CLINICAL REVIEW

Application Type	NDA EFFICACY SUPPLEMENT, Prior Approval Efficacy Supplement
Application Number(s)	205836 (Tablet), 205837 (injection), 205838 (oral solution)
Priority or Standard	Standard
Submit Date(s)	July 10, 2017
Received Date(s)	July 10, 2017
PDUFA Goal Date	May 10, 2018
Division/Office	DNP / ODE1
Reviewer Name(s)	Steven Dinsmore
Review Completion Date	3/21/18
Established/Proper Name	Brivaracetam
(Proposed) Trade Name	Briviact
Applicant	UCB, Inc
Dosage Form(s)	Tablet, Oral solution
Applicant Proposed Dosing Regimen(s)	Weight ≥50 kg: The recommended starting dosage for monotherapy and adjunctive therapy is 25 mg twice daily (50 mg per day). The recommended maintenance dosage is 50 mg twice daily (100 mg per day). Weight <50 kg: The recommended starting dosage for monotherapy and adjunctive therapy is 0.5 mg/kg twice daily (1 mg/kg per day). The recommended maintenance dosage is 1 mg/kg twice daily (2 mg/kg per day).
Applicant Proposed Indication(s)/Population(s)	This supplement proposes the use of BRIVIACT as monotherapy and adjunctive therapy in the treatment of partial onset seizures (POS) in patients 4 to younger than 16 years of age with epilepsy in accordance with required pediatric studies 3042-1 and 3042-4
Recommendation on Regulatory Action	approval
Recommended Indication(s)/Population(s) (if applicable)	the treatment of partial-onset seizures in patients 4 years of age and older with epilepsy

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AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

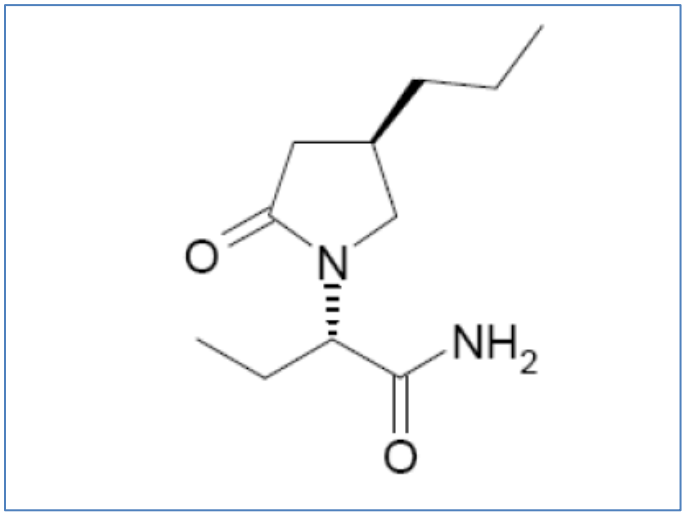
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PCST	possibly clinically significant treatment-emergent
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
POS	partial onset seizures
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Brivaracetam (BRV, ucb 34714), is a 2-pyrrolidone derivative. Brivaracetam is both the INN and the USAN name for (2S)-2-[(4R)-2-oxo-4- propyltetrahydro-1H-pyrrol-1-yl] butanamide (IUPAC).

Brivaracetam displays a high and selective affinity for brain-specific binding site synaptic vesicle protein 2A (SV2A). This appears to be the primary target for its pharmacological activity.



Brivaracetam is available in an oral tablet, solution and injection for intravenous use where only tablets and suspension are relevant to this application. Tablets are available in 10mg, 25mg, 50mg, 75mg, and 100mg strength. Oral solution is available in 10mg/ml solution. It is also available in injection form (NDA 022254), for the indication of short-term management of seizures in adult patients with POS unable to tolerate oral therapy. The injection form is included by reference in this supplement for labeling purposes only, as all three forms share Full Prescribing Information, but is not recommended for use in pediatric patients pending the completion of further studies.

The sNDA expansion of indication is the addition of ages 4 to < 16 years of age.

1.2. Conclusions on the Substantial Evidence of Effectiveness

There are no pediatric efficacy study data included in this Application. This sNDA proposes an expanded indication for adjunctive and monotherapy treatment of partial onset seizure in the

population of patients aged 4 to less than 16 years of age.

This expanded indication must meet the conditions identified in the Guidance for Industry, Drugs for the Treatment of Partial Onset Seizure: …"[1]. This expanded indication requires an approved indication for the treatment of POS in adults and dosing in the proposed pediatric population that provides similar drug exposure to levels demonstrated to be effective in adults.

The efficacy of BRV for POS adjunctive treatment was established by the 3 adequate and well-controlled studies N01252, N01253, and N01358 submitted in the NDA (11/24/2014). Monotherapy use in treatment was approved on 9/14/2017. Evidence for the achievement of exposures similar to adult dosing of BRIVIACT is based on the results of modeling report CL0187 (Population Pharmacokinetic Analysis of Brivaracetam in Epileptic Pediatric Patients from Study N01263) and modeling report CL0258 (Brivaracetam PD Predictions in Pediatric Subjects Aged 4-16 Years with Partial Onset Seizures: Extrapolation of Levetiracetam Adult-Pediatric Scaling to Brivaracetam).

Overall the requirements for extrapolation of efficacy have been met. Following examination of the sponsor's data the Clinical Pharmacology team recommended an additional tier of weight based dosing at the threshold of 20kg body mass. The tiers on above and below have separate boundaries for maintenance dose. Also see sections 3.2 Summary of Presubmission/Submission Regulatory Activity and section 4.5 Clinical Pharmacology.

1.3. Benefit-Risk Assessment

[1] Drugs for Treatment of Partial Onset Seizures: Full Extrapolation of Efficacy from Adults to Pediatric Patients 4 Years of Age and Older Guidance for Industry February 2018. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm596731.pdf

Benefit-Risk Integrated Assessment

Expansion of this currently available treatment to the pediatric population 4 to <16 will bring the pediatric therapeutic armamentarium closer to that available for adults. There are no apparent selective safety vulnerabilities in the pediatric to change the established benefit-risk balance.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Approximately 30% of patients remain refractory to available antiepilepsy drug therapy.[2]	The large proportion of patient's resistant to current pharmacotherapy leaves room for additional AED treatment options. This is additionally true for the pediatric population.
Current Treatment Options	• From among the available AEDs only a subset are approved in the pediatric age range.	As shown in Table 1 the treatment options are more limited in the pediatric population, more so for monotherapy. Expanding AED treatment options will be a public health benefit for this population.
Benefit	• Reduction of seizure frequency	Efficacy of brivaracetam treatment is measured by reduction of seizure frequency. This reduction reduces morbidity and mortality and increases quality of life for patients.
Risk and Risk Management	• Currently labeled risks do not exceed those of other established antiepilepsy drug therapies. None are a barrier to expansion into the pediatric population	There is now extensive experience with brivaracetam in the population 16 years and older. No new concerning signals have emerged in post marketing.

[2] Kwan P, Sander JW. The naural history of epilepsy: an epidemiological view. J Neurol Neurosurg Psychiatry 75:1376-81.

1.4. Patient Experience Data

none

2. Therapeutic Context

2.1. Analysis of Condition

"Up to 5% of the world population experience nonfebrile seizures at some point in life, with a bimodal onset seen in children and older adults. Within epilepsy are many different types of seizures that vary widely in severity, appearance, cause, consequence, and management. Prolonged or repetitive seizures are potentially life-threatening.

Management of epilepsy is focused on 3 main goals: controlling seizures, avoiding treatment adverse effects, and maintaining or restoring quality of life. Following a new diagnosis, it is critical to accurately identify seizure type in order to select the appropriate initial antiepileptic drugs (AEDs). Drug-specific adverse effects and patient preferences ideally are evaluated prior to AED selection. Monotherapy with AEDs is effective in reducing seizures for 70% to 80% of patients. The remaining 20% to 30% have refractory seizures and/or significant adverse effects from AEDs." [3]

2.2. Analysis of Current Treatment Options

From among the antiepilepsy drugs approved for POS in adults only a small subset is currently approved for treatment of the pediatric population with a smaller proportion approved for monotherapy use, Table 1.

Table 1 Currently Available AEDs approved for Partial Onset Seizures[4]

AED	Adjunctive therapy in Pediatric POS	Monotherapy in Pediatric POS
Levetiracetam	Yes (≥ 1 month)	No
Valproic Acid	Yes (age not specified in dosing but label mentions age 3 months)	Yes (≥ 10 years)
Topiramate	Yes (≥ 2 years)	Yes (≥ 2 years)
Lamotrigine	Yes (≥ 2 years)	No (yes ≥ 16 years)
Gabapentin	Yes (≥ 3 years)	No
Oxcarbazepine	Yes (≥ 4 years)	Yes (≥ 4 years)

[3] Kappes JA, Hayes WJ, Strain JD, Farver DK. 2017. Brivaracetam: An Adjunctive Treatment for Partial-Onset Seizures. Journal of Clinical Pharmacology 57:811-817.
[4] From sNDA 22253, lacosamide (Vimpat) Clinical Review page 7, Freilich E, 9/29/2017

AED	Adjunctive therapy in Pediatric POS	Monotherapy in Pediatric POS
Vigabatrin	Yes (10-16 years), but not first line due to safety issues	No
Tiagabine	Yes (≥ 12 years)	No
Perampanel	Yes (≥ 12 years)	No
Primidone	Yes, generally	No
Phenytoin	Yes (age not specified)	No
Carbamazepine	Yes (age not specified)	No
Phenobarbital	seizure type not specified in label	No
Eslicarbazapine	Yes (≥ 4 years)	Yes (≥ 4 years)
Lacosamide	Yes (≥ 4 years)	Yes (≥ 4 years)
Zonisamide	No	No
Pregabalin	No	No
Felbamate	No*	No
Rufinamide	No*	No
Clobazam	No*	No
*Approved for pediatric patients with Lennox-Gastaut Syndrome (LGS)		

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Brivaracetam oral tablets, oral solution and injection, for intravenous use was approved as adjunctive therapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy on February 18, 2016. A schedule V designation was added to the label on 6/3/2016. The indication was modified from "adjunctive therapy in the treatment of partial-onset seizures" to "treatment of partial-onset seizures" to allow for use as monotherapy on 9/14/2017.

