

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205836Orig1s000

205837Orig1s000

205838Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	1/26/16
From	Norman Hershkowitz, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	205,836 (0000)
Supplement#	205,837 (0000) 205,838 (0000)
Applicant	UCB
Date of Submission	11/24/2014
PDUFA Goal Date	11/20/2015 (original), 2/20/2016 (with 3 month extension)
Proprietary Name / Non-Proprietary Name	(b) (4) /brivaracetam
Dosage form(s) / Strength(s)	Tablet: 10 mg, 25 mg, 50 mg, 75 mg and 100 mg IV Solution: 50 mg/5 mL single-use dose vial Oral Solution: 10 mg/mL
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approval of all 3 formulations.
Recommended Indication(s)/Population(s) (if applicable)	Adjunctive therapy in the treatment of partial onset seizures in patients 16 years of age and older with epilepsy.

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The present application has provided evidence for the efficacy for the new medicinal entity brivaracetam (BRV) administered orally for the adjunctive treatment (concomitantly with other antiepileptic drug (AED) therapy) of partial onset seizures in epilepsy. Three parallel fixed-dose, randomized, double-blind, placebo-controlled trials were performed that examined patients with refractory partial onset seizures (POS). These studies provided evidence that doses of 50 and 100 mg administered twice daily were consistently effective, based upon their statistical significant reduction in seizure frequency as compared to placebo treatment. The effect was moderate, with little difference in magnitude between both of these doses (the mean percent reduction from baseline over placebo was 17% to 25% reduction). The dose of 25 mg administered twice daily was observed to produce a statistically significant reduction in one such study, but the reduction in seizure frequency, while greater than placebo, was not statistically significant in the other study. The mean percent reduction from baseline over placebo was smaller than the higher doses and ranged from 10% 17% in the two studies. The safety data for oral administered BRV was based on an adequate database and included 3776 unique subjects/patients exposed to BRV, with 1967 POS patients exposed for at least 6 months and 1517 POS patients for at least one year. The safety data indicated an acceptable safety profile that was similar to other anticonvulsants approved for this indication. The safety profile includes the following adverse reactions that will be described in the Warnings and Precautions section (Section 5) of the 1) neurologic adverse reactions including somnolence, fatigue, dizziness, as well as disturbances in gait and coordination, 2) psychiatric reactions including non-psychotic behavioral symptoms (reported as irritability, anxiety, nervousness, aggression, belligerence, anger, etc.) and psychotic symptoms (reported as psychotic disorder along with hallucination, paranoia, acute psychosis, psychotic behavior, etc.). Hypersensitivity in the form of bronchospasm and angioedema was noted and will be included in this section as well. Cases of suicidality were observed and, as part of class labeling for AEDs, suicidality will be discussed in the Warnings and Precautions section. Common adverse events largely parallel those just described that will be included in the Warnings and Precautions section. They largely fall under the categories of nervous system and psychiatric disorders and will be described in the section on Adverse Reactions (Section 6). There was a relatively shallow dose response profile for adverse events, with only a mild increase in incidence of some adverse reactions in the 100 mg/day and 200 mg/day range. Non-serious suppression of WBC count was observed and will be included in the Adverse Reactions section. Dr. Doi notes that no patients in the full epilepsy database developed treatment-emergent SAEs of acute hepatic failure (or hepatic failure), agranulocytosis, aplastic anemia, drug reaction with eosinophilia and systemic symptoms, pancytopenia, rhabdomyolysis, Stevens Johnson syndrome, toxic epidermal necrolysis, torsade de pointes, ventricular fibrillation, ventricular tachyarrhythmia, or sustained ventricular tachycardia in studies with BRV. Because one case of chronic interstitial nephritis was observed for which BRV causality could not be ruled out the applicant is being requested to monitor for post marketing cases of renal failure, interstitial nephritis and other reported alterations in renal function. There, however, is not sufficient evidence to determine causality and include in the label.

Approval of the oral solution is based upon its bioequivalence to the tablet.

The applicant is requesting approval of an intravenous formulation for iv treatment when oral dosing is not feasible. They request that administration include instructions for both slow infusion (15 minute) and rapid bolus (2 minute). The data provided for justification of this includes bioequivalence/bioavailability and safety studies. Studies indicated that the 15 minute intravenous bolus was bioequivalent to the oral formulation. With regard to the 2 minute bolus, the AUC was bioequivalent, but the Cmax was noted to be 30 to 40 percent greater with bolus

than with oral administration and somewhat outside the bioequivalence standards. While the safety data base examined a limited number of patients (n=177) for limited duration of administration (1 dose to 7 days of therapeutic dosing), no definitive adverse event associated with intravenous administration, either as an infusion or bolus, was identified. The safety profile in this series of studies appeared similar to that observed in studies examining the oral formulation. Cardiovascular effect of AEDs is always a concern, particularly when AEDs are administered by rapid intravenous infusion. There, however, did not appear to be an obvious signal for cardiovascular events with oral administration. Moreover, the fact that this product is an aqueous based solution at what is considered a safe pH (5.5) provides additional reassurance for this drug's safety; the (b) (4) used in other AEDs intravenous formulations have been thought to contribute to cardiac effects. While the Cmax of this drug was observed to be increased and outside the bioequivalence margins when administered in a 2 minute bolus, the fact that this drug had a relatively shallow dose response for adverse reactions and will be administered in a medical setting, indicates that the drug may be labeled for a 2 minute bolus.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	<ul style="list-style-type: none"> This is a serious condition, which not only results in interference of life style, but can have significant morbidity and mortality. 	New treatments are required.
<u>Current Treatment Options</u>	<ul style="list-style-type: none"> There are over 18 drugs used for the treatment of POS. However, even with such therapeutic alternatives approximately 35% of such patients with POS cannot achieve complete seizure control with the presently available drug therapies, indicating the need for new treatments. 	New drugs are still required.
<u>Benefit</u>	<ul style="list-style-type: none"> The present drug demonstrated a modest benefit as adjunctive treatment in patients who were already proven to have some degree of resistance to treatment. There was a mean percent reduction in seizures from baseline over placebo of 17% to 25% for the highest doses, accounting for the reduction of approximately two seizures a month. This is similar to the results for other approved anticonvulsants, and while this may seem to be small in magnitude, it must be understood that the population treated is rather refractory and these represent only mean values. 	Approval is indicated.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Risk</u>	<ul style="list-style-type: none"> Adverse reactions of all formulations of these drugs were found to be acceptable. Such adverse events will be described in the label and appear reversible. Moreover, such events may be monitored. 	Approval is indicated.
<u>Risk Management</u>	<ul style="list-style-type: none"> Other than request for limited postmarketing pharmacovigilance regarding interstitial nephritis, there is no need for any other risk management. No REMS or PMRs are required. 	<p>The one case of interstitial nephritis could not be definitely attributed to BRV treatment. There was no other question regarding other serious events.</p>

2. Background

The present application provides studies for the new medicinal entity, Brivaracetam¹ (BRV, ucb 34714), which is a 2-pyrrolidone derivative, for the adjunctive treatment of partial onset seizures (POS) in patients 16 years and older. The applicant believes that this drug's antiepileptic action is a result of its ability to interact with the brain-specific binding site synaptic vesicle protein 2A (SV2A).

Brivaracetam is both the International Nonproprietary Name (INN) and the United States Adapted Name (USAN) designation for (2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1H-pyrrol-1-yl]butanamide (IUPAC). This drug is chemically and pharmacologically similar to levetiracetam, a drug that has a wide spectrum of anticonvulsant activity, one of which includes the treatment of POS. Both drugs are members of the racetam class of drugs; not all members of this class are known for their anticonvulsant properties. Included in this submission for approval of the tablets are 3 pivotal double-blinded placebo-controlled trials, phase 1 and phase 2 studies and open-label long-term extension studies. The applicant is also requesting approval for an intravenous formulation; this approval request is based upon a number of bioavailability/bioequivalence and safety studies. Lastly, the applicant is requesting approval for an oral solution formulation based upon bioavailability/bioequivalence studies.

At least 18 other drugs are approved for the treatment of partial onset seizures. Epilepsy is a common disorder that affects approximately 1 percent of the US population. A majority of these patients suffer from POS. Approximately 35% of such patients with POS cannot achieve complete seizure control with the presently available drug therapies, indicating the need for new treatments.

In his review the Medical Reviewer, Dr. Dinsmore, notes that there were a total of 5 meetings with the applicant, where a number of issues were discussed including secondary endpoints, statistical analysis, and doses to be investigated. For details on these, the reader is referred to that review.

3. Product Quality

The technical lead on the CMC review was Dr. M Heimann, with Dr. C. Jewell on drug substance, Dr. A. Ponta on Drug Process, Dr. E. Jao on process, Dr. D. Miller on microbiology and Dr. O. Eradiri on Biopharmaceutics. There are three formulations of this product, which come in multiple dosages. These include: tablet: 10 mg, 25 mg, 50 mg, 75 mg and 100 mg; IV Solution: 50 mg/5 mL single-use dose vial (an aqueous solution adjusted to a pH of 5.5); Oral Solution: 10 mg/mL. As per the CMC review (8/10/15), pending final inspections there were

¹ (2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1H-pyrrol-1-yl]butanamide (IUPAC)

“no other outstanding issues that would preclude an approval recommendation.” Moreover there are no Phase 4 commitments or issues that would require risk “management steps.” A follow up memo by Dr. Heimann on 12/16/15 notes that:

“Per the final facility review addendum (E. Dobbin, December 11, 2015), all manufacturing facilities are considered acceptable. The overall manufacturing inspection recommendation is for Approval of the application. Based on the Facility recommendation, and the previous approval recommendations from the other members of the review team, OPQ recommends approval of NDA 205837.”

4. Nonclinical Pharmacology/Toxicology

Dr. E. Fisher performed the nonclinical pharmacology/toxicology review, with Dr. L Freed, Team Leader, performing a secondary review. The data reviewed by the team included cardiovascular studies, long term oral toxicology studies in dogs, rats, and primates, 4-week continuous iv infusion studies in rats and dogs, carcinogenicity studies, reproductive and developmental toxicology studies, as well as juvenile animal toxicology studies in rat and dogs. In his review Dr. Fisher questioned whether sufficiently high doses had been achieved in reproductive and developmental toxicity studies based upon the lack of parental toxicity. Dr. Fisher suggested that the entire battery might be repeated at higher doses as postmarketing requirements. But, he believes this should be requested only if high doses can be achieved in these animals. Dr. Freed examined this data and determined that, based upon the available TK data, higher plasma would not be achievable. She concluded that such studies are not feasible and should not be requested.

