmitter release [10,11].

The discovery and preclinical development of BRV is strictly interlinked with that of the SV2A protein and the discovery of levetiracetam (LEV) as the first AED showing to bind the SV2A protein. In preclinical studies, LEV displayed protective effects against audiogenic and kindled seizures, 6-Hz electrical seizures [12] and spike-wave discharges in genetic models of absence epilepsy [13,14] but showed not to be effective in standard animal models used for

AED discovery, namely the maximal electroshock (MES) and pentylenetetrazol (PTZ) tests [15]. This preclinical profile of LEV correlated well with the broad-spectrum clinical efficacy shown by clinical studies [16] but the atypical antiepileptic properties suggested that LEV possessed a novel mechanism of action different from that of conventional AEDs [15]. Binding studies subsequently revealed a reversible, saturable, and stereoselective binding to the SV2A protein [11], resulting in a reduced exocytosis of synaptic vesicles and an increased induction of rate depression at excitatory synapses during epileptic activity [17]. Since then, research focused on the discovery of new agents targeting the SV2A protein that ultimately led to the development of BRV.

This is a narrative review aimed at providing a comprehensive overview of the preclinical discovery and subsequent clinical development of BRV. References were identified by searches of Medline/PubMed until May 2017 using the key word “Brivaracetam”. Only papers published in peer-reviewed journals were included. Additional publications were hand searched if relevant to the discussion.

2. DISCOVERY STRATEGY AND PRECLINICAL DEVELOPMENT

A number of animal studies suggested that the SV2A protein was a potentially good target for seizure control. SV2A knockout mice fail to grow and develop spontaneous seizures leading to death within 2-3 weeks after birth while heterozygous SV2A knockout mice do not show spontaneous seizures, but rather pro-epileptic traits such as enhanced susceptibility to the proconvulsant effect of pilocarpine and kainate, a decreased 6-Hz seizure threshold and an enhanced rate of corneal kindling [18,19]. Studies of cultured neurons from SV2A knockout mice demonstrate a reduced postsynaptic response due to a lower initial vesicle release probability and a decrease in neurotransmitters release during stimulation [20,21]. Furthermore, expressional and functional changes in SV2A are found in animal

models of epileptogenesis [22,23] and in brain tissue obtained from patients with epilepsy [24–26] suggesting that decreased SV2A expression/functioning contributes to the progression of epilepsy [8]. SV2A binding strongly correlates with the antiepileptic efficacy in different preclinical models of epilepsy like the audiogenic seizure-prone mice [11,19] and decreased levels of SV2A appear to be involved in the mechanisms underlying drug-resistant epilepsy [8]. All these evidence taken together strongly suggest that the SV2A protein has a clear involvement in the pathogenesis of epilepsy and can, therefore, play a role in its treatment; however, detailed functions and mechanisms (e.g. neurotransmitter specificity) of SV2A is still unclear [8].

As already mentioned, the discovery of the SV2A as the main molecular target of LEV and the subsequent evidence suggesting a potential role in the treatment of epilepsy, have led to the design of a major drug discovery program with the purpose of optimizing the therapeutic benefit of the SV2A mechanism. The goal was to identify selective and more potent SV2A ligands providing a more complete seizure suppression than LEV [27]. Approximately 12,000 compounds were screened in vitro for SV2A binding affinity; 1,200 were further screened in vivo for seizure protection in audiogenic seizure-susceptible mice, and about 30 compounds were selected and largely characterized in different animal models of seizures and epilepsy [27]. These studies indicated that substitution on the 4-position of the pyrrolidine ring of LEV could enhance binding affinity. In this systematic investigation of substitutions at this site, various small hydrophobic groups were found to confer increased affinity to SV2A as compared to LEV and an enhanced activity in the audiogenic seizure test [27]. Among the analogues with enhanced binding affinity, BRV, a 2-pyrrolidone derivative structurally related to LEV with a molecular weight of 212, was selected as a candidate for drug development [27].

BRV is a highly selective and reversible ligand of the SV2A with an affinity and ability to inhibit synaptic transmission and vesicle release that is superior to LEV. Furthermore, results from SV2A knockout mice show that up to the concentration of 600 nM (the highest concentration tested), [3H]BRV is highly selective, labelling the SV2A protein only [28,29]. The in vitro binding of [3H]BRV in rat and human brain shows that, similarly to LEV, BRV displays identical affinity for rat and human SV2A (Kd of 62 nM) [30,31]; however, BRV shows an about 15-30 fold higher affinity than LEV for the presynaptically located SV2A that actually corresponds to a higher efficacy in the animal models of epilepsy and in studies with human brain slices than the post-synaptic SV2A [30,32].