3.2. Summary of Presubmission/Submission Regulatory Activity

The primary regulatory activity relevant to this submission is the determination that efficacy may be extrapolated from adults to pediatric patients ≥ 4 years of age. This was communicated to the sponsor in a General Advice letter on 11/12/2015. This was subsequently fully articulated in a Draft Guidance in February of 2018.[5] This guidance states that "These analyses, conducted for drugs with a variety of putative mechanisms of action, have allowed FDA to conclude that

[5] Drugs for Treatment of Partial Onset Seizures: Full Extrapolation of Efficacy from Adults to Pediatric Patients 4 Years of Age and Older Guidance for Industry. Clinical Pharmacology/Clinical, February 2018

the efficacy of drugs approved for the treatment of POS can 57 be extrapolated from adults to pediatric patients 4 years of age and older."

Pediatric extrapolation is conditional on the following factors:

1. The treatment population has partial onset seizures
2. Patients are ≥ 4 years of age
3. Proposed dosing provides exposures similar to that of effective treatment levels in adult patients
    a. To support extrapolation, blood concentrations of active drug/metabolites should be obtained from an adequately designed pharmacokinetic and tolerability study in which single and/or multiple doses of the investigational drug are administered in patients 4 to 16 years of age.
    b. Pharmacokinetic data from that study should be used to determine pediatric dosages and regimens that provide drug exposure similar to levels shown to be effective in adult patients with POS.
4. Safety data cannot be extrapolated from adults to children. Clinical study should be performed to adequately characterize the safety of the drug in pediatric patients 4 years of age and older with POS, with all ages well represented.
    a. In general, a minimum of 100 pediatric patients should be exposed to the drug for at least 6 months of treatment.

Monotherapy may also be extrapolated. This determination was communicated by the following statement to the sponsor on September 13, 2016:

- The Division of Neurology Products has determined that it is acceptable to extrapolate the efficacy and safety of drugs approved as adjunctive therapy for the treatment of partial onset seizures (POS) to their use as monotherapy for the treatment of POS. This extrapolation applies to both adult and pediatric populations, provided that efficacy and safety as adjunctive therapy for the treatment of POS have been previously established in the respective age range.

On 9/14/2017 the indication for brivaracetam treatment changed from "BRIVIACT is indicated as adjunctive therapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy" to "BRIVIACT is indicated for the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy". This change broadened the indication to allow for use as adjunctive or monotherapy.

A Pre-NDA meeting concerning this supplement was conducted on March 9, 2017. Key points from this meeting are identified in the following list:

- Pediatric safety data may support the proposed indication for both adjunctive and monotherapy. The monotherapy use was contingent at the time on a pending supplement for extrapolation of monotherapy in the population age 16 year and older.
- It was agreed the pooling strategy and analyses described in the ISAP (Integrated Statistical Analysis Plan) are adequate to support filing and review.
- the safety database cut off dates for both clinical study (8/31/16) and post marketing safety data (10/14/16) were proposed and agreed as well as the date for the 120 day safety update.
- This meeting also contained extensive discussion on concerning the scaling of pediatric dosing based on sponsor studies CL0258 and CL0187. Please see the Clinical Pharmacology Review.

3.3. Foreign Regulatory Actions and Marketing History

The date of first authorization worldwide was January 14, 2016 in the EU. Since US approval up toe September 17, 2017 Worldwide marketing authorization has been expanded to Canada, Australia, Mexico, Turkey and Russia, and Switzerland. Overall holds the marketing authorization for BRV in 38 of countries worldwide. Brivaracetam has not been withdrawn in any country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No OSI audit was initiated. There was no efficacy study for this expanded population.

4.2. Product Quality

No new quality information was included in this submission.

4.3. Clinical Microbiology

N/A

4.4. Nonclinical Pharmacology/Toxicology

Non-Clinical was covered in the initial brivaracetam NDA review. There were no new non-clinical issues for this submission.

4.5. Clinical Pharmacology

Brivaracetam (BRV) ((2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1H-pyrrol-1-yl]butanamide) is indicated as adjunctive therapy in the treatment of partial-onset seizures (POS) in adults with epilepsy. Brivaracetam displays a high and selective affinity for synaptic vesicle protein 2A (SV2A) in the brain. Binding to SV2A is believed to be the primary mechanism for BRV anticonvulsant activity.

Metabolism

Brivaracetam is primarily metabolized by hydrolysis of the amide moiety to form the corresponding carboxylic acid metabolite, and secondarily by hydroxylation on the propyl side chain to form the hydroxy metabolite. The hydrolysis reaction is mediated by hepatic and extra-hepatic amidase. The hydroxylation pathway is mediated primarily by CYP2C19. In human subjects possessing genetic variations in CYP2C19, production of the hydroxy metabolite is decreased 2-fold or 10-fold, while the blood level of brivaracetam itself is increased by 22% or 42%, respectively, in individuals with one or both mutated alleles. CYP2C19 poor metabolizers and patients using inhibitors of CYP2C19 may require dose reduction. An additional hydroxy acid metabolite is created by hydrolysis of the amide moiety on the hydroxy metabolite or hydroxylation of the propyl side chain on the carboxylic acid metabolite (mainly by CYP2C9). None of the 3 metabolites are pharmacologically active.[6]

Excretion

Brivaracetam is eliminated primarily by metabolism and by excretion in the urine. More than 95% of the dose, including metabolites, is excreted in the urine within 72 hours after intake. Fecal excretion accounts for less than 1% of the dose. Less than 10% of the dose is excreted unchanged in the urine. Thirty-four percent of the dose is excreted as the carboxylic acid metabolite in urine. The terminal plasma half-life (t1/2) is approximately 9 hours.[7]

Pediatric Dosing

The sponsor performed two PK – PK/PD modeling and simulation studies to support pediatric adjunctive therapy and monotherapy. The objectives of these studies and the source data for each are provided in Table 2.

[6] BRIVIACT (brivaracetam) label, 9/14/2017
[7] Ibid.

Table 2 Summary of BRV PK and PK/PD modeling and simulation studies supporting pediatric adjunctive therapy and monotherapy

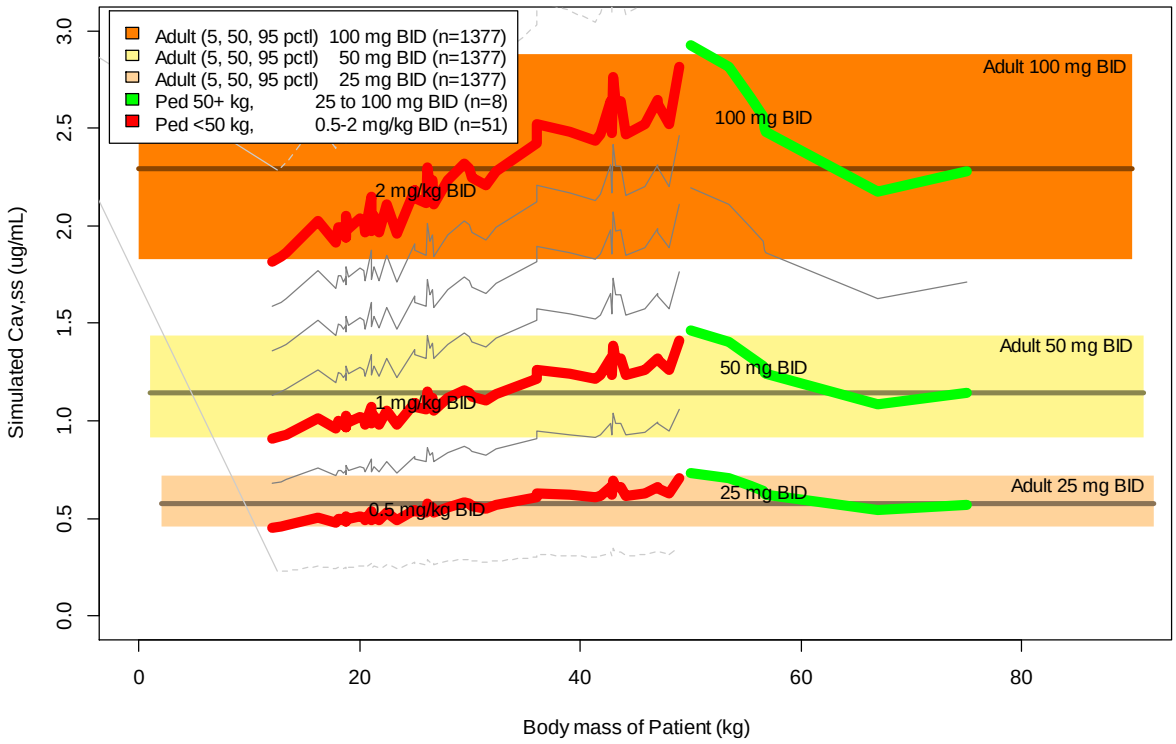
Study number	High-level objectives	BRV study data included	Total number of subjects
CL0187 (Amended report)	1) To develop a population PK model for BRV in pediatric patients 2) To perform simulations to provide pediatric dosing adaptations	N01263 (pediatric Phase 2a)	96
CL0258	1) To develop a combined population PK/PD model for LEV in pediatric and adult subjects, to assess the potential change in PK/PD relationship between adult and pediatric subjects 2) To use the obtained scaling in LEV PK/PD relationship from adult to pediatric subjects to predict the BRV efficacious dose in pediatric subjects based on the existing PK/PD model for BRV in adult subjects	N01252 (adult Phase 3) N01253 (adult Phase 3) N01358 (adult Phase 3) N01263 (pediatric Phase 2a)	1549 (adult) 96 (pediatric)
BRV=brivaracetam; LEV=levetiracetam; PK=pharmacokinetic; PK/PD=pharmacokinetic/pharmacodynamics			

The sponsor proposed weight based dosing for pediatric patients. For patient with a weight greater than 50kg the proposed recommended starting dose is 25mg twice a day (50mg/day). This represents half the recommended adult starting dose for patients 16 years and older which is 50mg twice daily (100mg/day). The proposed recommended starting dose for pediatric patients 50kg> is 0.5mg/kg/day.