With the latter in mind, Drs. Freed and Fisher agreed that the nonclinical data are adequate to support marketing approval with appropriate labeling. This labeling information includes information from animal studies on fetal toxicity, effects on growth and development observed in juvenile studies, and findings in carcinogenicity studies.

5. Clinical Pharmacology

The Clinical Pharmacology review was performed by Drs. M. Bewernitz and Dr. X Yang, as reviewers, and Dr. A Men, as Team Leader. As per the Clinical Pharmacology review BRV is nearly completely absorbed after oral administration and has a T_{max} of about 1 hour without food. It is 10% protein-bound and is primarily metabolized by hydrolysis of it's of the amide group by both hepatic and extra-hepatic amidases to form a carboxylic acid derivative. Secondary and tertiary metabolism occurs through hydroxylation of the propyl side chain by CYP2C19 and hydrolysis by amidase and 2C9 enzymes of the hydroxy metabolite into the hydroxy acid metabolite. No metabolites are active. BRV plasma half-life is 7 to 9 hours as per

the Clinical Pharmacology review. Steady state is achieved after 4 to 5 days of dosing. The C_{max} is proportional from 10 to 1400 mg. The AUC is proportional from 10 to 600 mg. The AUC is 24% to 28% greater than proportional at doses >600 mg.

The Clinical Pharmacology review notes that BRV AUC_{0-∞} is 21% greater in subjects with severe renal impairment compared to healthy controls. They conclude that because of the relatively flat exposure-safety/tolerability relationship, the 21% BRV increase is not expected to result in tolerability issues. Another issue raised regarding renal failure is that while there is no substantial change in BRV levels there are changes of up to 21-fold in some of BRV's metabolites. The safety of these metabolites at exposures higher than those expected in severe renal failure was explored in non-clinical studies and, according to the Clinical Pharmacology review, the increased metabolite exposures were not considered a safety concern as these metabolites appeared pharmacologically inactive. In sum, the Clinical Pharmacology review does not believe dose adjustment is required for severe renal failure. I agree.

The Clinical pharmacology review notes that BRV AUC_{0-∞} increased 50-58% in subjects with Child-Pugh Grade A, B, and C compared to healthy controls. The Clinical Pharmacology review notes that, "no dose adjustment is required for patients with hepatic impairment." As per the Clinical Pharmacology review, however, there was no consistent change in the C_{max}. As per the clinical review the applicant originally proposed that no dose adjustment was necessary and that titrating to patient safety and efficacy is sufficient in patients with hepatic impairment. The applicant in a later submission suggested limiting the dose of BRV to no more than 75 mg twice daily (as opposed to 100 mg twice daily). The Clinical Pharmacology reviewer, however, disagrees with the applicant as there was only a modest increase in AE rates in the high dose (e.g. 100 mg twice daily) as compared to low dose (50 mg twice daily) groups in pivotal trials. Also adverse events did not appear to be a significant issue in study N01111, which examined the Pharmacokinetics in patients with hepatic impairment. I recommend the dose adjustment for the following reasons: 1) although well tolerated we have little experience with exposures at doses greater than 100 mg twice daily, which hepatically impaired patients may experience, 2) adverse event experience in hepatic impaired patients is limited in study N0111, which compared 6 healthy volunteers to 20 patients with varying degrees of hepatic impairment for a relatively short period of time (4 weeks), 3) It is usually felt that an increase greater than 30% would require dose adjustment with other anticonvulsants. I admit this is a close judgment call.

Small reductions in clearance are noted in the elderly; however, the Clinical Pharmacology team does not believe these require dose adjustment. I agree. No significant changes in PK were identified based upon sex, race or ethnicity.

The Clinical Pharmacology review notes that BRV: 1) inhibits epoxide hydrolase, 2) does not significantly inhibit CYP enzymes, 3) does not significantly induce CYP enzymes, 4) is not a substrate of major transporters, and does not inhibit major transporters.

The following table (transcribed from the Clinical Pharmacology review) provides a summary of pertinent studied DDIs with recommended advice to the prescriber:

Concomitant AED	Influence of AED on BRIVARACT	Influence of BRIVARACT on AED
Carbamazepine	30% decrease in plasma concentration. No dose adjustment required.	None Consider dose reduction, if tolerability issues arise (due to increase of carbamazepine epoxide. See below.)
Lacosamide	No data	None
Lamotrigine	None	None
Levetiracetam	None	None
Oxcarbazepine	None	None (monohydroxy derivative, MHD)
Phenobarbital	24% decrease in plasma concentration. No dose adjustment required.	None
Phenytoin	27% decrease in plasma concentration. No dose adjustment required.	20% increase in plasma concentration. Consider a dose reduction if tolerability issues arise.
Pregabalin	No data	None
Topiramate	None	None
Valproic Acid	None	None
Zonisamide	No data	None

These have been agreed upon by all reviewers including me.

The observation that food reduces C_{max} by 37%, and the AUC by 5%, as well as delaying T_{max} by 3 hours has led to the conclusion in the Clinical Pharmacology review that BRV can be administered without regard to meals.

DSI inspections on the clinical pharm/ Bio analytic portions of this program were determined to be acceptable (noted in the Final Inspection Memo from Drs. Cai and Mada from OSI, 11/17/2015).

The Clinical Pharmacology review concluded that with regard to the tablet formulation “NDA is acceptable from a clinical pharmacology perspective.”

The applicant conducted a study that supported the bioequivalence of the oral solution and the commercial tablet. The Clinical Pharmacology review agreed with the applicant that “single doses of 50 mg BRV tablets and 50 mg oral solution are bioequivalent in terms of C_{max}, AUC_{0-t}, and AUC.” Although the Clinical Pharmacology review does not specifically address the generalizability of this to higher dose tablets, in a response to an email query of mine (1/26/2016), Dr. Bewernitz notes, “...it is acceptable to generalize the BE findings from the 50 mg tablets and 50 mg oral solution to the 100 mg tablets and 100 mg oral solution.”

The applicant conducted two studies examining bioavailability/bioequivalence of intravenous injection to the oral tablets. Study N01256(A) was a randomized, single-center, open-label, three-way crossover study in 24 healthy volunteers that compared the bioavailability of the 10 mg IV solution (administered as a 12-second bolus or 15-minute infusion) with a 10 mg oral tablet. The OCP reviewer concluded that the results of the study “support the bioequivalence of 10 mg of the clinical-development oral tablet with 10 mg of the commercial IV solution (whether administered as a 12-second bolus or a 15-minute infusion).” A second, more definitive, study (EP0007) consisted of a randomized, single-center, open-label, 5-way crossover, single-dose

bioavailability/bioequivalence comparison of brivaracetam oral tablets (10 mg, 50 mg, 75 mg, and 100 mg) and brivaracetam intravenous 2 minute bolus injection (100 mg) in 25 healthy volunteers. Similar bioavailability according to bioequivalence standards were observed between the 15-minute infusion and oral administration. The AUC was bioequivalent, but the Cmax was noted to be 30 to 40 percent greater with bolus injection as compared to that of oral administration and was somewhat outside the bioequivalence standards. The reviewer opined that the increase in Cmax is not worrisome as the drug is well tolerated with the only adverse events of “dizziness/fatigue/headache,” and intravenous administration will be performed in an inpatient setting. The implications are that in this setting one needs to be more concerned with lower doses and break through seizures, which is not the case. I agree, but also see the Section on Safety. The OCP reviewer concludes that “BRV can be administered as an IV infusion or IV bolus at the same dose level as oral tablets.” An additional intravenous study (N01258), which was principally designed as safety study, provided supportive PK data. This study was 4-arm, randomized, parallel-group trial enrolled that enrolled 105 adults with localized-related or generalized epilepsy. Subjects were started on either placebo or 100 mg BRV tablets twice daily and treated for a period of 7 days. Each patient was then switched to 100 mg of a 15-minute BRV infusions or 100 mg of 2-minute BRV boluses twice daily. Limited PK samples were collected on the day of the switch and 5 days after continued intravenous treatment. The OCP reviewer, however, concluded that “overall, this study is supportive of IV bolus or IV infusion of 100 mg bid BRV.” Safety features of these studies will be discussed in the section on Safety in this review.

6. Clinical Microbiology

In the CMC review, Microbiology issues are summed up as follows:

“The sponsor has provided adequate information supportive of the low risk of the product for microbial contamination in the manufacturing process and in the historical testing results. The continuation of microbial testing of the product in the stability program is acceptable. The bioburden testing method is supported by the method suitability testing.”

As per the final CMC review (see section 3), no microbiological issues were identified, and the requested products may be approved. This includes all 3 requested formulations.

7. Clinical/Statistical- Efficacy

Dr. Steve Dinsmore performed the clinical efficacy review and Dr. Sharon Yan performed the statistical review. The application relies on the results of 3 placebo-controlled, double-blind pivotal trials for proof of efficacy of the tablets. These studies are summarized in the table below (transcribed from Dr. Dinsmore’s review).

Primary Efficacy Trials

Study number	# subjects	LEV use ¹		Study Characteristics	Age range	patients / treatment Arm	Treatment Period (= maintenance period)	1 ^o Efficacy variable
		Yes	No					
N01252	398	76	322	Multi-center, multinational double blind, parallel group, placebo controlled, randomized	≥16 to 70	PBO= 100 20mg/day= 99 50mg/day= 99 100mg/day= 100	Treatment period= 12 weeks	POS ² frequency /week (7 days) over treatment period
N01253	396	76	320	Multi-center, multinational double blind, parallel group, placebo controlled, randomized	≥16 to 70	PBO= 98 20mg/day= 100 50mg/day= 101	Treatment period= 12 weeks	POS ² frequency /week (7 days) over treatment period
N01358	764	Concomitant LEV excluded		Multi-center, multinational double blind, parallel group, placebo controlled, randomized	≥16 to 80	PBO= 261 100mg/day= 253 200mg/day= 250	Treatment period= 12 weeks	POS ² frequency /28 days over treatment period

¹LEV= levetiracetam
²POS= partial onset seizures

All studies were of similar design. Thus, they all were parallel fixed-dose, randomized, double-blind, placebo-controlled studies studying patients with refractory partial onset seizures (POS) with or without secondary generalization. Doses of 20 to 200 mg/daily, administered twice daily, were compared to placebo. All recruited patients were 16 years and older. They were required to have at least 2 partial seizures, with or without generalization, during the preceding 3 months despite the use of 1 to 2 concomitant AEDs (vagal nerve stimulation was considered equivalent to a concomitant AED). Drug dosage/vagal stimulation was required to be stable for 1 month (3 months for phenobarbital and Primidone) prior to the treatment period. Patients with a history of or present seizures occurring only in clusters, presence of status epilepticus during the year preceding recruitment or during the Baseline Period were excluded. To be randomized patients were also required to have at least 8 partial onset seizures, whether or not secondarily generalized, during the initial 8 week baseline study period. In study 1252 and 1253 concomitant use of levetiracetam, which is pharmacologically similar to BRV, was limited to approximately 20% of recruited patients. Study 1358 excluded patients on levetiracetam. For additional inclusion and exclusion criteria the reader is referred to Dr. Dinsmore's review.