At therapeutically relevant doses, BRV occupies 80% to >90% of SV2A in the brain [33]. Ex vivo binding experiments in the mouse brain shows that BRV reaches maximal SV2A occupancy within 5 to 15 min after administration, a time range that also displays maximal protection against seizures [34]. Studies in vitro in human cells revealed that BRV has a higher lipophilicity (LogD 1.04) than LEV (LogD -0.64) resulting in a more rapid brain penetration that is paralleled by a faster onset of seizure protection in an audiogenic mouse model of seizures [35,36]. A seven-fold difference was observed in brain entry speed, with BRV having a predicted drug entry half-time of only 3 min against the almost 23 min of LEV [35]. Likewise, ex vivo binding studies in the same audiogenic mouse model showed maximal SV2A occupancy and maximal activity within 5–15 min following intraperitoneal (i.p.) dosing with BRV, compared to 30–60 min for LEV [30]. Therefore, this more rapid entry into the brain of BRV correlates with a shorter latency of action that may be clinically relevant in the treatment of emergencies such as status epilepticus or seizures clusters [37,38].

Rat hippocampal slice studies comparing BRV and LEV using high-frequency neuronal stimulation, demonstrate that BRV augments synaptic depression and thereby decreases synaptic transmission at 100-fold lower concentrations than LEV. Additionally, BRV is more effective than LEV in reducing synaptic vesicle mobilization [39].

BRV has shown a low therapeutic index (ratio between the TD50 of motor impairment on the rotarod test in fully kindled animals and the ED50 for seizure protection against generalized motor seizures the same animals) but still more favourable than LEV (46 and 148, respectively). In the rotarod test in amygdala-kindled rats BRV has a higher therapeutic index than LEV (4 and 2, respectively). Nevertheless, it was noticeably higher than that observed for classical and other newer AEDs (therapeutic indexes ranging from 2 to 21) [32].

In comparison to LEV, BRV lacks any direct activity on inhibitory and excitatory receptors including AMPA, glycine, and GABA-A with the exception of a weak inhibition of the NMDA receptor mediated currents at very high concentrations, which will likely be not relevant at therapeutic doses [40] (Table 1). Although BRV shares with LEV an ability to oppose the action of negative modulators on the two main inhibitory receptors, namely GABA-A and glycine, this finding has been thought not to be clinical relevant but further studies are needed [40]. Studies exploring other potential mechanisms demonstrate that BRV has no effect on high and low voltage–activated calcium channels [28] or on voltage-gated potassium currents in isolated rat hippocampal neurons at therapeutically relevant concentrations. Some authors suggest that BRV, as opposed to LEV, inhibits voltage-dependent sodium channels in rats' primary cortical neurons in culture [41] but other studies do not replicate these findings and demonstrate a substantial lack of effect of BRV in reducing the neuronal firing mediated by a blockade of voltage-gated sodium channels [42]. In particular, some studies investigate the effect of BRV on voltage-gated sodium currents in comparison to carbamazepine (CBZ) in different cell systems (i.e. neuroblastoma cells, rat

cultured cortical neurons, CA1 neurons from mouse hippocampal slice) in order to explore the potential efficacy of BRV in reducing sustained repetitive firing [42]. These studies seem to suggest that BRV inhibits voltage-gated sodium currents in mouse neuroblastoma cells and in rats' primary cortical cultures, but not in CA1 pyramidal neurons of adult mice and does not reduce sustained repetitive firing induced in native or cultured neurons. These findings suggest that none of the antiepileptic properties of BRV are mediated by a CBZ-like blockade of voltage-gated sodium channels [42]. This is anyway in agreement with the protective effects of BRV against MES occurring only at supratherapeutic doses [28].

In vitro studies show that BRV possesses higher potency and efficacy than LEV against epileptiform responses in two different in vitro rat hippocampal slice models of epilepsy in a dose range which is relevant for its clinical efficacy [32,43]. The increased affinity of BRV for the SV2A as compared to LEV well correlates with the markedly higher increased potency for seizure protection observed in different in vivo models of epilepsy [32]. The efficacy of BRV has been studied in both partial and generalized seizure models including audiogenic mice, Genetic Absence Epilepsy Rats from Strasbourg (GAERS), amygdala and corneal kindling models [27,32] and in a rat model of post-hypoxic myoclonus [44]. In these models, BRV consistently demonstrates a more potent and complete seizure suppression than LEV [32,45]. In particular, in amygdala-kindled mice, BRV (6.8–210 mg/kg) dose-dependently reduces seizure severity, with nearly complete suppression of seizures observed at the highest tested dose. In contrast, LEV (17-540 mg/kg) provides only limited protection even at high doses [28,32]. BRV also produces a more complete suppression of motor seizure severity and after-discharge duration than LEV in fully amygdala-kindled rats; in particular, BRV induces an important suppression in motor-seizure severity from a dose of 21.2mg/kg, while LEV produces an analogous effect from a dose of 170mg/kg. BRV also significantly

decreases the after-discharge duration at the highest dose tested (212.3mg/kg), whereas LEV has no effects on this parameter up to 1700mg/kg [32,45].