The conditions for extrapolation require the proposed pediatric dose provide exposures corresponding to the adult dose level. The Clinical Pharmacology team simulated exposure by weight at the proposed dosing. This simulation reveals a trend of decreasing exposure with body mass below 50kg. At approximately 20kg body mass the simulated pediatric exposure approaches the lower confidence band of adult exposures for each of the adult doses including 25mg twice a day, 50mg twice a day and 100mg twice a day. The most critical of these observations applies to the match between 25mg twice a day adult dose and the proposed pediatric starting dose of 0.5mg/kg/day, Figure 1.

The strategy to optimize exposure in at the lower spectrum of pediatric body mass in the 4 to <16-year age spectrum will be tiered dosing with a transition at 20kg body mass. This plan will maintain the proposed starting dose of 0.5mg/kg twice daily but widen the recommended pediatric maintenance dose boundaries to shift exposure toward the point estimate of adult exposure at 25mg twice a day dosing, Table 29.

Figure 1 Pediatric Simulated Exposure by Body Mass Compared to Adult Exposure at 25mg, 50mg and 100mg Twice a Day Dosing.



5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The safety pool for pediatric subjects ≥1 month to <17 years of age with epilepsy (Pool Pediatric Studies) included data from the completed open-label core study (N01263) and ongoing open-label, follow-up study (N01266). Study N01263 was an open label, single arm, multicenter PK, safety and efficacy study of adjunctive administration of brivaracetam in subjects in the age range ≥ 1 month to < 16 years with epilepsy. Inclusion criteria for study N01263 include Localization-related, generalized or undetermined focal or generalized epileptic syndrome (i.e., infantile spasms, Lennox-Gastaut Syndrome, myoclonic-astatic epilepsy, absence epilepsies [childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), and myoclonic absence

epilepsy]), and other symptomatic generalized epilepsies, according to the ILAE classification, and subjects taking at least 1 but no more than 3 concomitant AEDs. Ninety-nine patients received brivaracetam in the safety dataset of study N01263, see Table 3

.

N01266 was initially designed as a long-term follow-up (LTFU) to N01263 (enrolled subjects with either focal epilepsy or generalized epilepsy), but was amended to allow direct enrollment of subjects ≥4 to <17 years of age with focal epilepsy. Inclusion criteria for patients enrolled directly into study N01266 for long term follow up was limited to patients with a clinical diagnosis of partial onset seizures (POS) treated with at least 1 AED, see Table 4.

Table 3 Studies of Pediatric Patients with epilepsy, N01263 and N01266

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Studies to Support Safety							
N01263	open-label, single arm, multicenter, fixed 3-step up-titration study in subjects with epilepsy	BRV 1, 2, 4mg/kg/day for subjects <8 years; BRV 0.8, 1.6, 3.2mg/kg/day for subjects ≥8 years with max BRV 50, 100, 200mg/day oral solution	steady-state PK of BRV and its metabolites in subjects, safety, tolerability	5 weeks	100	epilepsy	29 sites, 26 investigators in Belgium, Czech Republic, Mexico, Poland, Spain, USA with 26 investigators
N01266	Open label single arm, multicenter long term follow-up study including patients enrolled in study N01263 and patients enrolled directly	Flexible dose (min 1.0mg/kg/ day) to max BRV 5.0mg/ kg/day; not to exceed max 200mg/day for subjects >40kg Subjects <7 years: oral solution Subjects ≥7 years: oral tablets	Long term safety and tolerability and assess efficacy of long term BRV therapy	Mean = 698 days, median = 656 days, range 7 – 1800 days (4.9 years)	206	epilepsy	32 sites, 32 investigators, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Czech Republic, Estonia, Finland, France, Germany, Hong Kong, Hungary, India, Ireland, Israel, Italy, Japan, Latvia, Lithuania, Mexico, Montenegro, Netherlands, Norway, Poland, Puerto Rico, Republic of Korea, Réunion, Romania, Russia, Serbia, Singapore, South Africa, Spain, Sweden, Switzerland, Taiwan, Tunisia, Turkey, Ukraine, United Kingdom, USA

Table 4 Demographic profile of studies N01263 and N01266

Demographic Parameter	N01263 SAFETY POPULATION (n=99) ADaM -ADSL	N01266 SAFETY POPULATION (n=206) ADaM - ADSL
Sex		
Male	48	91
Female	51	115
Age		
Mean years (SD)	6.3	8.4
Median (years)	5.5	8.5
Min, max (years)	0.17, 15.6	0.25, 16.9
Age Group		
< 4 years	38	33
4 ≤ age <16 years	61	170
16 ≤ age <17 years	0	3
Race		
White	79	146
Black or African American	4	3
Hispanic	13	54
Biracial	3	3
Ethnicity		
Hispanic or Latino	20	
Not Hispanic or Latino	79	
Region		
United States	29	51
Mexico	19	59
EU	51	96

5.2. Review Strategy

The clinical review is directed at assessment of brivaracetam safety in the patient cohort of the expanded age range (patients age 4 to <16 years of age). This information is provided by studies N01263 and N01266 shown in Table 3.

6. Integrated Review of Effectiveness

6.1. Assessment of Efficacy Across Trials

There are no pediatric efficacy study data included in this Application. This sNDA proposes an expanded indication for adjunctive and monotherapy use of BRV for the treatment of partial onset seizure in the population of patients aged 4 to less than 16 years of age based on extrapolation of efficacy data, see section 1.2 Conclusions on the Substantial Evidence of Effectiveness.

7. Review of Safety

7.1. Safety Summary

See Integrated Assessment of Safety, section 7.11

7.2. Safety Review Approach

Pool Pediatric Studies

Pool Pediatric Studies consisted of subjects who received BRV in core study N01263 and long-term study N01266. Pool Pediatric Studies differs from the original application's Pool Pediatric in that it includes only subjects from N01263 and N01266 and does not include pediatric subjects from the panel of adult studies from initial brivaracetam NDA where there were 29 patients < age 17 and 2 patients under age 16 years from a total phase 2/3, open label follow up safety pool of 2388 patients.[8]

An analysis ADaM dataset that directly represented the "Pool Pediatric Studies" used for analysis and discussion in the sponsor module 2 Summary of Clinical Safety or module 5 ISS could not be identified in this efficacy submission (7/10/17). Only the individual study 1263 and 1266 ADaM or SDTM were available to the reviewer. The ISS datasets section 5.3.5.3. (Reports of Analyses of Data from More than One Study) were carryover sets from the original NDA submission and did not include an integration of studies 1263 or 1266 into the dataset pool. This is confirmed by examination of the ISS ADaM, ADSL dataset where 1263 and 1266 are absent.

"Pool Pediatric Studies" consists of adverse events from study studies N01266 and N01263.

[8] Supplement 5, section 2.7.4, Summary of Clinical Safety, page 19.

Study N01266 was a long term follow up study N01263. Study N01263 was a PK, safety and efficacy study in the original brivaracetam NDA submitted 11/24/14. The "Pool Pediatric Studies" contains patients from study N01266 who entered long term follow up from study N01263 as well as pediatric patients in the age range 4 to <16 years who could be directly enrolled in study N01266. This Pool also contains the subset of study N01263 patients who did not proceed into study N01266 for long term follow up but whose brivaracetam exposure was limited to 5 weeks during study N01263. These patients, although with a shorter exposure interval, may contribute events to the "Pool Pediatric Studies".

As noted in the above paragraph an analysis (ADaM) xpt adverse event dataset of the "Pool Pediatric studies" was not provided so the reviewer assembled an equivalent "Pool Pediatric Studies" adverse event dataset. The methodology for assembling the dataset is provided in the following paragraphs. The first step is to identify those patients from study N01263 adsl.xpt dataset who did not enter LTFU in N01266. There were 13 patients in study N01263 who did not proceed into long term follow up (N01266). These patient ID (USUBJID) numbers were used to capture associated adverse events from the study N01263 data analysis ADaM adverse event dataset, adae.xpt. These adverse events were then concatenated to the N01266 ADaM, adae.xpt dataset that was submitted with this efficacy supplement on 7/10/17.

This process yielded a total of 219 pediatric patients (study ID) of all seizure types with a safety population flag from both studies N01263 and N01266. From among these patients there were 168 patients with a partial onset seizure (POS) flag. From among these 168 patients there were 16 patients in the <4yr age group and 149 patients in the <4 yrs to ≤16 yr age group. There were an additional 3 patients with 16< age <17 years. These sample groups match the numerical subsets presented in the sponsor "Summary of Clinical Safety" and ISS.