All trials had an initial 8-week Baseline Period followed by a 12-week Treatment Period. Study 1252 was conducted in Eastern Europe, Western Europe, and India. Study 1253 was conducted in Latin America, North America, and Australia. Study 1358 was conducted in Western Europe,

Eastern Europe, North America, Asia/Pacific/other, and Latin America. There was no titration period; i.e. patient was started on their randomized dose. Randomization was equal across all treatment groups (e.g. 1:1:1). At the end of the Treatment Period, subjects had the choice of entering a long term open-label long-term study, or a Down-Titration Period of 1 to 4 weeks, depending on the dose they were on and the study they were in.

The primary outcome measure consisted of POS (Type I seizure) frequency during the Treatment Period. Note, baseline was corrected by considering it a covariate in the final analysis (see below). Patient's epileptic seizures were recorded on a daily record card (DRC), documenting the date, number and type of seizures.

Secondary endpoints in all studies included: 1) 50% responder rate² 2) frequency of all seizures (Type I, II, and III), 3) Percent reduction of seizures from baseline, 4) categorized quartile percent reduction in seizure frequency (e.g. 0-25%, >25%-50% ... reduction), 5) seizure freedom over the Treatment Period time. Additional endpoints in Studies N01252 and N01253 included the following 3 outcome measures, which was adjusted for multiplicity, as a variety of sub-scales were also analyzed : 1) Total Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score, 2) Seizure Worry QOLIE-31-P score, 3) Daily Activities/Social Functioning QOLIE-31-P score. Many of the secondary endpoints are within the same domain as the primary endpoint, representing some derivative of seizure frequency. Only some of these secondary endpoints will be described in this review. For more information the reader is referred to Dr. Dinsmore's review.

The primary analysis was performed on the set of subjects, referred to as the intention to treatment set (ITT,) in studies 1252 and 1358 using all patients who received at least a single dose of drug and who had a measurable outcome. For study 1253 the analyses set excluded 3 randomized subjects due to serious and persistent noncompliance with applicable FDA regulation, GCP, and ICH guidelines at Site 404, along with a subject Site 404 who as per Dr. Yen noted was "was an extraordinary outlier" and who had other eligibility issues (e.g. no POSs during baseline). The applicant referred to the set that excludes these patients as a modified intent to treat set (m-ITT). This small number of patients excluded is unlikely to affect results, particularly when one considers the magnitude of effect of the drug (see below). I believe this is reasonable.

Based upon protocol driven specifications the seizure frequency was calculated as 7 day frequency in Studies N01252 and N01253, and a 28 days frequency in Study N01358³. All calculations used a last observation carried forward analysis. Days with missing data were not included in the calculation. Dr. Yan notes that missing data was at a "low level." To normalize the distribution for the primary outcome seizure frequencies were log-transformed according to the formula " $\ln(\text{frequency} + 1)$." The log-transformed frequency over the Treatment Period was analyzed applying an ANCOVA model that including treatment and stratification effects as

² The 50% responder rate is considered the primary endpoint by the EMA.

³ Frequency was calculated by the following formula:

$$\frac{\text{Total number of Type I seizures over the Treatment Period}}{\text{Total number of days with no missing seizure count in the Treatment Period}}$$

The results were then multiplied by 7 or 28 for 7 day and 28 day seizure frequencies, respectively.

factors and the log-transformed Baseline seizure frequency as covariate. Each dose arm was compared to placebo. These statistical procedures are commonly used in such epilepsy studies. Multiplicity was adjusted by as follows:

- Study N01252: protocol driven sequential analysis ($p < 0.05$) in the following order: 50mg/day, then the 100mg/day, and finally the 20mg/day dose. It is noteworthy that the Division usually recommends that sequential analyses proceed from the high to the low dose, particularly if the study arms are of equal size.
- Study N01253: protocol driven sequential analysis ($p < 0.05$) in the following order: 50mg/day, then the 20mg/day, and finally the 5mg/day dose.
- Study 01358: Hochberg procedure ($p < 0.05$; with alternate of $p < 0.025$ if the largest p-value is > 0.05).

Retention of patients in the 3 studies was high with anywhere from 89% to 95% of patients able to complete the studies in the various BRV arms. There was not much difference in retention rates in the placebo arms, which varied from 85 to 94%. The most common cause of discontinuation was that from adverse events, with 4 to 8% of patients discontinuing for this reason in all the drug treatment arms. Demographic variables (age, race and sex) were generally well matched between all arms for each of the studies. Caucasians represented the most commonly studied racial group (approximately 75%). Other racial groups included Asian, black, American Indian, and mixed. These were similar in all arms for each study, but differed between studies (e.g. Study 1252 had about 24% Asian while no Asians were recorded studied in Study 1253).

The number of baseline AED that patients were on when entering the study was consistent across arms of the each study and somewhat similar between the studies, with the exception that study 1358 had few patients on three or more AEDs when compared to the other studies. Patients were most commonly on 2 AEDs (70 to 83%) on entry; this was followed by a single drug, and least frequently on 3 drugs. Median age of onset and duration of epilepsy was relatively similar across treatment arms in studies and similar across the various studies. The baseline seizure frequencies were similar between studies, Study 1252 being slightly lower (20%) than the other two studies; the arms within each study were well matched (see results tables below, note the baseline seizure frequency in those tables are based upon frequency over different time periods, 7 and 28 day).

Dr. Yan performed subgroup analysis for gender, age and geographic region. As pointed out by Dr. Yan, this analysis was complicated by the skewed distribution of the frequencies, even when log transformed. Further analysis of the subgroups, limiting the population size, may further complicate analyses. Dr. Yan presents simple central tendency descriptive statistical examination for each study for these variables. While she notes marked differences between baseline seizure frequency for geographic regions, which might be attributed to the pattern of treatment and recruitment, she notes that that “no substantial discrepancies in treatment difference were found in these subgroup analyses.”

It is noteworthy that an error in calculation by the Applicant of the percent reduction of seizures reported in this submission was identified late in the review. This was identified as a result the observation that mean effect size for similar doses were different in studies that utilized a

calculation of frequency based upon 7 days (studies N01252, N01253) compared to those based upon 28 day (study N01358). The error was introduced as a result of the incorrect back transformation of the logarithmically transformed data that was performed to obtain a percent frequency reduction. For further information on this the reader is referred to Dr. Yan's review addendum. The values presented below include only the corrected calculations.

Analysis by Study

Study N01252

The table below presents an analysis of the primary endpoint of the logarithmically transformed frequency (LS mean), along with calculation of percent change from baseline and two protocol driven sensitivity analyses. The table was adapted from Dr. Yan's review except it contains the corrected "adjusted mean percent reduction." The p values achieved statistical significance ($p < 0.05$) only for the 100 mg/day dose. As the protocol driven method to correct the alpha required that the 50 mg/day dose be studied first, the 100 mg/day dose cannot be considered to be significant. However, it is usual to examine the higher doses first in a sequential analysis, and while the value is considered nominally significant, the fact that other studies in this series demonstrate significance at 100 mg/day and lower doses (see below) suggest that this is a meaningful result. The sensitivity analyses are important because of the observation, as noted above, that the logarithmically transformation for the data did not result in a normal distribution. Nonetheless, the two protocol driven non-parametric analyses (i.e. Mixed Effect and Rank), achieved similar results. This attests to the statistical significance of the result. There was mean 17% reduction in seizures from baseline over placebo in the 100 mg/day treatment arm. Based upon a back calculation estimate, this accounts for a mean reduction of 1.4 seizures per 28 days in the 100 mg/day treatment group over the placebo treatment group.

Results of efficacy analysis of seizure frequency per week – N01252

	Placebo N=100	BRV		
		20 mg/day N=99	50 mg/day N=99	100 mg/day N=100
Baseline median seizure frequency*	2.07	1.93	1.80	2.02
Treatment median seizure frequency*	1.75	1.34	1.49	1.26
Adjusted Mean Percent Reduction in Seizure Frequency over Placebo		9.9	9.5	17.0
Primary analysis				
LS mean	2.21	1.99	2.00	1.84
% reduction (95% CI)		6.8 (-4.8, 17.1)	6.5 (-5.2, 16.9)	11.7 (0.7, 21.4)
p-value		0.239	0.261	0.037
Sensitivity analysis-mixed effect				
LS mean	1.77	1.57	1.66	1.52
% reduction (95% CI)		7.4 (-3.6, 17.3)	3.9 (-7.5, 14.2)	8.9 (-1.9, 18.5)
p-value		0.178	0.484	0.104
Sensitivity analysis- ranks				
p-value		0.174	0.246	0.021

*The frequency value is based upon the protocol driven endpoint of #seizures/7days.

N.B.: The table is based upon that which presented in Dr. Yan's primary NDA review, but with the addition of the corrected values for "Adjusted Mean Percent Reduction in Seizure Frequency over Placebo" added, which is included in her the addendum to the review and corrects a miscalculation of the Applicant.

Dr. Yan notes similar statistical significance of the 50% responder rate, a value that the EMA utilizes as a primary endpoint. That is, the 50% responder rate was statistically significant in the 50 mg/day dose only. Dr. Dinsmore notes QOLIE-31-P analysis revealed no obvious difference with placebo.