Similarly, another study demonstrates the efficacy of BRV (0.68, 2.1, 6.8 or 21 mg/kg) in the amygdala-kindling model of temporal lobe epilepsy [46]. The focal seizure threshold (ADT) was significantly increased by BRV at 0.68 and 21 mg/kg, but not at intermediate doses showing an effect not entirely dose-dependent. Instead, seizure severity recorded at the focal seizure threshold was dose-dependently decreased by BRV. In addition, the most marked anticonvulsant effect of BRV was determined by significant increase, at all doses and in a dose-dependent fashion, of the generalized seizure threshold (GST).

In audiogenic seizure-susceptible mice, BRV provides more potent and complete protection from clonic convulsions than LEV (ED_{50} values = 2.4 vs. 30 mg/kg, i.p.) [32].

In the GAERS model of absence epilepsy, BRV exerts a more complete suppression of spike–wave discharge (SWDs) than LEV. BRV significantly suppresses spontaneous SWDs in GAERS rats from a dose of 2.1mg/kg with complete inhibition appearing at the highest tested dose (67.9mg/kg). In contrast LEV induces significant suppression of SWDs from a dose of 5.4mg/kg but does not attain complete inhibition, even at the highest tested dose (170mg/kg) [13,14,32].

BRV also differs from LEV in its ability to protect against seizures induced by the maximal electroshock (MES) and PTZ seizure tests; BRV, administered i.p. 30 min before seizure induction in mice, protects against clonic convulsions induced by PTZ and against tonic hind limb extension induced by MES in mice, although with higher ED_{50} values (ED_{50} values = 30 (PTZ) and 113 (MES) mg/kg, i.p.) [32,47].

In a rat model of post-hypoxic myoclonus, BRV (0.3mg/kg, the minimal effective dose) shows a 10-fold higher potency than LEV (3mg/kg, the minimal effective dose) against myoclonus and generalized seizures [44].

BRV has also shown potent anticonvulsant effects in animal models of partially drug-resistant such as the self-sustaining status epilepticus (SSSE) and 6-Hz seizures in mice, supporting its potential efficacy in treatment-resistant epilepsy [40]. The SSSE rat model is characterized by stimulation of excitatory pathways that can create reverberating limbic circuits in which seizures are self-sustaining and thereby inducing damage to the brain. This process, once set in motion, is refractory to standard anticonvulsants such as diazepam and phenytoin [44]. BRV (20 and 300 mg/kg, i.v.) reduces the total duration of seizures in this model to 11% and 0.8% of vehicle-treated controls, respectively, while LEV (200 mg/kg) reduces to 35% of control. The combination of BRV and diazepam has demonstrated a synergistic action in decreasing the duration of active seizures to 3% of controls, which suggests a potential potent anticonvulsant activity in status epilepticus [49]. Furthermore, in addition to the acute short-term effect on SSSE, BRV also reduces the number of chronic spontaneous recurrent seizures occurring both 6 weeks and 1 year after treatment. This seems to suggest that BRV has not only anticonvulsant effects but may also have disease-modifying properties in refractory SSSE rats. However, this effect needs to be confirmed also in other models and might be due to its effects on acute SE seizures.

Studies using a newly developed 6-Hz corneal-kindling model in mice confirmed the high potency and efficacy of BRV against both partial and secondarily generalized seizures [40]. In corneally kindled mice, a model of partial epilepsy, BRV protects animals from secondarily generalised seizures at concentrations several-times lower than those of LEV (ED50 = 1.2 vs. 7.3 mg/kg, i.p.) [40]. In the same corneal kindling model, pre-treatment with BRV, prior to corneal stimulation, leads to suppression of kindling development at doses 10 times lower than those of LEV (0.21-6.8 mg/kg vs. 1.7-54 mg/kg, i.p.). In addition, continued corneal stimulations following cessation of treatment and a wash-out period, results in a significant and persistent reduction in the incidence of generalized motor seizures in the

group previously treated with the highest dose of BRV (6.8 mg/kg); an effect that was not observed in any animal pre-treated with LEV [40]. This reduction in previously BRV-treated groups can certainly be due to the enhanced affinity of BRV for SV2A, compared to that of LEV [32] and further supports the hypothesis of possible disease-modifying properties of BRV.