The Study N01263 USUBJID list was used to capture adverse events from the ADaM adverse event dataset for study N01263 data submitted with the original brivaracetam NDA submitted 11/24/14. This adverse event subset was then concatenated with the study N01266 ADaM adverse event (adae.xpt) dataset to yield an adverse event dataset to represent "Pool Pediatric studies" comparable to the sponsor (not submitted) dataset.

The concatenated dataset yielded a total of 2371 adverse events from among 209 patients. From among these adverse events there were 2369 events from among 207 patients with a positive safety population flag. Patients from study phase "baseline" and "post-treatment" (variable SPHASE) are excluded. This exclusion yields 2301 adverse events from among 205 patients. Difference, 68 adverse events. This does not match the sponsor TEAE overall summary table 6-1, ISS page 98, for Pool Pediatric Studies where a total of 2239 adverse event are recorded from 205 patients. The number of patients in the sponsor tally and reviewer tally is equal at 205 but total reviewer adverse events from these 205 patients exceeds the sponsor's count by 62 adverse events. The reviewer adverse event dataset will be used to populate subsequent sections for "Deaths", "Serious Adverse Events", "Dropouts and Discontinuations",

"Significant Adverse Events" and "Treatment Emergent Adverse Events" with supplementation from the sponsor tables and discussions in the ISS and from patient narratives when needed. Some tables corresponding to the sponsor tables in the ISS, the row and column layout will be used but populated with results derived from the reviewer assembled, ADaM "Pool Pediatric Studies "dataset.

3 Patients exceeding age 16 years

There are three patients in this dataset with an age between 16 and 17 years. Two of these patients contributed adverse event entries to the total "Pediatric Pool" and the subset from the total pool of ages 4 to <16 with partial onset seizures. These two patients had 19 adverse event entries under 12 preferred terms with one SAE associated with a PT of convulsion and one discontinuation due to "suicidal ideation". There is an exception in the evaluation of "Psychiatric Events" in section 7.6.1 where these two patients were excluded. Overall the adverse event entries from these patients contribute 0.8% of the total entries. These patients are 11 months outside the 16 year age boundary at maximum and do not notably influence the conclusions for the 4 to <16 population.

120 Day Safety Update

In the initial submission safety dataset analysis, the "Pool Pediatric Studies" is examined as described above. To assess the change in safety events over the interval from the initial submission to the 120-day safety update study 1266 alone is examined. The change from the initial submission of study 1266 to the 120-day update will reflect the accrual of safety events relevant to this submission

7.3. Review of the Safety Database

7.3.1. Overall Exposure

Pool Pediatric Studies included subjects from N01263 and N01266. In this integrated safety analysis pool, subjects in the pediatric studies were given doses of BRV from 0.8 to 5.0mg/kg/day, not exceeding 200mg/day. In "Pool Pediatric Studies", the calculation of BRV modal daily doses considered the administration of both oral solution and oral tablets, where oral solution was administered in mg/kg doses and tablets were administered in mg doses. Tablet doses (mg/kg) were converted to mg/kg/day.

Table 5 Overall duration of exposure to BRV by pediatric summary group (Pool pediatric studies N01263 and N01266)[9]

	BRV overall			
	POS summary group			All pediatric subjects N=219
	<4y N=16	≥4 to <16y N=149	Total POS N=168	
Number of subjects exposed, n (%)	16 (100)	149 (100)	168 (100)	219 (100)
Subject-years of exposure	36.9	249.7	290.0	399.5
Duration of exposure, n (%)				
≥1 month	14 (87.5)	143 (96.0)	160 (95.2)	211 (96.3)
≥3 months	13 (81.3)	125 (83.9)	140 (83.3)	185 (84.5)
≥6 months	13 (81.3)	116 (77.9)*	131 (78.0)*	166 (75.8)*
≥12 months	11 (68.8)	104 (69.8)*	117 (69.6)*	146 (66.7)
≥18 months	11 (68.8)	81 (54.4)	93 (55.4)	119 (54.3)
≥24 months	10 (62.5)	58 (38.9)	69 (41.1)	93 (42.5)
≥30 months	8 (50.0)	27 (18.1)	35 (20.8)	57 (26.0)
≥36 months	8 (50.0)	20 (13.4)	28 (16.7)	50 (22.8)
≥42 months	6 (37.5)	15 (10.1)	21 (12.5)	42 (19.2)
≥48 months	2 (12.5)	14 (9.4)	16 (9.5)	33 (15.1)
≥54 months	0	4 (2.7)	4 (2.4)	6 (2.7)
≥60 months	0	2 (1.3)	2 (1.2)	3 (1.4)

*Reviewer Confirmed from ADEXS and ADSL, study 1266 ADaM dataset, counts include 3 patients > 16 years of age with 0.175, 1.17 and 2.06 yrs of exposure.

Table 6 Overall exposure and duration of exposure to BRV for subjects ≥4 to <16 years with POS by BRV modal daily dose (Pool pediatric studies N01263 and N01266)[10]

	BRV modal daily dose (mg/kg/day)					BRV Overall N=149
	0.0 to 1.0 N=15	>1.0 to 2.0 N=10	>2.0 to 3.0 N=19	>3.0 to 4.0 N=79	>4.0 N=26	
Number of subjects exposed, n (%)	15 (10.1)	10 (6.7)	19 (12.8)	79 (53.0)	26 (17.4)	149 (100)
Subject-years of exposure [a]	13.0	12.5	29.7	151.0	43.6	249.7
Number of subjects exposed by duration of exposure, n (%)						
≥1 month	9 (6.3)	10 (7.0)	19 (13.3)	79 (55.2)	26 (18.2)	143 (96.0)

[9] From Sponsor Table 5-3, ISS page 67
[10] From Sponsor Table 5-4, ISS page 68

	BRV modal daily dose (mg/kg/day)					BRV Overall N=149
	0.0 to 1.0 N=15	>1.0 to 2.0 N=10	>2.0 to 3.0 N=19	>3.0 to 4.0 N=79	>4.0 N=26	
≥3 months	9 (7.2)	5 (4.0)	17 (13.6)	69 (55.2)	25 (20.0)	125 (83.9)
≥6 months	8 (6.9)	5 (4.3)	15 (12.9)	64 (55.2)	24 (20.7)	116 (77.9)
≥12 months	7 (6.7)	5 (4.8)	12 (11.5)	58 (55.8)	22 (21.2)	104 (69.8)
≥18 months	3 (3.7)	4 (4.9)	12 (14.8)	46 (56.8)	16 (19.8)	81 (54.4)
≥24 months	1 (1.7)	3 (5.2)	7 (12.1)	37 (63.8)	10 (17.2)	58 (38.9)
≥30 months	1 (3.7)	1 (3.7)	2 (7.4)	20 (74.1)	3 (11.1)	27 (18.1)
≥36 months	1 (5.0)	1 (5.0)	1 (5.0)	16 (80.0)	1 (5.0)	20 (13.4)
≥42 months	1 (6.7)	1 (6.7)	1 (6.7)	12 (80.0)	0	15 (10.1)
≥48 months	0	1 (7.1)	1 (7.1)	12 (85.7)	0	14 (9.4)
≥54 months	0	0	0	4 (100)	0	4 (2.7)
≥60 months	0	0	0	2 (100)	0	2 (1.3)

Table 5 reveals that 166 pediatric patients (any <16 years) had brivaracetam exposure for 6 months or longer with 146 patients having exposure for 12 months or longer. Table 6 is an examination of modal dose by duration. This examination reveals that 103 patients had a modal dose of brivaracetam greater than 2mg/kg where 24 of these patients had a modal dose >4mg/kg. There were 92 patients who had a modal dose of >2mg/kg for ≥ 12 months where 22 of these patients were treated with a modal dose >4mg/kg.

Reviewer comment: There were 108 pediatric patients exposed to a range of brivaracetam dose from 1.0mg/kg/day to >4mg/kg/day. This is adequate for an sNDA where brivaracetam use in the broad adult population is extensive in both the pre-marketing and post marketing intervals.[11]

7.3.2. Relevant characteristics of the safety population:

Examination of the age distribution of the Pool Pediatric Studies is divided into 4 subgroups each of 3 years duration, Table 7. The examination reveals excesses or deficits seen in the age 4 to 16 years spectrum. The distribution of the population had a favorable quality due to a modest excess in the youngest age strata, Table 25. There was a small excess of male over female participants. Both of these features support adequate generalizability to the population of this indication expansion.

There was a more restricted distribution of racial composition with predominantly Caucasian and other/mixed participants, Table 25. The category other/mixed is not defined further in the submission. Broad racial generalizability is not well supported by the makeup of the Pool

[11] Drugs for Treatment of Partial Onset Seizures: Full Extrapolation of Efficacy from Adults to Pediatric Patients 4 Years of Age and Older Guidance for Industry, February 2018.

Pediatric studies. Generalizability is inherently limited across subgroups due to small study population leaving the broader adult studies to inform the racial subgroup generalization.

Table 7 Age Strata for Pool Pediatric Study examination.

age strata
4 to <7
7 to < 10
10 to < 13
13 to 16

7.3.3. Adequacy of the safety database:

As noted in section 7.3.1 the safety database is adequate.

7.4. Adequacy of Applicant's Clinical Safety Assessments

7.4.1. Issues Regarding Data Integrity and Submission Quality

A single site was identified with recurrent entries of systolic blood pressure measurements of 125 or 120 mmHg from site 402, Dr. B. Senkowska. Examination of the profile of adverse event frequency and preferred terms does not reveal notable deviation from other study sites.