Study N01253

The table below presents an analysis of the primary endpoint of the logarithmically transformed frequency (LS mean), along with calculation of seizure frequency percent change from baseline and two sensitivity analyses using. The table was adapted from Dr. Yan's review except it contains the corrected "adjusted mean percent reduction." The p values reached statistical significance at $p < 0.05$ only for the 50 mg/day dose. Correction for multiplicity required a sequential analysis from high to low analysis, which is a more conventional approach. Sensitivity non-parametric analyses, similar to the above study, were performed and revealed similar results to the primary analysis. There was mean 17% reduction in seizures from baseline over placebo in the 50 mg/day treatment arm. Based upon a back calculation estimate, this accounts for a mean reduction of 1.9 seizures per 28 days in the 100 mg/day treatment group over the placebo treatment group.

Results of efficacy analysis of seizure frequency per week – N01253

	Placebo N=96	BRV		
		5 mg/day N=96	20 mg/day N=99	50 mg/day N=101
Baseline median seizure frequency*	2.63	2.32	2.23	2.85
Treatment median seizure frequency*	2.15	1.80	1.96	1.70
Adjusted Mean Percent Reduction in Seizure Frequency over Placebo		-1.2	5.4	16.9
Primary analysis				
LS mean	3.13	3.17	2.96	2.60
% reduction (95% CI)		-0.9 (-13.9, 106)	4.1 (-8.1, 15.0)	12.8 (1.7, 22.6)
p-value		0.885	0.492	0.025
Sensitivity analysis-mixed effect				
LS mean	2.65	2.47	2.36	2.07
% reduction (95% CI)		4.8 (-7.8, 16.0)	7.9 (-4.1, 18.6)	15.9 (4.9, 25.6)
p-value		0.437	0.189	0.006
Sensitivity analysis- ranks				
p-value		0.698	0.303	0.003

*The frequency value is based upon the protocol driven endpoint of #seizures/7days.

N.B.: The table is based upon that which presented in Dr. Yan's primary NDA review, but with the addition of the corrected values for "Adjusted Mean Percent Reduction in Seizure Frequency over Placebo" added, which is included in her the addendum to the review.

As noted by Dr. Dinsmore, like study 1252, no treatment effect was noted for the QOLIE-31-P.

Study N01358

The table below presents an analysis of the primary endpoint of the logarithmically transformed frequency (LS mean), along with calculation of seizure frequency percent change from baseline and two sensitivity analyses using. The table was adapted from Dr. Yan's review except it contains the corrected "adjusted mean percent reduction." The p values reached significance at $p < 0.05$ for both the 100 mg/day and 200 mg/day doses with and without multiplicity testing of treatment arms using a Hochberg multiple comparison procedure (see Dr. Dinsmore's review). There was mean 25% and 26% reduction in seizures from baseline over placebo in the 100 mg/day and 200 mg/day treatment arms. Based upon a back calculation estimate, this accounts for a mean reduction of 2.4 seizures per 28 days in both BRV treatment group over the placebo treatment group.

As above the 50% responder rate exhibited similar statistical significance.

Results of efficacy analysis of seizure frequency per 28 days – N01358

	Placebo N=259	BRV	
		100 mg/day N=252	200 mg/day N=249
Baseline median seizure frequency*	10.0	9.5	9.3
Treatment median seizure frequency*	8.7	6.3	5.8
Adjusted Mean Percent Reduction in Seizure Frequency over Placebo		25.2	25.9
Primary analysis			
LS mean seizure freq per 28 days (seizure frequency per week)	9.2 (2.3)	6.9 (1.7)	6.8 (1.7)
% reduction (95% CI)		22.8 (13.3, 31.2)	23.2 (13.8, 31.6)
p-value		<.001	<.001
Non-parametric rank ANCOVA			
p-value		<.001	<.001
EU primary outcome, 50% respond			
Responders, n (%)	56 (21.6)	98 (38.9)	94 (37.8)
Odds ratio ¹		2.39	2.19
p-value		<.001	<.001

**The frequency value is based upon the protocol driven endpoint of #seizures/28 days.

N.B.: The table is based upon that which presented in Dr. Yan's primary NDA review, but with the addition of the corrected values for "Adjusted Mean Percent Reduction in Seizure Frequency over Placebo" added, which is included in her the addendum to the review.

General Explorations

Results from subgroup analyses, using descriptive statistics, for drug induced effects of seizure frequency by gender, age group and race were examined by Dr. Yan. She notes that no

substantial discrepancies in treatment difference are observed in this subgroup analyses. An analysis by Dr. Dinsmore confirms this conclusion.

Using descriptive statistical evaluation Dr. Dinsmore examined the persistent of effect. This was performed by evaluating the frequency for each of 28-day epochs over the 3-month Treatment Period. No significant change in frequency was apparent at the dose of 100 mg/day; a small, likely clinically insignificant decrement occurred at a dose of 200 mg/day in the later epochs.

Considering the fact 20% of patients in study N1252 and N01253 were on concomitant levetiracetam, and the fact that this is chemically similar to BRV and may share a similar mechanism of action, its concomitant used was explored. The analysis is only limited to the two aforementioned studies, and therefore to the lower doses (50 and 100 mg daily). Both Drs. Yan and Dinsmore believe that no additional benefit could be identified in the subset of patients who were on concomitant levetiracetam. This can be appreciated from Dr. Dinsmore's analysis, presented in the table below that provides the combined data from the two studies and indicates that while seizures are reduced when levetiracetam was not present as a concomitant medication there appeared to be a slight increase in seizures in the presence of concomitant levetiracetam.

Table 1 Study 1252-1253, Concomitant LEV- No Concomitant LEV, Median Treatment Sz Frequency by Treatment Arm, mITT-ITT (n=790)

TREATMENT ARM	1252-1253, LEV-NO LEV	Number of patients	Median Treatment Sz Frequency	Effect
PBO	CON LEV	37	8.28	
PBO	NO LEV	159	7.53	
5mg	CON LEV	18	10.66	-2.38
5mg	NO LEV	78	6.91	0.62
20mg	CON LEV	37	8.68	-0.4
20mg	NO LEV	161	5.63	1.9
50mg	CON LEV	39	9.14	-0.86
50mg	NO LEV	161	5.63	1.9
100mg	CON LEV	20	9.76	-1.48
100mg	NO LEV	80	4.48	3.05

While the data is limited, because of the small n sizes, the effect is dramatic and consistent with the understanding of the structure and shared mechanism of these two drugs, this information should be included in the label. While there may have been a subtle trend, a decrement in effect was not as apparent for those patients who had a history of levetiracetam use, but who are not presently on, levetiracetam. Both Drs. Yan and Dinsmore agree to the above stated conclusion regarding concomitant as well as a history of use of levetiracetam. Information on concomitant use should be included in the label, but it should be noted that it is only applicable to the doses of 50 mg/day and 100 mg/day.

The use of BRV appears to increase the levels of the active epoxide metabolite of carbamazepine. As this metabolite is considered an active, both Drs. Dinsmore and Yan performed an analysis to determine if this interaction may influence the therapeutic effect size in

patients started on BRV who were and who were not on concomitant carbamazepine. Neither reviewer concluded an impact on the BRV effect size.

Conclusions

Both Drs. Dinsmore and Yan agree that BRV has been demonstrated to produce a therapeutic benefit in POS at the dose of 100 mg daily, while the lower dose of 50 mg daily produced a smaller magnitude of effect, which was only statistically significant in 1 out of 2 studies. The higher dose of 200 mg daily produced a statistically significant effect with a magnitude similar to that of 100 mg daily. Based upon this information both Dr. Dinsmore and I believe the drug should be labeled for an initial dose of 100 mg daily. Knowing the fact that only a mild increase in some adverse events are apparent when one compares the 100 mg to 200 mg daily dose, and the fact that there is some degree of individual variability in drug response, both of us believe that the label can advise an increase in dose increase if the patient requires a higher therapeutic effect and tolerates the drug. Dr. Yan recommended that it be labeled for doses of 100 mg/day and 200 mg/day. Knowing that there is always some degree of variability in patients response in this class of drugs, and one study showed a significant effect at a dose of 50 mg daily, both Dr. Dinsmore and I believe we can recommended that if the dose of 100 mg daily dose is not tolerated that a trial 50 mg daily is worthwhile. Although cross study comparisons to other trials in research programs are difficult, I would note that the magnitude of effect, in terms of percent reduction from baseline over placebo, is similar to many other drugs approved for this indication by this Division. I would refer to this magnitude as of moderate size.

8. Safety

Dr. M. Doi performed the DNP safety review. Dr. S. Yasuda was the safety Team Leader who wrote a supervisory review.

Dr. Doi notes that the applicant defined four major epilepsy adjunctive BRV safety data pools: S1) Pivotal blinded controlled POS epilepsy controlled studies, S2) Blinded controlled phase 2 POS studies, S3) All epilepsy controlled blinded epilepsy studies (e.g. POS and primary generalized), S4) All epilepsy studies (controlled and open label). Other separate pools included those consisting of intravenous administration, monotherapy other indications and pediatric epilepsy. Dr. Doi examined all such pools. This review will concentrate on discussing the S1 and S4 pools, and will reference other pools when they are pertinent. Studies on intravenous administration will be discussed in a separate section.

The safety database for the intravenous formulation consisted of a total of 177 exposures. This safety data was derived form 3 clinical pharmacology studies in normal subjects who received 1 to 2 doses of the drug. A single large study in patients (n=105), that compared tablets to iv administration where patients received up to 9 doses over a period of 4.5 days in a double-dummy design, was also included. These were reviewed by Dr. G. Boehme, and are discussed in a separate section below.

The total safety database contains data from 3776 unique subjects/patients exposed to BRV. This includes 754 subjects in phase 1 studies, 2531 patients with partial seizures, and 173 pediatric patients (the applicant is requesting labeling down to and including patients 16 years of age). The remaining patients included those with other seizure disorders and other diagnoses (e.g. essential tremor). As of the safety update 1967 POS patients were exposed for at least 6 months and 1517 POS patients for at least one year. As per tables presented by Dr. Doi, greater than 60% of the one year exposures in the S4 pool were at doses 150 mg/day or greater daily and greater than 80% exposed for 1 year in the S4 pool were exposed to 100 mg/day or greater. Considering the initial dosage that will be recommended is 100 mg/day, this appears consistent with the ICH guidelines for the required safety data exposure requirements in the approval of an NME.