The higher efficacy of BRV as compared to LEV in several animal models of epilepsy could be also due to individual differences in the interaction with the SV2A protein [50]. In fact, studies with an SV2A allosteric modulator demonstrate that the interaction of BRV with SV2A differs from that of LEV, likely inducing or stabilizing different SV2A protein conformations which may provide the molecular rationale for their distinct pharmacodynamic properties of BRV as compared to LEV [51]. Actually, LEV and BRV act at different binding sites or interact with different conformational states of the SV2A protein [50]. This probably explains findings from electrophysiological studies in rat hippocampal slices showing a greater ability of BRV to inhibit synaptic transmission and vesicle release [28,39,50].

Interestingly enough, recent studies suggested an age-dependent antiepileptogenic effect of BRV (10 and 100 mg/kg) at different ages in rats (P14, P21, P28, and P60) in a rapid kindling model measured by an increase of after-discharge threshold (ADT) [47]. BRV, at the dose of 100 mg/kg, significantly increases ADT at all ages, while, at the dose of 10mg/kg, was effective in increasing ADT in P60, P28, and P21 rats only. BRV also reduces the after-discharge duration, and data indicate that 10 and 100 mg/kg doses of BRV are significantly effective at P60, whereas only the 100 mg/kg dose is effective at P21. At P60, the administration of BRV determines an increased number of stimulations to reach stage 4-5 seizures in a dose-dependent manner and significantly reduces the number of stage 4-5 seizures at 100 mg/kg. Likewise, at P28 and P21, the administration of BRV determines the almost complete abolition of stage 4-5 seizures and determines a higher number of

stimulations to develop stage 4-5 seizures in a dose-dependent manner. Thus, BRV displays a dose-dependent anti-ictogenic effect with consistent efficacy from P14 to P60 in the rapid kindling model and such an effect may be age-dependent [47] and this may be due to developmental differences in SV2A expression. In fact, the expression of the SV2A is age-dependent, with lower levels in younger animals. In rat hippocampus, SV2A expression is lower at P14 than at P21 and P40 [52,53]; this reduced SV2A expression at P14 may explain the lack of antiepileptogenic effects of BRV at this age, despite the presence of an anticonvulsant effect [47].

In conclusion BRV seems to possess properties superior to LEV as both an antiepileptic and antiepileptogenic agent in many experimental models of epilepsy. This profile has triggered the decision to focus on BRV for further clinical development.

3. PHARMACOKINETICS OF BRIVARACETAM

The pharmacokinetics of BRV was initially studied in healthy volunteers in two Phase I randomized, double-blind, placebo-controlled trials [54,55] and subsequently in patients with epilepsy, and subjects with hepatic or renal impairment [56,57].

In healthy adults, BRV exhibits a linear and dose-dependent pharmacokinetic profile over a broad range of doses (single doses: 10–1400 mg; multiple doses: 200–800 mg daily) with low interindividual variability [54,55]. After oral administration, BRV is rapidly and almost completely absorbed with a t_{max} between 1 and 2h, nearly identical to LEV t_{max} (0.5 -1h), with low coefficients of variation of C_{max} (<25%), between 10 and 1400 mg for BRV or 1500 mg for LEV, when given in a single dose [54,58]. Steady-state is reached after 2 days and similarly to LEV, BRV has an almost 100% bioavailability [54,59] **(Table 2**). Food may decrease the absorption of BRV but has no effect on its pharmacokinetics. In fact, a high-fat meal prolongs t_{max} by 3 h and reduces C_{max} by one-third, but does not affect the area under

the curve (AUC) [54]. BRV is highly water soluble and distributes over the total volume of body water. The volume of distribution of BRV is 0.6 L/kg, slightly lower than total body water [54,59]. Protein binding is low for both BRV (<20%) and LEV (<10%). BRV is highly water soluble and easily crosses mucous membranes as shown by very similar saliva and plasma levels. This obviously suggests that saliva could be a suitable sample for monitoring BRV plasma concentrations when blood samples are unavailable [55]. As already mentioned, BRV has a fast onset of action and the pharmacological peak activity and peak plasma levels occur simultaneously, after a single oral dose. On the contrary, LEV maximum pharmacological activity follows maximum plasma concentrations by almost 1 h. This is due to the high lipophilicity of BRV that enables a rapid brain penetration [35].