7.4.2. Categorization of Adverse Events

For all Phase 2 and Phase 3 studies (along with the clinical pharmacology studies) an AE was any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product that did not necessarily have a causal relationship with this treatment. An AE could, therefore, have been any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Signs or symptoms of the condition/disease for which the investigational product was being studied were recorded as AEs only if their nature changed considerably or their frequency or intensity increased in a clinically significant manner as compared to the clinical profile known to the Investigator from the subject's history or the Baseline Period.

In all pooled studies, adverse events were coded to MedDRA version 15.0. For all studies, once it was determined that a subject experienced an AE, the seriousness of the AE was determined. An SAE met 1 or more of the following criteria:

Death, Life-threatening: Life-threatening did not include a reaction that might have caused death had it occurred in a more severe form. Significant or persistent disability/incapacity. Congenital anomaly/birth defect (including that occurring in a fetus). Important medical event that, based upon appropriate medical judgment, might have jeopardized the patient or subject and might have required medical or surgical intervention to prevent one of the other outcomes listed in the definition of serious. Initial inpatient hospitalization or prolongation of hospitalization.

7.4.3. Routine Clinical Tests

The profile of routine clinical tests obtained in the Pool Pediatric studies is shown in Table 8. This profile is appropriate to inform assessment of clinical safety.

Table 8 Routine Clinical Laboratory Studies Obtained during Patient Treatment in Pool Pediatric Studies.

Hematology	Clinical chemistry	Urinalysis
White blood cells (WBC) Red blood cells (RBC) Hemoglobin Hematocrit Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Platelet count Lymphocytes Monocytes Neutrophils Eosinophils Basophils	Glucose Sodium Potassium Calcium Chloride Bicarbonate Phosphorus (inorganic) Total protein Albumin Total bilirubin Alkaline phosphatase Aspartate aminotransferase (AST/SGOT) Alanine aminotransferase (ALT/SGPT) Gamma-glutamyltransferase (GGT) Uric acid Urea Creatinine Triglycerides Cholesterol (total, high-density lipoprotein and low-density lipoprotein)	Glucose Ketones Occult blood Protein Nitrites Leukocytes Microscopic examination including bacteria, cells, casts, and crystals

7.5. Safety Results

7.5.1. Deaths

In the Pool Pediatric Studies, a total of 4 subjects had TEAEs with fatal outcome during the BRV clinical development program as of the clinical cutoff date of 31 Aug 2016; 3 subject deaths were reviewed with the original application and 1 subject died since the original application was reviewed. The TEAEs with fatal outcomes were aspiration, septic shock/pneumonia, pneumonia, and circulatory collapse. All fatal events were considered not related to study drug by the Investigator and the sponsor.

Table 9 Patient TEAE with Fatal Outcome, Pool pediatric studies N01263 and N01266*

Subject number	Age (at time of death)/ gender	BRV dose at TEAE onset	Cause of death per PS database (Clinical database)	Causality per Investigator/ sponsor	Duration of exposure to BRV (months)
Death reported since original application was reviewed					
(b) (6)	**6y/F**	**4mg/kg/day**	**Septic shock/ pneumonia**	**Not related/ Not related**	**30.2**
Deaths reviewed with original NDA submission					
(b) (6)	2y/M	4mg/kg/day	Aspiration (aspiration/acute respiratory failure/ circulatory collapse)	Not related/ Not related	12.8
(b) (6)	1y/F	4mg/kg/day	Pneumonia	Not related/ Not related	5.6
(b) (6)	14y/M	200mg/day	Circulatory collapse	Not related/ Not related	6.3
* From sponsor table 6-15, ISS page 137					

Four brief mini-narratives are presented for these four patient deaths in the following bullets:

- (New) A 6-year-old female subject (b) (6) with de Lange's syndrome, concomitantly treated with valproic acid, clobazam, fluticasone, oxymetazoline, melatonin, and omeprazole, developed fatal septic shock and community-acquired pneumonia 30.2 months of exposure to BRV. Diagnosis at the death was refractory septic shock with pulmonary sepsis in community-acquired pneumonia with multiorgan failure (acute renal failure, disseminated intravascular coagulation, acute respiratory distress syndrome, and distributive shock). An autopsy was not performed. The Investigator assessed the event as not related to study drug.

- A 1-year-old female subject ((b) (6)) with a history of cerebral palsy, choreoathetosis, and chronic malnutrition, experienced pneumonia after 5.6 months of exposure to BRV. She was concomitantly taking phenobarbital and sodium valproic acid. There was no autopsy. The Investigator assessed the event of pneumonia as not related to the study drug.

- A 2-year-old male subject (b) (6)) with a history of lissencephaly, aspirated some food when swallowing after 12.8 months of exposure to BRV. He was concomitantly taking sodium valproic acid and topiramate. There was no seizure activity at the time of the aspiration. He died the following day from respiratory. complication. There was no autopsy. The Investigator assessed the event of aspiration as not related

to the study drug.

- A 14-year-old male subject (b) (6)) with history of aortic valve stenosis, moderate mental retardation, hyperprolactinaemia, and choreoathetosis, concomitantly taking lamotrigine, hydroxyzine, and gabapentin, experienced fatal circulatory collapse after 6.3 months of exposure to BRV. An autopsy was not performed. The Investigator assessed the event as not related to study drug.

Reports (b) (6), and (b) (6) were captured in the original NDA safety review. The new event, report (b) (6) occurred since the original evaluation. This patient was treated for approximately 2.5 years before onset of the fatal event of sepsis. The study 1266 laboratory dataset (ADaM ADLB) is examined and does not reveal evidenced of a shift from normal to low in hemoglobin, leukocytes, lymphocytes, neutrophils or platelets. There is also no numerical trend for decline in these values during the available 24-month laboratory sampling interval.

120-day safety update

Examination of the study 1266 safety update did not reveal any new deaths.

Reviewer Comment: The additional report of death in the pediatric population since the original NDA review does not support a new safety signal or pediatric vulnerability. There is no evidence of blood dyscrasia related immunosuppression. There is no supportive temporal relationship to the sepsis event with a long latency of 2.5 years from start or brivaracetam treatment.

7.5.2. Serious Adverse Events

Pooled Pediatric Studies

The sponsor table 6-20 in the ISS indicates there were 59 (26.9%) patients who experienced an SAE where 39 (23.2%) were from the subset of patients with POS. From among these there were 8 in the age group < 4 years, and 30 in the age group ≥4 to <16y years of age. The table also provided frequency by age band and seizure type (POS) and "all epilepsy" subsets, see Table 10. This table has been verified by the reviewer by recreation of the pooled pediatric studies datasets for studies 1263 & 1266.[12] One exception to sponsor table 6-20 was identified, one less patient was found with an SAE for the PT "convulsion" by the reviewer. The SAE

[12] Table 6-20 page 146 ISS summary row for SAE by age strata and POS All is tested and duplicated using concatenated 1263 -1266 ADSL with POS and SAFETY flag joined to concatenated ADaM ADAE sets from 1263-1266 with all 1266 patients plus 24 1263 patients who did not move forward into 1266 LTFU.

analysis reveals there were 140 SAE events from 59 patients. For terms from the all pediatric epilepsy subjects (219) that had >1 event identified, 8 SOCs contained 18 preferred terms.

The most frequent event was convulsion. When the PT "grand mal convulsion" is recoded to convulsion there were 18 (8.2%) patients from among all patients in the pediatric pool with a convulsion. In the original NDA submission Pool S4 there were 88 patients from among 2437 (3.6%) in the pool who experienced an SAE of "convulsion" or "grand mal convulsion". The next most frequent SAE event was status epilepticus in the overall pediatric epilepsy (pooled pediatric studies) group at 2.7%. This compares to 1.15% in the S4 pool of the initial NDA submission core and long-term follow-up studies. Pyrexia was the 3rd term in frequency at 2.3%. No other events exceeded 2%.

Table 10 Treatment-emergent SAEs reported in >1 subject by pediatric summary group (studies 1263 & 1266)*

Primary SOC PT	BRV Overall			
	POS summary group			All pediatric subjects N=219 n (%)
	<4y N=16 n (%)	≥4 to <16y N=149 n (%)	Total POS N=168 n (%)	
At least 1 treatment-emergent SAE	**8 (50.0)**	**30 (20.1)**	**39 (23.2)**	**59 (26.9)**
Gastrointestinal disorders				
Gastrooesophageal reflux disease	1 (6.3)	0	1 (0.6)	2 (0.9)
Vomiting	0	0	0	2 (0.9)
General disorders and administration site conditions				
Pyrexia	1 (6.3)	1 (0.7)	2 (1.2)	5 (2.3)
Infections and infestations				
Pneumonia	0	2 (1.3)	2 (1.2)	4 (1.8)
Gastroenteritis	1 (6.3)	0	1 (0.6)	3 (1.4)
Bronchitis	1 (6.3)	1 (0.7)	2 (1.2)	2 (0.9)
Upper respiratory tract infection	0	0	0	2 (0.9)
Urinary tract infection	0	0	0	2 (0.9)
Metabolism and nutrition disorders				
Dehydration	1 (6.3)	0	1 (0.6)	4 (1.8)
Nervous system disorders				
Convulsion	2 (12.5)	9 (6.0)	12 (7.1)	16 (7.3)
Status epilepticus	1 (6.3)	5 (3.4)	6 (3.6)	6 (2.7)
Grand mal convulsion	0	0	0	3 (1.4)
Somnolence	0	2 (1.3)	2 (1.2)	3 (1.4)
Epilepsy	0	1 (0.7)	1 (0.6)	2 (0.9)
Psychiatric disorders				
Suicidal ideation	0	1 (0.7)	1 (0.6)	2 (0.9)
Respiratory, thoracic, and mediastinal disorders				
Respiratory distress	0	2 (1.3)	2 (1.2)	2 (0.9)
Respiratory failure	0	1 (0.7)	1 (0.6)	2 (0.9)
Vascular disorders				
Circulatory collapse	0	1 (0.7)	1 (0.6)	2 (0.9)
* The reviewer is able to confirm this sponsor table 6-20, ISS page 146 by spot check of all pediatric totals with the exception of convulsion where the reviewer identifies 15 SAE events				

SAE of Interest

One 12-year-old male patient ((b) (6)) had an SAE in a category of special interest that was of severe intensity. This patient who did not have POS, reported the SAE of homicidal ideation. This event was reported in the original application. This patient had a psychiatric history of mood disorders, attention deficit/hyperactivity disorder, and aggression. The SAE was considered related to study drug by the Investigator, led to permanent discontinuation of study drug, and resolved in 8 days.