With regard to the S1 pools approximately 25% of subjects in the safety dataset were from Western Europe, approximately 23% of subjects were from North America (21% from the United States and 2% from Canada), approximately 20% were from Eastern Europe, approximately 17% were from Latin America, and approximately 14% were from Asia/Pacific countries.

Deaths

As per the safety update 44 deaths were noted in the full database of this application. Thirty-five were observed in the POS database and 9 were observed in studies for other indications.

Of the controlled epilepsy studies (S3 pool) Dr. Doi notes the occurrence of 1 death of 686 patients (0.015%) for patients receiving placebo and 5 deaths of 1717 (0.29%) for those on BRV. In her review Dr. Doi notes that the difference between drug and placebo was mainly driven by 3 Sudden Unexpected Death in Epilepsy (SUDEP) patients, categorized as “definite,” a cause that more likely results from the underlying condition than the drug. Moreover, upon more careful examination of the 3 SUDEP cases, 2 were off of drug for a period of 9 to 14 days, making it unlikely that BRV was a contributing factor. The remaining 2 deaths in the controlled epilepsy trials was a case of respiratory failure after a witnessed seizure and a death due to drowning after diving into a river. Such causes of death are not uncommon in this population of patients with refractory seizures and are likely attributable to the underlying seizure disorder.

On further examination of SUDEP in the database Dr. Doi notes that there were 10 total cases of SUDEP (definite, probable, and possible) in all adult POS studies (combining the POS controlled and open-label extension studies) and 3 in the pediatric open label studies. Using this data Dr. Doi calculated a SUDEP rate of 1.8 per 1000 subject years, which she notes is lower than reported rates for SUDEP in a refractory epilepsy population. In conclusion Dr. Doi notes that “BRV is unlikely associated with an increased risk for SUDEP.”

A total of 30 deaths were noted in all POS studies (controlled and open label studies). Outside of the cases of SUDEP noted above there were 7 neoplasms, 2 suicides, 2 status epilepticus or seizure related events, 3 cardiovascular related events, and, 1 fall, 1 multi organ-failure

(discussed below) , 4 while off BRV or due to other clear etiologies such as drowning, encephalitis due to ventriculo- peritoneal shunt failure, or motor vehicle/train accidents.

With regard to the, malignancies, the most common causes of death in the population, Dr. Doi notes that with the limited database, “it is difficult to establish a causal role of BRV in these deaths caused by malignancies. She also notes, after reviewing all the individual narratives, that it is difficult to draw a causal role of BRV for the other cases of death. Thus, other clear etiologies or risk factors were identified as causally related. It should be noted that some of the causes of death are not uncommon in this population. These include accidents and falls, status epilepticus, drowning and suicide.

Dr. Doi notes 9 additional deaths for indications other than that for adjunctive treatment of epilepsy. She could not attribute such deaths to BRV.

Both Drs. Doi and Yasuda conclude that there is no evidence to “draw any definitive conclusions” regarding the role of BRV in the observed deaths. I agree

Serious Adverse Events

In her analysis of the S1 data pool Dr. Doi notes that there was a similar incidence of serious adverse events (SAEs) in BRV subjects (2.5%; 27/1099) compared to placebo subjects (2.8%; 13/459). This was observed in other data pools (i.e. S3) that included controlled trials.

The following table (transcribed from Dr. Doi’s review) provides a list of common SAEs, defined as $\geq 2\%$, in the S1 pool.

Table 49. SAEs in SOC's with ≥ 2 BRV subjects and greater than placebo in the SOC, Pool S1

MedDRA SOC and PT	Placebo n = 459	BRV n = 1099
Any SAE	13 (2.8)	27 (2.5)
SOC Gastrointestinal disorders	0	2 (0.2)
Gastritis erosive	0	1 (<0.1)
Inguinal hernia	0	1 (<0.1)
SOC General disorders	0	3 (0.3)
Chest pain	0	1 (<0.1)
Death	0	1 (<0.1)
SUDEP	0	1 (<0.1)
SOC Infections and infestations	1 (0.2)	3 (0.3)
Bronchitis	0	1 (<0.1)
Localised infection	0	1 (<0.1)
Pneumonia	1 (0.2)	1 (<0.1)
SOC Injury, poisoning, procedural	2 (0.4)	5 (0.5)
Fall	0	3 (0.3)
Humerus fracture	0	2 (0.2)
Craniocerebral injury	0	1 (<0.1)
Jaw fracture	0	1 (<0.1)
Rib fracture	0	1 (<0.1)
Traumatic renal injury	0	1 (<0.1)
Clavicle fracture	1 (0.2)	0
Joint dislocation	1 (0.2)	0
SOC Psychiatric disorders	0	5 (0.5)
Adjustment disorder	0	2 (0.2)
Psychotic disorder	0	2 (0.2)
Conversion disorder	0	1 (<0.1)

Source: ISS Table 6-36, Safety Information Amendment 8/11/15 Table 5.5.1.1

The most notable observation is the preponderance of psychiatric SAEs associated with BRV treatment, as compared to placebo. Of note the preponderance of psychiatric events is similar to that observed for levetiracetam, a drug with similar chemical structure and presumed mechanism of action.

In her analysis of the S4 data pool Dr. Doi noted that the most frequent SOC were that of Nervous System Disorders (6.6%), followed by Injury, poisoning and procedural complications (4.4%), Psychiatric disorders (2.9%), and Infections and infestations (2.5%). Within these SOC's Dr. Doi notes that the most common preferred term events were convulsion (2.7%) and status epilepticus (0.9%) followed by epilepsy (0.6%), suicide attempt (0.6%) and ideation (0.6%), pneumonia (0.5%), and fall (0.5%).

Seizure related events are not uncommon in patients with seizures and can be attributed to the underlying disorder. Suicide related events are believed to be, in part, related to the class of drugs, although seizure patients do have a higher incidence of such events in general. As such suicidal ideation AED class labeling will be included in section 5 of the label. Injuries may be related to drug or the underlying seizure condition. Examination of controlled data on injuries does not suggest these to be related to drug treatment. This is discussed below. As will be seen below, psychiatric events were observed as a signal in the controlled database for treatment emergent adverse events (TEAE), and will be included Section 5 of the label.

Dr. Do notes that in the S4 pool no patients developed treatment-emergent SAEs of acute hepatic failure (or hepatic failure), agranulocytosis, aplastic anemia, drug reaction with eosinophilia and systemic symptoms, pancytopenia, rhabdomyolysis, Stevens Johnson syndrome, toxic epidermal necrolysis, torsade de pointes, ventricular fibrillation, ventricular tachyarrhythmia, or ventricular tachycardia.

There was 1 case of septic shock in a patient with hip fracture. Cases that require further discussion derived from the S4 pool includes one case each of bronchospasm, one case each of acute pancreatitis and 3 cases of renal failure/acute renal failure. These, along with pertinent cases including rhabdomyolysis in other pooled groups, are discussed below.

Dr. Doi does not highlight any particular SAE case in the other data pools that contributed to an understanding of potential SAEs beyond those described in the S1 and S4 pools.

Dropouts and/or Discontinuations

Dr. Doi notes that a higher percentage of BRV subjects (6.6%, 72/1099) discontinued as a result of adverse events in the S1 pool as compared to placebo subjects (3.5%, 16/459).

Discontinuations from any cause (e.g. adverse events, lack of efficacy, loss to follow up,, etc.) was also greater in the BRV treatment group. There was no apparent dose dependency for discontinuations. Approximately 35% of patients discontinued because of adverse events in the S4 pool. An additional 22% discontinued because of lack of efficacy in the S4 pool.

Interestingly, discontinuations from adverse events appeared to exhibit a reverse dose response relation in the S1 and S4 pool. I suspect that this likely represents sampling error; low doses tended to examine fewer patients and, at least for the S4 pool, for a shorter period of time.

Dr. Doi utilized a Forrest Plot analysis of the risk for discontinuations in the S1 population to compare BRV treated patients to those treated with BRV to placebo and identified that the SOC for Nervous System Disorders and Psychiatric Disorders exhibited the greatest risk as compared to placebo. Off the preferred term under these two SOC those that contributed to this signal were dizziness, convulsion, headache, depression, aggression, insomnia, irritability, ataxia, and agitation. It is difficult to understand why seizures appeared more common in the drug treated group considering the statistical evidence of the drug being therapeutic. A more granular examination of seizures as an adverse event by Dr. Dinsmore, who included several reported seizure term, identified no apparent seizure signal.

In the S4 pool the MedDRA preferred term for which the BRV subjects most frequently discontinued was convulsion (1.5%) and pregnancy (1.1%) followed by dizziness (0.9%), depression (0.9%), fatigue (0.7%), somnolence (0.7%), irritability (0.5%), and suicide attempt (0.5%), and ideation (0.6%). Again, in general seizures would be expected as a disease related event. Suicidality, as noted above, is class labeled. Somnolence, fatigue, dizziness depression are likely drug related and will be included in the label (both sections 5 and 6). With regard to pregnancy, the division requested a consult form DBRUP (Dr. G Willett) to determine whether this signal may represent decreased hormonal; birth control interaction. The DBRUP consults notes:

“Based on the DDI studies, there appears to be little clinical concern for potential unintended pregnancies based solely on drug-drug interactions between BRV and combination oral contraceptives containing ethinyl estradiol and levonorgestrel. Evidence of ovulatory inhibition persisted despite hormonal decreases... DBRUP does not believe it would be useful to describe the pregnancy findings in labeling unless additional information were provided that would allow us to determine whether the pregnancies that occurred in women reported to be using hormonal contraception are indicative of a clinically significant DDI. A statement recommending use of back-up or alternative contraception is not warranted based on the available information.”

The consulting reviewer recommended that we obtain more granular data to explore this issue. In examining the data it appeared that a majority of patients may not have been on hormonal birth control and with the many uncontrolled factors, such as birth control compliance, DNP determined that further exploration of this data would not be fruitful.