Renal clearance of BRV is as low as 0.06 mL/min/kg (whereas the metabolites have a high renal clearance) [55]. BRV is eliminated by renal excretion within 72 h, about 5–8% unchanged and >90% as pharmacologically inactive metabolites suggesting predominantly metabolic clearance [4,5,45,54,59]. In fact, BRV is extensively metabolized through two main metabolic pathways, namely hepatic hydrolysis of the acetamide group, mediated by CYP2C8, and to a lesser degree by the isoforms CYP3A4 and CYP2C19 [59]. The two main metabolites in the human urine, (2-[2-oxo-4-propylpyrrolidin-1-yl]butyric acid (35%) and 2-[2-oxo-4-propylpyrrolidin-1-yl]-4-hydroxy-butanamide (< 10%), are not pharmacologically active [59]. As already mentioned, the elimination of BRV is dependent on the activity of the CYP450 system and CYP2C8 induction can increase the hydroxylation of BRV and decrease the plasma concentrations by up to 50%, while CYP450 inhibitors may affect effective BRV concentrations to a lesser degree [40].

The metabolic clearance of BRV is increased in a time-dependent manner at supratherapeutic doses and the steady state is reached within a week of repeated administration. The half-life of BRV is approximately 7-8 h (range 7.26 - 8.18 h) and does not vary with the applied

doses, which allows twice-daily dosing [54,55,59]. Studies in patients with chronic liver disease show that, the total body clearance of BRV is reduced by 25% to 35% (0.04 per min/kg) and the plasma half-life is accordingly increased from 14.2 to 17.4 h. Unrelated to the degree of liver dysfunction, BRV blood levels are increased by 50% to 60%. In such patients, a reduction by one-third of the maximum daily dose of the drug is needed [45]. In patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m^2), there are increased blood levels of BRV (>20%) and increased levels of its metabolites [56,57]. Nevertheless, dose reduction is not required due to the inactivity and low toxicity of BRV metabolites [57].

The pharmacokinetic profile of BRV in the elderly [54,57] or subjects with renal impairment [40] is similar to that observed in healthy subjects.

A Japanese study investigated the role of CYP2C19 genotype on BRV metabolism in healthy subjects, showing a clearance reduced by 30% in poor metabolizers as compared to extensive CYP2C19 metabolisers [60]. Subjects with inactive mutations of the CYP2C19 show only minor reduction (29%) in BRV clearance, which is probably not clinically significant. Thus, individuals with CYP2C19 genetic polymorphisms do not require any dose adjustment [60].

In terms of drug-drug interactions, there is no evidence of an inducing or inhibiting effect of BRV on CYP3A4 activity [61]. BRV adjunctive treatment does not affect plasma concentrations of concomitantly administered AEDs, except for plasma concentrations of carbamazepine-10,11-epoxide which increases during co-administration with BRV [40]. AEDs with inducing properties such as carbamazepine, phenytoin and phenobarbital/primidone reduce BRV plasma concentrations by 26%, 21%, and 19%, respectively, but this does not seem to be clinically significant and dose adjustments do not seem to be required [62,63]. Rifampin significantly decreases the AUC of BRV by 45%,

mostly through CYP2C19 induction, without significantly affecting the C_{max}. Adjustment in BRV dose should be considered in patients on treatment with rifampin [64].

A moderate reduction of the oestrogen and progesterone components of low-dose oral contraceptives is observed after BRV administration, but this does not seem to be clinically relevant [40,45] and BRV concentrations are not affected by oral contraceptives [65]. At the supratherapeutic dose of 400 mg/day, BRV reduces plasma concentrations of oestrogen and progesterone components of contraceptives, but does not affect blood levels of endogenous hormones (LH, FSH, estradiol, and progesterone) during the menstrual cycle [66].

4. CLINICAL DEVELOPMENT

4.1 Brivaracetam for the adjunctive treatment of focal epilepsies

BRV has been initially investigated for the adjunctive treatment of adults with focal epilepsies in a number of Phase II and III studies. Two phase IIb studies investigated efficacy of BRV across different dosage. In study NO1193, patients 16-65 years are randomized (1:1:1:1) to placebo (PBO), BRV 5 mg/day, 20 mg/day, or 50 mg/day, administered BID without up titration during a 7-week treatment period. The primary efficacy endpoint (seizure frequency/week during the treatment period relative to placebo) was statistically significant only for BRV 50 mg/day but the secondary efficacy endpoint (≥50% responder rate and median per cent reduction from baseline in POS frequency/week) provided supportive evidence for the 20 mg/day [67]. A second study (N01114) mainly compared BRV at dosages of 50 and 150 mg/day and failed to show any difference against PBO for the primary efficacy endpoint [68]. For this reason four Phase III randomised, double blind studies have been subsequently completed [69–72]. Two studies used a fixed-dose design and included patients with focal epilepsy only [69,71], one study adopted a flexible dose design and enrolled also

patients with primary generalized seizures [72], the fourth study (NO1258) excluded patients exposed to LEV during the three months before visit 1 [70] (**Table 3**) .