Although severe, there is evidence the patient had a severe baseline aggressive and violent behavior based on the following statement from the child behavioral checklist: The checklist revealed complaints of somewhat/sometimes on the following: argues a lot, demands a lot of attention, destroys things belonging to family and others, disobedient at home and school, does not get along with other kids, does not feel guilty after misbehaving, breaks rules at home/school, gets in many fights, physically attacks people, sets fire, steals at home, strange behavior, stubborn/sullen/irritable, and threatens people.

120 Day Safety Update

Examination of the 120-day safety update for study 1266 did not reveal new SAE entries. The total of SAE entries remained at 59.

Reviewer Comment: There is an increased frequency of SAE under the PT “convulsion” and “status epilepticus” in the age <4 to ≥16 yo group compared to the adult S4 pool. This may be due to the smaller sample size in an uncontrolled dataset. Although both the S4 Pool and “Pool Pediatric Studies” are both long term outpatient settings they may not be comparable and or the background seizure frequency may be higher in pediatrics. The uncontrolled nature of the data does not rise to a level of evidence that a new safety signal is present in the pediatric POS population. The remaining SAE preferred terms are not notably divergent from the Pool S4 adult population. The severe behavior disturbance reported in a 12-year-old patient is not possible to differentiate from his severe baseline behavioral features.

7.5.3. Dropouts and/or Discontinuations Due to Adverse Effects

From the pooled pediatric studies 1263 & 1266, there were 26 patients who discontinued with a total of 36 adverse events leading to discontinuation. The profile of SOCs and Preferred terms is shown in Table 11. There were 27 preferred terms from among 10 system organ class terms generated by the 26 patients with TEAE leading to discontinuation.

Table 11 System organ class and preferred terms associated with patient discontinuation in pooled pediatric studies

SOC	Preferred term
EYE DISORDERS	Eye movement disorder
GASTROINTESTINAL DISORDERS	Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Fatigue
INFECTIONS AND INFESTATIONS	Pneumonia
	Septic shock
INVESTIGATIONS	Alanine aminotransferase increased
	Aspartate aminotransferase increased
	Gamma-glutamyltransferase increased
	Hepatic enzyme increased
	Weight decreased
METABOLISM AND NUTRITION DISORDERS	Decreased appetite
NERVOUS SYSTEM DISORDERS	Convulsion
	Epilepsy
	Grand mal convulsion
	Hypotonia
	Psychomotor hyperactivity
	Somnolence
	Status epilepticus
PSYCHIATRIC DISORDERS	Abnormal behaviour
	Aggression
	Depression
	Homicidal ideation
	Sleep disorder
	Suicidal ideation
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Acute respiratory failure
	Aspiration
VASCULAR DISORDERS	Circulatory collapse

Table 12 shows the frequency of patient discontinuation by TEAE preferred terms and SOC. This table is derived from the adverse event dataset for study 1263 submitted in the initial brivaracetam NDA submission and the study 1266 interim update submitted in the July 10, 2017 pediatric efficacy supplement. Only unique patients contributing to the joined AE datasets are included in the analysis. The independent analysis was performed due to a minor divergence in total patient discontinuation between the sponsor ISS and the datasets provided

by the sponsor. Sponsor ISS table 6-22 identified 25 (11.4%) patients who discontinued due to TEAE while the reviewer dataset analysis identified 26 (11.9%) patients who discontinued due to TEAE. Reviewer Table 12 below is based on sponsor ISS table 6-22 but derived from the reviewer's independently assembled dataset.

In the patient cohort with POS aged <4 years there was a single discontinuation due to decreased appetite. In the ≥4 to <16 years POS group the most frequent discontinuations were in the "Psychiatric disorders" SOC with 3 due to aggression and 1 due to suicidal ideation. A single patient in the POS pediatric cohort discontinued due to pneumonia. In the total pediatric pool that included patients with POS and "any seizure type", the most frequent SOC with events leading to discontinuation was "Psychiatric disorders" where 3 (1.4%) patients each discontinued due to TEAE under the preferred terms "aggression" and "suicidal ideation". There were also two patients each with TEAE preferred terms of "pneumonia", "Gamma-glutamyltransferase increased", "decreased appetite", "convulsion" and "circulatory collapse".

In both cases of "circulatory collapse" the patients died. In one case, the event may have been initiated by an aspiration. In the second case, the event appears to be spontaneous onset of a cardiac dysrhythmia with ventricular fibrillation identified by first responders. Both deaths were captured in the initial NDA safety review completed 11/5/15.

A TEAE of pneumonia leading to discontinuation occurred in 2 patients. In both cases there was a fatal outcome. These cases are included in section 7.5.1 Deaths, above. One report, patient (b) (6) had De Lange's syndrome and developed pneumonia after 30.4 months of brivaracetam treatment was captured in the initial NDA safety review of 11/5/15 while patient (b) (6) had a history of chronic malnutrition and experienced pneumonia after 5.6 months of brivaracetam exposure.

A TEAE of " Gamma-glutamyltransferase increased" leading to discontinuation occurred in 2 patients. In report number 1 patient (b) (6) developed a Gamma-glutamyltransferase 11 x ULN after 22 days of brivaracetam treatment. The patient was on concomitant valproic acid and had a baseline GGT of 5 x ULN. The GGT began to decrease upon discontinuation. In the second report of patient (b) (6) the adverse event occurred at baseline measurement.

A TEAE of "decreased appetite" leading to discontinuation occurred in 2 patients. The first report of patient (b) (6) was captured in the safety review of the original NDA submission completed on 11/5/15. This patient was a 6-month-old male who developed decreased appetite 2 days after starting study drug with resolution on day 3, the first day after study drug discontinuation. In the second report patient (b) (6) a 16 year old female developed decreased appetite 653 days after first study drug dose. The patient was taking brivaracetam 200mg / day at the time.

A TEAE of "convulsion" leading to discontinuation occurred in 2 patients. The first report, patient (b) (6) was a 6 year old male who had an event of increased seizure activity 28 days after first brivaracetam dose on 4mg/kg/day. The second patient (b) (6) was a 14.5 year old female. The patient had only 1 day of brivaracetam treatment associated with nausea and dizziness. On day 2 the patient did not take brivaracetam and had a convulsion. This discontinuation and convulsion was captured in the initial NDA safety review completed 11/5/15.

A TEAE of "aggression" leading to discontinuation occurred in 3 patients. Two of these reports were contained in study 1263 submission in the original brivaracetam NDA. These were captured in the initial NDA safety review completed 11/5/15. The new report in patient (b) (6) occurred in a 15.8 year old male with a history that included cortical dysplasia, left frontal cortical resection, and encephalomalacia. The event occurred 64 days after 1st study drug dose. At the time of the aggression, the subject was taking BRV 150mg/day and had been at this dose for 49 days in this study. the subject experienced an episode of aggressive outburst with depression. On the same day, the subject was hospitalized again with a complaint of aggressive and violent behavior towards his mother.

A TEAE of "suicidal ideation" leading to discontinuation occurred in 3 patients. Patient 1 of this group (b) (6), was a 13.6-year-old female. This event occurred 70 days after first study drug treatment. Study drug was discontinued but 11 days later the patient had an event of "suicide attempt". Patient 2 of this group (b) (6) was a 13 year old female who experienced events of self-injurious behavior and suicidal ideation on day 104 from 1st study drug administration. Patient 3 of this group, (b) (6), was a 16.9 year old female who experience an event of suicidal ideation on day 50 from 1st study drug administration.

Table 12 Frequency of TEAE preferred in >1 patient (Pediatric pool), terms leading to discontinuation in the pooled pediatric studies shown by all seizure types (total pediatric pool) and POS patients by age group

		Overall Brivaracetam							
		POS group						Total Pediatric Pool	
		subgroup n=16		Subgroup n= 149		Subgroup n=168		Subgroup n=219	
		n	%	n	%	n	%	n	%
Any Event		**2**	**12.5**	**12**	**8.05**	**16**	**9.52**	**26**	**11.87**
Age band		**< 4 years**		**≥4 to <16y**		**Total POS**			
SOC	**Preferred term**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
INFECTIONS AND INFESTATIONS	Pneumonia			1	0.67	1.00	0.60	2	0.91
INVESTIGATIONS	Gamma-glutamyltransferase increased			2	1.34			2	0.91
METABOLISM AND NUTRITION DISORDERS	Decreased appetite	1	6.25		0.00			2	0.91
NERVOUS SYSTEM DISORDERS	Convulsion			1	0.67			2	0.91
PSYCHIATRIC DISORDERS	Aggression			3	2.01			3	1.37
	Suicidal ideation			1	0.67			3	1.37
VASCULAR DISORDERS	Circulatory collapse			1 (b) (6)	0.67			2 (b) (6)	0.91

120 Day Safety Update

The study 1266 update is examined. There were two additional events from two patients leading to discontinuation. One of the events ((b) (6)) was an SAE, however the TEAE was an ongoing event, PT = Astrocytoma, low grade that was also entered as an SAE in the initial adverse event dataset but did not result in discontinuation. This patient had an underlying history of tuberous sclerosis and was on brivaracetam treatment for 996 days at the time of discontinuation due to the astrocytoma. In the updated dataset, this event was associated with a discontinuation.