Dr. Doi notes that there were no BRV subjects who discontinued in the S4 pool as a result of acute hepatic failure (or hepatic failure), agranulocytosis, anaphylactic reaction, aplastic anemia, drug reaction with eosinophilia and systemic symptoms, pancytopenia, rhabdomyolysis, Stevens Johnson syndrome, toxic epidermal necrolysis, torsade de pointes, ventricular fibrillation, ventricular tachyarrhythmia, or ventricular tachycardia. There were, however, discontinuations from 1 case each of bronchospasm, 1 form drug hypersensitivity/erythema multiforme, 1 from acute pancreatitis, 1 from chronic pancreatitis (N01254-161-A113), septic shock (hip fracture)/renal failure, and 1 from acute renal failure. Pertinent cases will be discussed in more detail in below.

Significant Adverse Events

Neurologic

Adverse events associated with neurologic symptoms, a common adverse reaction observed in most AEDs, were commonly observed with BRV treatment. Thus, in the S1 pool, as per Dr. Doi's analysis, the SOC for Nervous system Disorders were observed in 35% and 39% of patients exposed to BRV < 50 mg/day, and BRV ≥ 50 mg/day, respectively, as compared to 29% of patients on placebo.

Dr. Doi notes that this was largely driven by somnolence and fatigue; with an incidence of somnolence of 12% for patients on BRV < 50 mg/day and 15% of patients on BRV ≥ 50 mg/day, compared to 8% of patients on placebo, and an incidence of fatigue of 7% for patients on BRV < 50 mg/day, and 9% in BRV ≥ 50 mg/day, compared to 4% in placebo. Examination of Dr. Doi's analysis of Study 1358, which studied patients on the highest therapeutic doses BRV dose (100 mg/day and 200 mg/day), reveals that discontinuations for somnolence and fatigue were higher in the drug treatment groups (0 for placebo and 1.2% and 0.8% for 100 mg/day and 200 mg/day, respectively). In her analysis, examining the 95% confidence interval of the Risk Ratio, there appeared to be a greater risk for these events the first 7 days of exposure.

Dr. Doi's examination of “Dizziness/Gait” disturbance revealed a rate of 12 % for BRV < 50 mg/day and 15% in BRV ≥ 50 mg/day, compared to 10 % in placebo. The dizziness/Gait disturbance group consisted of search terms including dizziness, vertigo, nystagmus, ataxia, gait disturbance, balance disorder, coordination abnormal, and cerebellar syndrome. Like somnolence, discontinuations in this group of adverse events were greater at higher therapeutic

doses than that observed for placebo in study 1358. Moreover, the risk for these events was higher during the first 7 days of exposure.

Dr. Doi and Yasuda recommend that this information on Somnolence/Fatigue and Dizziness/Gait Disturbances be included in the Warnings and Precautions section of the label. While, I believe that such events may be less common than with other anticonvulsants the fact that they have led to discontinuations and are so common suggest that they belong in Section 5.

Dr. Doi performed an analysis of Falls and Injury data from the S1 pool and notes a high incidence for such events, which is slightly greater in drug treated patients. While Dr. Doi recommends to label these events in Section 5, Dr. Yasuda disagrees noting that the treatment differences are not great, confounded by seizure occurrence, and I would add they are inconsistent when you look at subcategories. For example, “site specific injuries” were observed in 1.7% and 1.0% of patients receiving BRV <50 mg/day and \geq 50 mg/day, respectively, as compared to 1.3% of patients on placebo. I agree with Dr. Yasuda.

Psychiatric

A greater percent of patients treated with BRV experienced events associated with the SOC of Psychiatric Disorders in the S1 pool. Thus, 12 % for BRV < 50 mg/day and 13% in BRV \geq 50 mg/day experienced such events as compared to 8 % in placebo. Dr. Doi notes that this was driven largely by Anxiety symptoms and Depressive disorders. Psychiatric disorders in the S1 drug treatment groups also led to a slightly greater discontinuation rate and were more commonly classified as serious. Thus, no cases in the placebo were described as serious whereas 5 cases (0.5 %) were classified as such for patients receiving \geq 50 mg daily. Dr. Doi performed a number of psychiatric SMQ searches. A slightly greater incidence in treatment groups were noted for an SMQ search for depression and a broad SMQ search for hostility and aggression. No differences were apparent for SMQ searches for suicide or psychosis. Differences in SMQ search for hostility/aggression were more apparent when limited to study 1358, which examined the highest studied dosages. Thus, 100 mg/day and 200 mg/day resulted in a 5.1% and 3.6% incidence, respectively, compared to a 1.9% incidence for placebo. Dr. Doi examined SAE psychiatric SMQ search in the S4 pool and identified the following SAEs: 38 patients (1.6%) with SMQ Depression and suicide/self-injury, 13 patients with SMQ Psychotic and Psychotic disorders, and 5 patients (0.2%) with SMQ Hostility and Aggression. In the same S4 pool 100 patients discontinued for psychiatric reasons, mostly for the SMQ Depression and suicide/self-injury, but others for SMQ Psychotic and Psychotic disorders and SMQ Hostility and Aggression. As noted above, Dr. Doi and Yasuda believe that psychiatric symptoms should be included in Section 5 of the label. I agree.

An important issue is whether psychosis or psychotic symptoms should be labeled, as there is a definite comorbidity between epilepsy and psychosis. Dr. Doi reviewed the cases associated with Psychotic and/or Hostility/Aggression and noted that, “While some events developed after a long latency or were confounded by concomitant medications (levetiracetam) or previous history, there were several cases with temporal association with BRV initiation and positive dechallenge without prior history of psychiatric disease.” Based upon this, and upon review of the case vignettes, I agree with Dr. Doi that this information should be included in Section 5 of

the label. To support this, levetiracetam, which is rather similar to BRV (see above), shares labeling for psychosis and other behavioral effects described above.

Cases of suicide and suicidality were noted in the study. Suicidality will be included in the label in section 5 as part of this Division's class labeling policy for AEDs.

Hypersensitivity

In her examination of the S1 pool there is a small but consistent greater incidence for events classified under the preferred term of hypersensitivity (0 subjects taking BRV < 50 mg/day and 0.2% of subjects taking BRV \geq 50 mg/day, compared to 0 placebo patients), skin and subcutaneous tissue disorders (approximately 8% of subjects taking BRV < 50 mg/day, in 6% of subjects taking BRV \geq 50 mg/day, compared to 6% of placebo subjects). SMQ searches for angioedema and anaphylaxis also showed a small predominance in drug treated patients (e.g. for anaphylaxis approximately 1% of BRV < 50 mg/day, 0.1% of BRV \geq 50 mg/day, and no placebo subjects). However, no patients experienced such events in the S1 pool who were discontinued from the study or had such an event classified as serious, and none had cardiovascular or respiratory elements suggesting anaphylaxis. A close examination of cases picked up by the SMQ search notes that the identified elements identified included cough, pruritus, eye pruritus, and rash, making it unlikely that the cases identified in the SMQ were obvious clinical anaphylaxis. Dr. Doi notes that in the S4 pool, there one patient receiving BRV who suffered angioedema with close temporal association with BRV use and positive dechallenge. Also noted was a case with the development of sudden dyspnea with rhonchi associated myalgia and asthenia, which resolved after treatment with steroids and BRV discontinuation. There appeared to be no description of skin, cardiovascular changes or wheezing. Because of this Dr. Doi has recommended that information about angioedema and anaphylaxis be placed in Section 5 of the label. Dr. Yasuda and I discussed this and agree a description of this case should be included in the label, but because of the absence of documentation of the full syndrome we agreed that the section should be described as "bronchospasm and angioedema."

While Dr. Doi notes that some cases were coded as DRESS in the S4 pool, she noted that they were unlikely related to BRV use. Moreover, no BRV subjects identified with SJS or TEN in the entire BRV safety database.

Cardiovascular

Similar percentages of patients in both the placebo and the BRV groups experienced TEAE attributable to the cardiac SOC in the S1 pool. Reported discontinuations or serious AEs observed in the cardiac SOCs were not substantially different between placebo and BRV treatment groups. There was a slight disparity in the reporting of bradycardia for patients who received BRV than those who received placebo. Thus, approximately 0.4% (3 patients) in the BRV \geq 50 mg/day group, none in the < 50mg/day group and none in placebo were reported to have bradycardia. None of these cardiac events were classified as serious or lead to discontinuation. Dr. Doi notes that in the S4 pool there were rare cases in which BRV subjects developed SAEs of arrhythmias and cardiac ischemic events. Such events were noted to resolve with BRV continuation and as per Dr. Doi "lacked a close temporal relationship with BRV

initiation, or were in subjects who had either underlying cardiac risk factors or coexisting conditions.” Except for a subtle potential signal for bradycardia, neither Drs. Doi nor Yasuda believe there is an observable cardiac signal. I agree there is no obvious cardiac AE signal.

Hepatobiliary disorders

Two patients on BRV and none on placebo had an AE linked to the SOC hepatobiliary events in the S1 pool; one had already existing chronic cholecystitis and the other experienced elevations in transaminases without elevated bilirubin during an upper respiratory tract infection and paracetamol treatment. These were not classified as serious nor did they result in drug discontinuation. Considering the setting, Drs. Doi and Yasuda do not believe these are related to BRV treatment. I agree. Analysis of transaminase labs in the S1 pool revealed 2 patients who have potentially clinically significant (PCS) elevated AST or ALT in the BRV group; none in the placebo exhibited PCS elevations (one >5 times ULN and the other >10 times). No patients in the S1 group experienced significant bilirubin elevations. Drs. Doi and Yasuda do not believe these represent signals. I agree.

Ten subjects reported hepatobiliary SAEs, in the S4 pool, most of these cases developed after one year, resolved with continued BRV treatment, or were identified as causally related to other drugs. None were associated with significant bilirubin elevation. One of these cases was associated with pancreatitis that was confounded by the use of other drugs (valproic acid), a drug which has been associated with pancreatitis. Additional analysis for outlier transaminase values in the S4 pool, along with other study pools, demonstrated additional 31 cases of elevation of AST or ALT, a few occurring within the first 6 months of treatment, and in which drug discontinuation resulted in resolution. None were classified as serious and none could be classified as having met Hy’s Law. Examination of the cases led Dr. Doi to conclude BRV treatment is unlikely associated with serious liver injury. Dr. Yasuda agrees, as do I. The incidence of elevated transaminase in the S1 pool over placebo is too small to represent a definitive signal. Other elevations in the full database are confounded by the concomitant use of multiple other medications, and other underlying medical conditions. At this time this cannot be considered a signal. Importantly no cases fulfilled Hy’s law.