In study NO1252, the efficacy of BRV (20 mg, 50 mg, and 100 mg/day) was investigated against PBO in adult patients with uncontrolled focal seizures [71] but the primary efficacy end-point (per cent reduction over PBO in baseline-adjusted focal seizure frequency/week over the 12-week treatment period) was statistically significant only for BRV 100 mg/day [71,p.20]. In study NO1253, adult patients with uncontrolled epilepsy were randomized (1:1:1:1) to PBO or BRV 5 mg, 20 mg, or 50 mg/day without up titration [69]. The primary efficacy endpoint (per cent reduction over PBO in baseline-adjusted partial-onset seizure frequency/week during the 12-week treatment period) was statistically significant only for BRV 50 mg. In study NO1258, 768 patients were randomised to placebo, BRV 100 mg and BRV 200 mg respectively [70] and seizure reduction over placebo was 22.8% for BRV 100 mg and 23.2% for BRV 200 mg. Finally, study NO1254 adopted a flexible-dose design in adult patients with uncontrolled epilepsy but up to 20% of subjects had generalized epilepsies [72]. Patients were randomized (3:1) to BRV or PBO and initiated at 20 mg/day and increased, as needed, up to 150 mg/day during an 8-week dose-finding period followed by another 8-week stable-dose maintenance period. During the 16-week treatment period, median per cent reduction from baseline in POS frequency/week was not statistically significant while 50% responder rate was 30.3% for BRV and 16.7% for PBO ($p = 0.006$). The relevance of this study is the suggested potential efficacy as adjunctive BRV in adults with generalized epilepsy [72].

In terms of safety, all Phase IIb and Phase III studies reported no difference in treatment emergent adverse events (TEAEs) for patients treated with BRV as compared to PBO. TEAEs were usually mild to moderate in severity and mainly characterized by

headache, fatigue, nasopharyngitis, nausea, somnolence and dizziness. Phase IIb studies reported 2.6% for BRV (5-50 mg) [67] raising up to 67.3% for BRV 150 mg [68]. The two Phase III fixed-dose studies reported at least one TEAE in 56.6% to 79.0%, with a high proportion of completers (84.5% - 94.0%) and low discontinuation rates (4.0%-8.2%) [69,71]. These data are similar to those reported by the Phase III flexible-dose trial, where patients reporting at least one TEAE were in the region of 66.0% for BRV against 65.3% of PBO subjects [72]. The most commonly reported TEAEs leading to discontinuation in all studies were psychiatric adverse events (PAEs). Phase III studies reported a detailed account of PAEs represented mainly by aggression, anxiety, irritability, depression and insomnia [69,71]. However, PAEs were reported in a low proportion of patients (3.0%, 4.0%, and 3.0% for BRV 20 mg, 50 mg and 100 mg/day) [71] and were described as occurring no more frequently than with PBO: insomnia (BRV 4.0% vs. PBO 2.0%), depression (BRV 3.7% vs. PBO 1.0%), irritability (BRV 3.7% vs. PBO 2.0%), anxiety (BRV 1.7% vs. PBO 1.0%), agitation (BRV 1.0% vs. PBO 0%) and depressed mood (BRV 1.0% vs. PBO 0%) [69].
Finally, one study investigated the potential impact of BRV on qT interval, demonstrating no significant effects on cardiac repolarization [73].

4.2 Brivaracetam for monotherapy in focal epilepsies

Two Phase III studies have just terminated (NO1276 and NO1306) and some partial results are available although none of them has been published yet. Both studies were double-blind, randomized, multicentre, parallel group, historical-control conversion to monotherapy studies in patients with partial-onset seizures [74]. In both cases, patients were randomised to either BRV 50 mg or 100 mg for a 17-week evaluation period. These studies have been designed according to FDA regulations to obtain a monotherapy license in the US.

5. POST-MARKETING STUDIES

During recent years, a number of post-hoc pooled data analyses have been published. A large pooled analysis of all Phase IIb and Phase III studies and further additional open label and long-term follow up studies [75] confirmed seizure freedom rates of 4.9%, 4.2%, 3% and 3.3% at 6, 12, 24 and 60 months respectively. This study included follow up data for more than 8 years in 41 patients showing a retention rate of 54% for more than 60 months [75]. A pooled data analysis [76] of three Phase III studies [69–71] investigating efficacy of BRV in focal seizures showed a mean seizure reduction of 19.5% for 50 mg, 24.4% for 100 mg and 24% for 200 mg and seizure free rates of 2.5%, 5.1% and 4.0%. Another post-hoc analysis of pooled data [77] from three Phase II studies [69–71] looked at the effect of BRV in controlling secondarily GTCs (SGTCs). The median percentage reduction from baseline was 66.6% for BRV 50 mg and almost one third of patients (30.4%) became seizure free from SGTCS during the 12-week treatment period for BRV >=50 mg. A post-hoc analysis of pooled data from the same three Phase III studies investigated efficacy in elderly patients (>65 years old) [78]. The authors reported efficacy and tolerability data very similar to those observed in the much larger overall pooled population but the sample size was made of only 30 subjects.