The second new TEAE event leading to discontinuation was an event of PT= pregnancy.

Reviewer Comment: There was no dose response seen in relation to all TEAEs leading to

discontinuation, the frequency of events in the SOC "psychiatric disorders" or SOC "nervous system disorders". The overall frequency of TEAE leading to discontinuation was lower in the pool pediatric studies compared to the pool monotherapy, pool ULD and Pool S4 patients of the initial brivaracetam NDA review. The profile of TEAE leading to discontinuation in pool pediatric studies was also similar to Pool S4 where the SOC "nervous system disorders" and "psychiatric disorders" were the most frequent TEAE leading to discontinuation. Neurologic and Psychiatric adverse reactions are in section 5 of the current brivaracetam label, therefore this observation does not indicate a new safety signal is present. The composition of the individual preferred terms within these SOCs was also similar between the Pool Pediatric studies and Pool S4 / Pool monotherapy.

7.5.4. Significant Adverse Events

Examination of the Pool Pediatric studies adverse event dataset reveals there were 62 adverse events judged as severe intensity from among 32 patients. The most frequent of these events was the preferred term "convulsion" with 12 events from among 8 patients. There were 5 instances for each of the preferred terms "pneumonia" and "status epilepticus" where 4 patients contributed the "pneumonia" terms and 4 patients contributed "status epilepticus" terms. There were 6 preferred terms with two instances for each term and 28 preferred terms with an AE entry of 1 instance each.

Three of these events, "epilepsy", "weight decreased" and "asthenia", were judged as related to brivaracetam treatment where 1 patient was from the POS cohort and 2 were from non-POS epilepsy cohort.

Unexpected or High Significance Preferred Terms

There were 6 preferred terms the reviewer judged as unexpected or high significance, each from a unique patient. These events are shown in Table 13. All events were SAEs, two were discontinuations. The report of "acute respiratory failure", patient (b) (6), is contained in section 7.5.1 "Deaths", and was captured in the initial NDA safety review. This event was related to an aspiration event on day 363 of brivaracetam treatment.

The report of "Deafness neurosensory", patient (b) (6) a 1.6 year old male with history of trisomy 21 and colostomy was identified after a severe infection event, pyrexia and hemodynamic instability. The patient had an interval of amikacin (aminoglycoside) treatment. The event of sensorineural hearing loss may be related to hemodynamic events or aminoglycoside treatment.

The report of preferred term "spina bifida" in patient (b) (6) a 2.9 year old male, was derived from verbatim term "spina bifida complications". The narrative does not identify

how the event was a complication of spina bifida. There is no evidence in the narrative of a central nervous system or spinal cord infection or change in the patient's neurologic status related to the spina bifida.

The report of the term "septic shock" in patient (b) (6) a 4.2 year old female is covered in section 7.5.1, "Deaths". This event occurred in the context of a pneumonia. At the time of the pneumonia and septic shock, the subject was taking BRV 4mg/kg/day and had been on this dose for 887 days in the study.

The report of the term "hypoxia" in patient (b) (6), a 6.8 year old male with a history of microcephaly and quadriparesis occurred in association with respiratory distress that occurred 70 days after 1st study drug dose. The patient had a lobar pneumonia, WBC count was elevated to 16.6 x 10^9/l. Concomitant antiepileptic drug(s) (AEDs) at the time included the following: phenobarbital, diazepam, and valproate.

The report of the term "Haemodynamic instability" in patient (b) (6) an 8.6 year old male with a history of developmental delay experienced events of haemodynamic instability and respiratory distress on (b) (6), during the Evaluation Period. The events occurred 343 days after the first study drug dose in N01266. The patient experienced refractory seizures due to AED treatment omission for 24 hours. The patient was taken to the emergency department due to somnolence. The event resolved on 12 May 2015, 3 days after onset.

Table 13 Unexpected or High Significance Preferred Terms

ID	TEAE preferred terms	# patients	SAE Y/N	Discontinuation Y/N	Relatedness designation Y/N
(b) (6)	Acute respiratory failure	1	Y	Y	N
(b) (6)	Deafness neurosensory	1	Y	N	N
(b) (6)	Spina bifida	1	Y	N	N
(b) (6)	Septic shock	1	Y	Y	N
(b) (6)	Hypoxia	1	Y	N	N
(b) (6)	Haemodynamic instability	1	Y	N	N

Reviewer Comment: The six events identified as significant adverse events do not have clear association with study drug. There is lack of temporal relationship, confounding by concomitant

medications and underlying medical illness. Events that were associated with infection do not reveal evidence of depressed WBC count although neutrophil counts are not provided in the case narratives. Overall, these events do not indicate there is a new safety signal for brivaracetam in the pediatric population.

7.5.5. Treatment Emergent Adverse Events and Adverse Reactions

Overview of TEAEs

Examination of the "Pooled Pediatric Studies" 1263 & 1266 reveal there were 2302 adverse event entries from 206 (94.1%) patients. Twenty-five (11.4%) patients experienced adverse events leading to discontinuation, 84 (38.4%) patients had 180 adverse events considered related to brivaracetam treatment. From among all adverse events 29 (13.2%) patients had serious adverse events (SAE) where 5 events from 5 patients were considered related to brivaracetam treatment, see Table 14.

Examination of the percent of patients with TEAEs identified in rows 1 to 6, TEAE to discontinuation, TEAE related to study drug, TEAEs rated as severe, and SAEs reveals the <4 year old age group has the highest percent of all groups. This may be related to the small group size of 16 and greater sensitivity to treatment in this population. There was no dose response relationship when TEAE frequency is examined by modal brivaracetam dose except for the subset of "severe TEAE" where there are no entries for severe TEAE in the 0-1 mg/kg, 1< to 2 mg/kg, and 2< to 3 mg/kg while there are 10.1% and 15.4% of patients in the 3< to 4 and >4 mg/kg groups respectively have entries for severe TEAE (*ISS page 100*). Entries of severe TEAE from study 1266 adae.xpt dataset are examined. No clear profile of adverse events is identified. The most frequent preferred terms with severe designation are "convulsion", "pneumonia" and "status epilepticus" with entries from 6, 4 and 3 patients respectively.

The overall (All Pediatrics), total POS patients and POS patients aged ≥4 to <16y have lower proportions of patients contributing to all categories when compared to the TEAE profiles of brivaracetam pooled monotherapy studies and Pool S4 from the adult brivaracetam NDA studies (*ISS pages 101- 102*).

Table 14 Overview of TEAE Frequency and Type by Age Group and Epilepsy Classification†

Row		POS											
		<4			≥4 to <16y			Total POS			All Pediatrics		
		N= 16			N= 149			N= 168			n = 219		
		N	%	# AE entries	N	%	# AE Entries	N	%	# AE Entries	N	%	# AE Entries
1	**Any TEAE**	16	**100**	449	138	**92.6**	1194	157	**93.5**	1662	206	**94.1**	2302
2	**TEAE to DC***	2	**12.5**	2	11	**7.4**	17	15	**8.9**	21	25	**11.4**	35
3	**Related**	9	**56.3**	13	54	**36.2**	109	65	**38.7**	124	84	**38.4**	180
4	**Severe**	7	**43.8**	18	12	**8.1**	27	19	**11.3**	45	29	**13.2**	59
5	**SAE**	8	**50**	31	30	**20.1**	54	39	**23.2**	86	59	**26.9**	140
6	**related SAE**	0	**0**	0	2	**1.3**	2	2	**1.2**	2	5	**2.3**	5
	* discontinued † based on sponsor table 6-1, ISS page 98, data compiled from reviewer "Pool Pediatric Studies", see section 7.2												

Reviewer Comment: Overview of TEAEs reveals lower frequencies of all events, related events, severe events and SAEs compared to the adult LTFU brivaracetam studies. The increase frequency of severe events and SAEs in the <4-year-old population compared to the adult studies is difficult to interpret from a sample of 16 patients. The cause of the dose response trend for TEAE entries assigned "severe" is uncertain. Overall, there is no evidence of a new safety signal compared to the adult study population.

TEAE Frequencies

Examination of TEAE by SOC and Preferred term in the total pediatric pool and age <4 to ≤16 years subset is performed. The total pediatric population and 4 to ≤16 years groups have a similar profile of SOC terms and frequencies. The SOC terms of highest frequency for both total pediatric and age 4 to ≤16 years, POS patients were "Infections and infestations", "Nervous system disorders", "Gastrointestinal disorders", "General disorders and administration site conditions", "Respiratory, thoracic and mediastinal disorders" and "Psychiatric disorders" with a frequency of approximately 30% or greater, see Table 15 and Table 17. The profile of the total pediatric and subgroup age 4 to ≤16 years, POS patients preferred term frequencies were very similar. Preferred terms associated with upper respiratory events were very common reflecting the high frequency of the "Infections and infestations" SOC, see Table 16 and Table 18.

The profile of TEAEs in the total pediatric population and the age 4 to ≤16 years subgroup is similar to the profile seen in the Pool S4 adult brivaracetam studies. The frequency of several terms is higher than the Pool S4 population, including preferred terms associated with respiratory infection as well as nausea and vomiting.