Infectious Disorders

Dr. Doi notes that the SOC for infections and infestations is somewhat similar between drug treatment and placebo treatment groups in the S1 pool. Although somewhat higher in the < 50 mg BRV group (22 % of patients) as compared to placebo, The \geq 50 mg/day group is identical to placebo, both being 16%. A similar finding exists when HLT terms for upper respiratory tract infections and influenza viral infections were compared between groups. The fact that the high dose group was similar to placebo indicated an absence of a signal. There were 2 discontinuations in the low dose group in the S1 pool and one serious event in the high dose group for the infections and infestations SOC. The SAE rate for the latter SOC was 2.4% in the S4 database. Dr. Doi believes this to be “low.” She concludes that there was no signal for infections. Dr. Yasuda and I agree.

Renal Disorders

Dr. Doi performed an analysis for Renal Disorders. The S1 pooled data revealed little difference between the SOC for renal and urinary disorders. No particular AE under this SOC receiving drug appeared to stand out significantly to that of placebo. There were no SAEs in this category of events in the S1 pool. There was one discontinuation in the group of patients taking <50 mg/day. Acute renal failure were observed in 2 patients in the S4 pool, but were not attributable to drug, as one appeared to resolve with continued BRV treatment and the other appeared attributable to rhabdomyolysis associated with status epilepticus. There was also one case of tubulointerstitial nephritis (biopsy confirmed) in a 26 year old male noted by Dr. Doi. Drug was discontinued without resolution. There was an absence of further information. Being an isolated unexplained single event, Dr. Doi felt that this could not be definitively attributed to BRV, but she recommend a postmarketing surveillance/enhanced pharmacovigilance for chronic interstitial nephritis as BRV causality could not be ruled out. Both Dr. Yasuda and I agree.

Common Adverse Events

In her review Dr. Doi established the following criteria for providing labeling information on common adverse events. They are:

- $\geq 2\%$ in either the 100 mg or 200 mg dose groups (and >placebo) in Pool S1 or
- $\geq 2\%$ in the 50 mg dose group only (and >placebo) in Pool S1 and $\geq 2\%$ in either the 100 mg or 200 mg dose group (and >placebo) in Study N01358

I believe these are reasonable.

The derived table using these criteria is presented below⁴.

⁴ To avoid error introduced by splitting in some cases Dr. Doi HLTs grouped presented AEs by certain PTs as follows: Visual disorders= vision blurred, diplopia or visual impairment; nausea and vomiting symptoms = Nausea or vomiting; memory loss excl dementia = memory impairment or amnesia; paraesthesias and dysaesthesias = paraesthesia or dysaesthesia; cerebellar coordination and balance disturbances = ataxia, balance disorder, coordination abnormal, or nystagmus; anxiety symptoms = anxiety, agitation, or nervousness. The particular cases of this grouping are denoted by the symbol “^”.

Table 93. Adverse drug reactions ^{(b) (4)} **Pool S1***

MedDRA (Version 15.0) Primary SOC PT [^]	PBO (N=459) %	BRV randomized dose/day		
		50mg (N=200) %	100mg (N=353) %	200mg (N=250) %
Ear and labyrinth disorders				
Vertigo	2	2	3	2
Eye disorders				
Visual disorders [^]	2	4	3	2
Gastrointestinal disorders				
Nausea/vomiting symptoms [^]	3	8	5	4
Constipation	<1	3	1	2
Toothache	1	2	<1	2
Infections and infestations				
Nasopharyngitis	3	3	3	4
Bacteriuria	1	1	1	2
Influenza	1	2	2	1
Injury, poisoning and procedural complications				
Fall	1	2	1	1
Metabolism and nutrition disorders				
Decreased appetite	1	3	1	2
Hyponatraemia	<1	0	1	2
Nervous system disorders[*]				
Somnolence	9	12	16	17
Dizziness	7	12	9	14
Fatigue	4	7	8	12
Cerebellar coordination and balance disturbances [^]	1	4	2	3
Memory loss (excl dementia) [^]	1	3	1	2
Tremor	1	2	1	2
Sedation	0	0	0	2
Paraesthesia/dysaesthesias [^]	1	2	1	1
Psychiatric disorders				
Anxiety symptoms [^]	2	5	3	3
Irritability	1	5	3	3
Insomnia	2	5	2	2
Respiratory, thoracic and mediastinal disorders				
Cough	2	2	3	2
Skin and subcutaneous tissue disorders				
Pruritus	1	2	1	2
Eczema	0	1	0	2
Rash	1	2	1	1

From this it is apparent that the most common adverse events, where the drug treatment group rate is greater than placebo, are nausea and vomiting, somnolence, dizziness, cerebellar coordination and balance disorders, anxiety, and irritability. There was not an obvious dose dependency in this selected data pool except for that seen for fatigue and somnolence. An examination of other pooled data (e.g. S4) provided little additional information to this analysis.

Laboratory Findings

Hematology

Examination by Dr. Doi of the frequency of shift from baseline for hematologic indices in S1 pool revealed a consistent but small shift to low leukocytes and neutrophils for doses greater than 100 mg/day as compared to placebo (e.g. leukocytes 4.4% for placebo compared to 7.3% and 5.0% for 100 mg/kg and 200 mg/day, respectively; neutrophils 3.5% for placebo and 5.6% and 4.1% for 100 mg/day and 200 mg/day, respectively). When classified by of the National Cancer Institute Common Terminology (NCICT) criteria, there were increased shifts in the aforementioned dose groups when compared to placebo for grade 2 and 3 shifts (e.g. Grade 3 neutrophil shift of 0% in placebo and 0.6% and 0.4% with 100 mg/day and 200 mg/day, respectively). There were no grade 4 shifts.

There were no SAE or discontinuations in the S1 pool for hematologic issues. In the S4 pool 1 patient had an SAE of neutropenia, but Dr. Doe's examination of this case suggested it was unlikely the result of BRV. Also in the S4 pool 9 patients discontinued due to hematologic TEAE. These were classified as follows: leukopenia (1) neutrophil count decreased (1), neutropenia (6), leukopenia/neutropenia (1). Upon a further request to Dr. Doi in an email requesting her to examine potential causality with BRV, she provided data that indicated 5 of the identified cases had abnormality identified before BRV treatment, 2 additional cases were identified after long periods of time (232 and 652 days), one appeared to be associated with an acute infection and occurred after 254 days, and the last case appeared to have resulted from another medication. These observations make it unlikely that BRV is causally involved. Other pools did not substantially contribute additional information. Similar decreases of WBCs have been noted for levetiracetam, a similar drug. This is described in section 5 of that drugs label; the description for levetiracetam, but includes a post marketing cases of agranulocytosis. Dr. Doi suggests that the information related to this adverse reaction should be in section 5. Dr. Yasuda and I believe that section 6 may be more appropriate. It should be noted that many AEDs produce suppression of bone marrow to different degrees, and the finding of low white cell count is not unusual, particularly that such patients are being treated adjunctively with these other AEDs. I therefore agree with Dr. Yasuda to include this in section 6.

Chemistry

Dr. Doi notes that except for a slight increase in GGT, which she describes as "not clinically meaningful", there were no significant changes in mean values of any of the monitored serum chemistries in the S1 pool (treatment groups were compared to placebo). Examination by Dr. Doi of shift tables revealed no shifts from normal value at baseline to greater than 1% over placebo values in both high dose drug treatment groups (100 mg/day or 200 mg/day). Dr. Yasuda did identify a shift in serum Na to lower values that was approximately 1.5 greater in in these higher dose groups compared to placebo. She notes that this shift is likely not a signal; she also notes that the shift seems to follow an inverse dose relationship, appearing greater at the low dose of 20 mg/day. I agree that this does not represent a safety signal.

A number of patients were noted to have elevated transaminase in the S4 pool. These were not thought to represent a safety signal and are discussed in the section on Significant Adverse in this review.

Both Drs. Doi and Yasuda conclude that incidences clinically significant or meaningful abnormalities in chemistry parameters were overall low and generally similar to placebo. I agree.

Urinalysis

Drs. Doi and Yasuda note that no meaningful signal was observed. I agree.

Vital Signs

Mean changes in a variety of vital sign measures (systolic and diastolic blood pressure, pulse, orthostatic systolic and diastolic blood pressure, and weight) in the S1 pool were examined by Dr. Doi. She concluded that no meaningful differences among treatment groups and placebo were detected. Potentially clinically significant value evaluation of vital signs also revealed no apparent meaningful differences between treatment and placebo groups, except for a subtle perhaps dose dependent increase in the number of patients with weight loss in the drug treatment pools. This was likely too small to be considered a signal. Drs. Yasuda and Doi do not comment on the significance of this. Other pooled data showed similar lack of a definitive signal. A small number of patients in the S1 (n=2) and S4 (n=4) pools reported TEAE associated with low blood pressure, but none resulted in discontinuation nor were rated as serious events. Drs. Doi and Yasuda concludes that BRV use is unlikely associated with changes in blood pressure (regular or orthostatic). I agree.

ECG

The application included results of a prior formal QT study that examined doses of up to 400 mg twice daily in normal patients (reviewed by the QT-IRT on 3/5/09). No significant changes in the QT interval were observed by the reviewers. Moreover as per that review there “were no clinically relevant effects on the PR and QRS.” The absence of a definitive QT signal will be noted in the label. The T QT-IRT review notes marked increases in metabolites of BRV in renal failure, even though adequate general exposures of BRV were studied. The Clinical Pharm review, however notes, that as these metabolites were examined in non-clinical studies and not found to be pharmacologically active, the data is sufficient to conclude safety with renal failure.

Dr. Doi notes that the Applicant categorized ECGs in the S1 pool as: 1) normal, 2) abnormal and not clinically significant, and 3) abnormal and clinically significant. There did not appear to be differences at the various time points measured (2 week, 4 week, 12 weeks or last measurement) in the various BRV dosage arms with that observed in the placebo group. Shift analysis of these categories of ECG changes likewise showed no difference between placebo and drug treatment arms. Other pooled analyses were consistent with above.

Adverse cardiac events are discussed above under Significant Adverse events, and as noted above, there was no significant cardiac signal.

There was no quantitative analysis of ECG parameters in the S1 pool (e.g. mean or median of QRS duration, QTc etc.). There, however, was the above noted formal QT study that supported the lack of a cardiac signal. Drs. Doi and Yasuda conclude that BRV is unlikely associated with changes in ECG parameters. I agree.