Real life data on BRV come mainly from German groups who focused on efficacy and tolerability in highly drug-resistant patients and the possible dose-equivalence between LEV and BRV. A multicentre, retrospective cohort study in 262 patients with epilepsy followed up to a maximum of 12 months showed a retention rate of almost 80% at 3 months and 75.8% at six months with seizure free rates of almost 15% at 3 months and 15.3% at 6 months [79]. The authors reported a TEAE rate of 37.8% but also pointed out that LEV-associated behavioural problems improved upon switch to BRV in 57.1%, while LEV-

associated somnolence improved in 70% of patients. In this study a small subset of patients, around 7%, had idiopathic generalised epilepsy with no significant worsening in seizure pattern and frequency [79] further confirming the promising role of BRV in generalised epilepsies.

A single centre retrospective study of BRV as adjunctive treatment in 101 patients with difficult to treat drug-resistant patients followed up to six months showed a retention rate of 51.5% and a seizure free rate of 7% [80]. TEAEs were reported in around one third of patients. Interestingly they reported also a retention rate of 57% in those with no previous exposure to LEV.

A few authors investigated specifically tolerability and safety of the rapid switch from LEV to BRV. In a German study 51 patients were switched with a ratio from 10:1 to 15:1 with no major problems [79]. Another German group report 43 cases of overnight LEV-BRV switch with no complications but a deterioration of seizures was observed in 5 cases [80]. An open-label, prospective, phase IIIb exploratory study investigated the effect of a rapid switch from LEV to BRV in patients developing behavioural adverse events of LEV within 16 weeks of LEV initiation [81]. Among the 26 subjects who completed the study, during the 12 week observation period, 93.1% of patients reported a clinically meaningful reduction in behavioural adverse events [81].

6. CONCLUSIONS

BRV is a new AED currently licensed for the adjunctive treatment of adult patients with focal epilepsies and it is a ligand of the SV2A protein. The preclinical development of BRV is quite unique and has raised several doubts on current methodologies adopted for AED development, reinforcing the need for new approaches. The preclinical and clinical

profile suggest that BRV is potentially an ideal compound in the emergency setting given the rapid onset of action associated with being water soluble and, therefore, available in intravenous formulation. In addition, data from Phase III studies have already suggested that BRV may be effective not only in focal epilepsies but also in generalised syndromes. Further data from special populations such as children and women of child bearing age are urgently needed.

7. EXPERT OPINION

BRV has shown an excellent antiepileptic activity in many experimental models of epilepsy and some promising properties as a disease modifying agent. Preclinical studies seem to suggest that BRV has a potentially greater efficacy as compared to LEV for its selective, high affinity, and different binding properties to SV2A, as well as a higher lipophilicity, correlating with a more rapid brain penetration in preclinical studies. However, there are no clinical studies supporting a greater efficacy of BRV over LEV and head to head comparison are needed to fully clarify this point.

In terms of preclinical development, it has to be acknowledged that the developmental program of BRV is quite unique. The role of SV2A is far from being completely understood, however, the demonstration of a correlation between the SV2A binding affinity and the antiepileptic effect has driven a drug development strategy with a highly probability of success. The identification of the SV2A protein and the subsequent approach to preclinical epilepsy research represents a milestone which has impacted on this field and has considerable implications. In fact, the discovery of LEV efficacy despite its lack of effects on classical animal models commonly used to screen for new compounds has raised several doubts on current methodologies and increased the debate in this area of research. The established efficacy of BRV further reinforces this point and the need for new approaches.

The discovery of the SV2A protein and the subsequent development of BRV have further confirmed the impression that none of the new AEDs marketed during the last 20 years have improved the proportion of seizure free patients because current agents have been developed adopting the same animal models that were based on the same assumptions and theoretical bases. New and innovative preclinical models of epilepsy are urgently needed in order to explore new molecular targets.

The preclinical and clinical profile of BRV clearly point out that it is probably the ideal AED to be used in an emergency setting given the rapid onset of action associated with being water soluble. Data on treatment of status epilepticus are currently just anecdotal and proper studies are needed. Data from patients with repetitive seizures and/or seizure clusters would be also of great interest.