Intravenous Studies

The applicant intends to obtain approval for an intravenous formulation of BRV (ivBRV). They have performed a number of intravenous studies to examine the pharmacokinetic and safety parameters of this formulation. The Clinical Pharmacology review determined that this formulation may be labeled for both a 15 minute infusion and a 2 minute bolus. The reader is referred to the Section on Clinical pharmacology for a more granular discussion of the pharmacokinetic considerations of this formulation. This section will describe the safety data. Dr. G Boehm, DNP safety reviewer, performed the review of safety for this formulation. A total of 177 patients were exposed in various dosages to ivBRV, for up to 7 days.

Some of the features of some of these studies are described in the section on Clinical Pharmacology, but all studies are briefly described as follows:

- Study N01256-A: This study was a 3-way crossover trial in healthy subjects (n=24) examining single doses of BRV 10mg tablet, BRV 10mg IV bolus (12 second bolus), and BRV 10mg IV infusion (15-minute infusion).
- N01256-B: This study examined (n=24) 2 administration of a single dose of ivBRV at two rates one week apart in the following 4 groups of 6 healthy subjects: 1) 25 mg administered as a 15-minute infusion and subsequent 30 second bolus IV, 2) 50 mg administered as a 15-minute ad subsequent 1-minute IV bolus, 3) 100 mg administered as a 15-minute IV infusion and subsequent 2-minute bolus, 4) 150 mg administered as a 15-minute IV infusion and subsequent 3-minute bolus.
- Study EP0007: This study is a 5-way crossover, single-dose trial in healthy subjects (n=25) comparing 2-minute infusions of ivBRV at dosages of 10, 50, 75, and 100mg/day to oral tablets.
- Study N01258: This study was 4-arm, randomized, parallel-group trial in adult seizure patients (n=105). Subjects were started on either placebo or 100 mg BRV tablets twice daily and treated for a period of 7 days. Each patient was then switched to 100 mg of 15-minute BRV infusion or a 2-minute BRV boluses twice daily.

As Dr. Boehm notes, that although the studies suffered from the disadvantage of examining only a small number of patients, for short periods of time, and an absence of a placebo comparator, the data indicated no difference in common adverse events to that observed with the oral formulation. In summary in the full database the most common TEAEs observed during the ivBRV were somnolence, fatigue, dizziness, and headache. Other AEs observed in ivBRV studies worth noting included: AV block second degree (1.7%, n=3; see discussion on heart block below), hypertension (1.7%, n=3), injection site extravasation (1.7%, n=3), nausea (1.7%,n=3), orthostatic hypotension (1.7%, n=3), and orthostatic tachycardia syndrome (1.7%,

n=3). There was one report of ventricular tachycardia (discussed below). None of these were classified as serious. Two events resulted in discontinuation; one was for anxiety and the other for elevated GGT. In the latter case the GGT was elevated prior to BRV treatment and other transaminases and bilirubin were normal. Some injection route based adverse events were noted and included infusion site pain (2.8%, n=5), injection site extravasation (1.7%, n=3), catheter site inflammation (1.1 %, n=2), injection site erythema (1.1%, n=2), injection site pain (1.1%, n=2), vessel puncture site hematoma (1.1%, n=2), and catheter site hematoma, infusion site extravasation, injection site hematoma, injection site inflammation, and injection site irritation (0.6%, n=1) . None of these were SAEs or lead to discontinuation. Such events also likely represent the expected background adverse events to be expected from any injection.

While outlier analysis in studies revealed occasional outlier values, these appeared to be sporadic, had pre-existing pre-treatment outlier values and did not appear to be clinically significant. Also no difference in the reporting of these events appeared between bolus and infusion. These conclusions, however, are limited by the number of subjects studied.

Examination of mean SBP and DBP in study N01258 indicated a slight increase in patients who received infusion and values slightly lower in those who received a bolus.

With regard to the difference between infusion and bolus Dr. Boehm notes that “there were few events where the AE risks appeared to differ by administration method and in no case was there robust evidence of risk difference.”

As some other known anticonvulsants are known to produce more prominent cardiac AEs when administered by intravenous routes, and such events increase with more rapid injection (e.g. phenytoin and phenobarbital), it was important to examine vital sign and EKG changes associated with injection and compare differences between rapid injection.

ECG was examined in the intravenous studies using both 12 lead and Holter monitor. A number of sporadic changes were observed in studies N01256 A and N01256B. These included Mobitz type I second degree block, incomplete bundle branch blocks ST deviation in V2 supraventricular), and a case of non-sustained (6 beat) ventricular tachycardia. Importantly the supraventricular tachycardia occurred 18 hours after bolus and the cases of AV block occurred one to 10 hours post infusion. Some patients had a post-dose Holter performed to examine baseline. Examination of this data revealed that many of the described cardiac events also occurred hours following treatment. Dr. Boehme notes that:

“Given that these events can occur in the background, several of the events occurred hours after administration, and that the only patient who experienced an abnormality twice (001-0031 had 2 episodes of Mobitz type 1 second degree heart block) had a similar event recorded on the post-trial Holter, attribution to BRV is not possible. These events should be interpreted in light of available ECG data from all BRV data sources.”

Study N01258 did not only examine 12 lead ECG at time points during the study but performed telemetry during infusion. Dr. Boehm reports on this telemetry data and notes that there appeared to be slight mean increases in heart rate from baseline in all treatment groups, at most recording time points. In addition, there appeared to be slight decreases from baseline in PR interval, particularly for the 2-12 hour post

dosing recordings. These changes appeared small and are of unknown clinical significance. There did not appear to be clear, consistent mean changes in QTcF. Some abnormalities in ECG were noted during the study (PACs, interventricular conduction delays, first degree heart block, etc.), but many were noted on screening ECGs and were not considered clinically significant. These data does not indicate a specific cardiac signal related to intravenous administration.

Although in his review Dr. Boehm does not make a definitive recommendation to approve or not approve the iv formulation, Dr. Yasuda notes there is nothing that would preclude approval. Factors that would support this are the relative general safety of the drug when administered orally and the absence of a safety signal in the intravenous studies in the limited intravenous dat. The demonstration of bioequivalence and similar bioavailability of the 2 to 15 minute infusion of the intravenous to oral formulations further supports the intravenous formulation safety. Moreover, the specific lack of a cardiovascular signal associated with both the intravenous and oral administration (even at very high doses in the QT studies) is reassuring. The fact that this product is an aqueous based solution in what is considered a safe pH (5.5) provides additional reassurance for this drugs safety, as the organic solvents and non-physiologic pH used in some AEDs intravenous formulations have been thought to contribute to their cardiac toxicity as well as other serious reactions. I believe the iv formulation can be approved. I also believe that considering the fact that intravenous injections will be performed by medical personal the 2 min bolus may be approved along with the 15 minute infusion.

9. Advisory Committee Meeting

None required.

10. Pediatrics

The Applicant provided and iPSP which was brought before PeRC in September 2014 (Dr. Lynne Yao, Chair). The iPSP was agreed upon by this Division, PeRC and DPMH (Hari Sachs, Team Leader). Thus, a partial waiver for the neonatal age group (birth to < 1 month of age) because studies are impossible or highly impracticable as diagnosis for this age group is rare. As the Applicant had completed a PK study examining oral administration in pediatric patients 1 month and above, the iPSP noted that the following studies are planned (table transcribed form Dr. H. Sach's review):

Cross Discipline Team Leader Review

Study	Description	Protocol submission	Study Initiation	Estimated Final Report Submission
N1266	Long term open-label safety study (1 mo to <17 y)	Mar 2011	(b) (4)	(b) (4)
(b) (4)	Double-blind, efficacy and safety study (1 mo to 4 years)			(b) (4)
	Intravenous PK and safety study (1 mo to <(b) (4) years)			(b) (4) Jun 2020

Information abstracted from agreed upon iPSP Tables 5-1 and 10-1.

(b) (4)

With this in mind, study (b) (4) would be unnecessary. All other studies are required (b) (4)

(b) (4)

11. Other Relevant Regulatory Issues

- **Financial disclosures:** Dr. Dinsmore notes that, while “there no disclosable financial interests (DFI) identified for investigators in studies EP0007, 1252⁵, 1256, 1287, and 1296...there were disclosable financial interests identified for investigators in studies 1258, 1253⁶, and 1358⁷.” For the pivotal trials 1253 and 1358, it appears that financial interests were reported for 23 investigators from 261 sites. Dr. Dinsmore performed data modeling analysis and concluded that an “analysis of sites in studies 1253 and 1358 where there are investigators with disclosable financial interests does not reveal evidence that these sites exert influence on the efficacy outcome of the respective studies.” For more detail the reader is referred to Dr. Dinsmore’s review.
- **Other Good Clinical Practice (GCP) issues:** No issues were identified (refer to Dr. Dinsmore’s review).
- **Office of Scientific Investigations (OSI) audits:** Two sites for each of two pivotal clinical efficacy trials (1358 and 1253) were inspected. As per Dr. Dinsmore, no issues were identified, which might undermine interpretation of study results. His review does note that, “For the preliminary/pending classifications, a summary addendum will be generated if conclusions change upon receipt and review of the EIRs.” A latter communication in DARRTS by OSI noted all sites are “considered reliable and appear acceptable in support of the pending application.”

12. Labeling

Please see final Label and discussions in the above review.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS): None determined to be necessary.

Postmarketing Requirements (PMRs) and Commitments (PMCs): Only PMRs related to PREA. See above Pediatrics section.

Postmarketing Pharmacovigilance: The applicant must provide postmarketing surveillance and enhanced pharmacovigilance for interstitial nephritis. All cases of renal failure or interstitial nephritis must be reported in an expedited fashion. The applicant should provide a semiannual report that provides a cumulative/synthesized analysis of all post marketing cases of renal failure, interstitial nephritis and other reported alterations in renal function. This should include an analysis of causality and information on pertinent laboratory values (serum creatinine, creatinine clearance, pertinent serum electrolytes, serum pH, and biopsy reports).

⁵ pivotal efficacy trial

⁶ pivotal efficacy trial

⁷ pivotal efficacy trial

14. Recommended Comments to the Applicant

The application should be approved for all formulations. See the above request for postmarketing pharmacovigilance.

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/s/

NORMAN HERSHKOWITZ
02/14/2016