The monotherapy license may represent the future of BRV. Emerging data are suggesting that the overnight conversion from LEV to BRV is not only safe and well tolerated but may provide further benefits in terms of tolerability especially in patients with paradoxical sedation from LEV or behavioural adverse events. Further data from larger samples are needed. Data from preclinical studies are also suggesting that BRV may be effective not only in focal epilepsies but may represent an alternative option in primary generalised syndromes and preliminary data from phase III and IV studies seem to confirm that. Drug options in generalised syndromes are still very limited and new drugs with a large spectrum of activity in both focal and generalised syndromes are more warranted. In this regard, data on safety from special populations such as children and women of child baring age are urgently needed.

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Table 1. Spectrum of activity of Brivaracetam and Levetiracetam on different preclinical models of epilepsy.

Model	Brivaracetam	Levetiracetam	References
Amygdala-kindled mice	Reduced dose-dependently the seizure severity Complete suppression of seizures (at the highest tested dose). Reduced the duration of the afterdischarge.	Limited protection even at the highest tested dose. No effects on this parameter.	[28]
Fully amygdala-kindled rats	Suppressed motor seizure severity from low doses Reduced the after-discharge duration at the highest dose tested	Similar effect from high doses No effects on this parameter	[32]
Audiogenic seizure-susceptible mice	Potent and complete protection from clonic convulsions	Lower protection from clonic convulsions at high doses	[32]
GAERS	Decreased SWDs from low doses Complete inhibition of the SWDs appearance at the highest dose	Same decrease of SWDs but from higher doses No complete inhibition of SWDs, even at the highest tested dose.	[32]
MES	Protection against tonic convulsions	NO anticonvulsant activity	[32]
PTZ	Protection against clonic convulsions	NO anticonvulsant activity	[32]
Cardiac arrest-induced post-hypoxic myoclonus in rats	Abolished post-hypoxic seizures at all doses	Abolished post-hypoxic seizures only at higher doses	[44]
SSSE	Shortened the cumulative duration of active seizures in a dose-dependent manner Reduced the number of chronic seizures occurring both at 6 weeks and 1 year after SE	Less reduction of cumulative seizures duration and only at the highest dose No effects	[40]
6-Hz corneal-kindling	Protected from secondarily generalized motor seizures Pre-treatment suppressed kindling development Reduced the generalized motor seizures during wash-out period	Same effect but at concentrations several-time higher Same effect but at doses 10 times higher No effects	[40]

GAERS = *Genetic Absence Epilepsy Rats from Strasbourg*; MES = *Maximal electroshock*; PTZ = *Pentylenetetrazol*; SSSE = *Self-sustaining status epilepticus*

Table 2. Pharmacokinetics of Brivaracetam and Levetiracetam.

	Brivaracetam	**Levetiracetam**
Absorption	Rapidly and almost-completely absorbed (about 100%)	Rapidly and almost-completely absorbed (>95%) No food interaction
Bioavailability	100%	>95%
T max after single dose	1 -2h	1.3h
Time to steady state	after 48h	24–48h
Protein binding	<20%	<10%
Volume distribution	0.6 L/kg	0.5 - 0.7 L/kg
Metabolism	Extensively metabolized: 60% by hydrolysis independent of the cytochrome P450 30% by hydroxylation mediated by CYP2C19	Minimal Not dependent on the hepatic CYP system
Inactive metabolites	acid, hydroxy, and hydroxy-acid derivatives	L057
Half-life	7–8 h	6–8h
Clearance	0.06 mL/min/kg	0.6 mL/min/kg
Elimination	Renal primarily by metabolism 8.6% unchanged drug; the rest as inactive metabolites	66% as parent drug, 24% as L057
Interactions	Carbamazepine Phenytoin Phenobarbital/Primidone. Rifampin Oral contraceptives	No pharmacokinetic interactions

Table 3. Efficacy results for Phase II and Phase III studies of Brivaracetam as adjunctive treatment in adults with focal epilepsies (median percentage reduction from baseline in POS frequency/week during the treatment period).

	Phase IIb		Phase III			
	NO1193	**NO1114**	**NO1252**	**NO1253**	**NO1254[§]**	**NO1258[#]**
Placebo	21.7%	16.3%	17.0%	17.8%	18.9%	17.6%
5 mg	29.9%	-	-	20.0%		-
20 mg	42.6%	-	30.0%	22.5%		-
50 mg	*53.1%	34.9%	26.8%	*30.5%	26.9%	-
100 mg	-	-	*32.5%	-		*37.2%
150 mg	-	28.3%	-	-		-
200 mg	-	-	-	-		*35.6%

*statistically significant; [§]Flexible-dose study (BRV 20-150 mg); [#]not primary endpoint

Figure Legend Figure 1. Brivaracetam