Table 15 All TEAE by SOC, All Pediatric Population (pooled studies 1263 & 1266) *

All pediatric, n=219			
SOC	# patients	% patients	# events
Infections and infestations	154	70.3	802
Nervous system disorders	112	51.1	306
Gastrointestinal disorders	93	42.5	278
General disorders and administration site conditions	86	39.3	204
Respiratory, thoracic and mediastinal disorders	72	32.9	122
Psychiatric disorders	64	29.2	104
Injury, poisoning and procedural complications	47	21.5	94
Investigations	36	16.4	80
Metabolism and nutrition disorders	40	18.3	65
Skin and subcutaneous tissue disorders	30	13.7	52
Reproductive system and breast disorders	10	4.6	35
Musculoskeletal and connective tissue disorders	20	9.1	33
Renal and urinary disorders	19	8.7	33
Eye disorders	16	7.3	23
Cardiac disorders	9	4.1	13
Ear and labyrinth disorders	12	5.5	13
Blood and lymphatic system disorders	6	2.7	8
Vascular disorders	8	3.7	8
Congenital, familial and genetic disorders	5	2.3	6
Immune system disorders	5	2.3	6
Surgical and medical procedures	3	1.4	6
Endocrine disorders	3	1.4	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	0.9	2
Social circumstances	2	0.9	2
Hepatobiliary disorders	1	0.5	1
* Reviewer Pool Dataset, see Pool Pediatric Studies			

Table 16 All TEAE by PT, All (total) Pediatric Population When >2% (pooled studies 1263 & 1266)*

PT (all Pediatric) N= 219	# Patients	% patients	# events	PT (all Pediatric)	# Patients	% patients	# events
Nasopharyngitis	60	27.4	129	Oropharyngeal pain	10	4.6	12
Pyrexia	50	22.8	123	Rhinitis allergic	10	4.6	11
Convulsion	44	20.1	80	Varicella	10	4.6	11
Vomiting	43	19.6	70	Laryngitis	9	4.1	14
Pharyngitis	42	19.2	68	Nausea	9	4.1	11
Headache	36	16.4	98	Gamma-glutamyltransferase increased	9	4.1	9
Diarrhoea	33	15.1	49	Suicidal ideation	9	4.1	9
Upper respiratory tract infection	29	13.2	52	Toothache	8	3.7	28
Pharyngotonsillitis	27	12.3	83	Sinusitis	8	3.7	14
Gastroenteritis	26	11.9	38	Rash	8	3.7	13
Cough	26	11.9	37	Conjunctivitis	8	3.7	10
Somnolence	26	11.9	35	Gastrooesophageal reflux disease	8	3.7	10
Decreased appetite	26	11.9	34	Respiratory tract infection	7	3.2	38
Irritability	26	11.9	34	Acute tonsillitis	7	3.2	12
Rhinitis	21	9.6	46	Dehydration	7	3.2	9
Bronchitis	19	8.7	46	Psychomotor hyperactivity	7	3.2	8
Influenza	18	8.2	19	Laceration	6	2.7	11
Fall	17	7.8	21	Abnormal behaviour	6	2.7	8
Abdominal pain	15	6.8	26	Epistaxis	6	2.7	8
Ear infection	14	6.4	17	Otitis media acute	6	2.7	8
Fatigue	13	5.9	19	Pharyngitis bacterial	6	2.7	7
Constipation	13	5.9	18	Ear pain	6	2.7	6
Insomnia	13	5.9	16	Dysmenorrhoea	5	2.3	29
Weight decreased	13	5.9	15	Rhinorrhoea	5	2.3	9
Abdominal pain upper	13	5.9	14	Head injury	5	2.3	8
Otitis media	12	5.5	38	Asthenia	5	2.3	7
Pneumonia	12	5.5	24	Contusion	5	2.3	7
Aggression	12	5.5	14	Status epilepticus	5	2.3	7
Dizziness	11	5.0	21	Blood triglycerides increased	5	2.3	6
Viral infection	11	5.0	17	Creatinine renal clearance decreased	5	2.3	5
Pharyngitis streptococcal	11	5.0	13	Dental caries	5	2.3	5
Urinary tract infection	10	4.6	15	Tonsillitis	5	2.3	5
				Viral pharyngitis	5	2.3	5

* Reviewer Pool Dataset, see Pool Pediatric Studies

Table 17 TEAE by SOC, Age <4 to ≤16, POS Patients Where ≥2.7% of Total Pediatric (pooled studies 1263 & 1266)*

SOC	# patients	% patients	# events
Infections and infestations	99	66.4	389
Nervous system disorders	70	47.0	198
Gastrointestinal disorders	59	39.6	120
General disorders and administration site conditions	53	35.6	83
Respiratory, thoracic and mediastinal disorders	47	31.5	66
Psychiatric disorders	43	28.9	69
Injury, poisoning and procedural complications	35	23.5	66
Investigations	20	13.4	33
Metabolism and nutrition disorders	20	13.4	24
Skin and subcutaneous tissue disorders	17	11.4	23
Musculoskeletal and connective tissue disorders	13	8.7	23
Renal and urinary disorders	12	8.1	24
Reproductive system and breast disorders	9	6.0	34
Ear and labyrinth disorders	6	4.0	6
Eye disorders	6	4.0	8
* Reviewer Pool Dataset, see Pool Pediatric Studies			

Table 18 TEAE by PT, Age <4 to ≤16, POS Patients Where ≥2.0% of Total Pediatric (pooled studies 1263 & 1266)*

Preferred term	# Patients	% patients	# events	Preferred term	# Patients	% patients	# events
Nasopharyngitis	38	25.5	78	Influenza	9	6.0	10
Pharyngitis	31	20.8	43	Bronchitis	8	5.4	15
Headache	27	18.1	77	Fatigue	8	5.4	10
Pyrexia	26	17.4	40	Rhinitis allergic	8	5.4	8
Convulsion	24	16.1	44	Weight decreased	8	5.4	8
Vomiting	22	14.8	31	Gamma-glutamyltransferase increased	7	4.7	7
Cough	19	12.8	25	Insomnia	7	4.7	9
Pharyngotonsillitis	19	12.8	52	Pharyngitis streptococcal	7	4.7	9
Diarrhoea	18	12.1	24	Psychomotor hyperactivity	7	4.7	8
Irritability	16	10.7	17	Suicidal ideation	7	4.7	7
Somnolence	16	10.7	21	Aggression	6	4.0	7
Decreased appetite	15	10.1	19	Constipation	6	4.0	7
Rhinitis	13	8.7	28	Oropharyngeal pain	6	4.0	8
Fall	12	8.1	15	Varicella	6	4.0	6
Abdominal pain	11	7.4	20	Viral infection	6	4.0	12
Gastroenteritis	11	7.4	16	Dysmenorrhoea	5	3.4	29
Dizziness	10	6.7	20	Ear infection	5	3.4	6
Upper respiratory tract infection	10	6.7	13	Rash	5	3.4	5
Abdominal pain upper	9	6.0	9	Sinusitis	5	3.4	9
				Status epilepticus	5	3.4	5
* Reviewer Pool Dataset, see Pool Pediatric Studies							

120 Day update

The 120-safety dataset update for study 1266 is examined. There were 215 new adverse event entries in 96 preferred terms where 26 of these preferred terms were not present in the initial submission AE dataset. There were 8 preferred terms with more than 5 additional entries over the initial submission.

In the overall study 1266 population the PT with the largest accrual of new entries was "pyrexia" with an addition of 19 new instances and 5 new patients, an increase of 3.2% of patients. In the subset of patients age 4 to <16 with partial onset seizures the highest frequency of new onset preferred terms was found for "headache" with 11 new instances and 3 (2.1%) new patients experiencing the event. The term with the highest percentage of new patients affected in both the total study population and the subset age 4 to <16 with partial onset seizures was for the term "convulsion" with 6 new patients all from the 4 to <16 cohort experiencing the event, see Table 19. Examination of the accrual of adverse events at the 120-

day safety update does not reveal a change from the initial submission safety conclusions for treatment emergent adverse events TEAE.

Table 19 Comparison of Preferred Term Frequency and % of New Patients Affected for Study 1266 at Initial Submission and 120 Day Safety Update. Total Study Population and Patients age 4 to <16 with Partial Onset Seizures with PT > 5 new instances. *

initial	Initial Submission		120 Day Update		Change during update interval		
Study 1266 All Pediatric Patients, n= 158							
AEDECOD	instances of PT	patients with events	instances of PT	patients with events	new instances of preferred term	# new patients with PT (n=158)	% new patients
Pyrexia	116	47	135	52	19	5	3.2
Headache	95	35	107	38	12	3	1.9
Convulsion	72	38	83	44	11	6	3.8
Nasopharyngitis	129	60	140	62	11	2	1.3
Dysmenorrhoea	29	5	36	5	7	0	0.0
Respiratory tract infection	36	6	43	6	7	0	0.0
Pharyngotonsillitis	78	26	84	28	6	2	1.3
Somnolence	26	21	32	22	6	1	0.6
	581	238	660	257	79	19	12.0
Study 1266, Patients ages 4 to <16, Partial Onset Seizures, n = 144							
	INITIAL		120 DAY		Change during update interval		
AEDECOD	instances of PT	patients with events	instances of PT	patients with events	new instances of preferred term	# new patients with PT (n=144)	% new patients
Headache	78	27	89	30	11	3	2.1
Convulsion	45	26	54	32	9	6	4.2
Dysmenorrhoea	29	5	36	5	7	0	0.0
Nasopharyngitis	80	39	87	39	7	0	0.0
Pyrexia	39	26	46	30	7	4	2.8
Somnolence	18	14	24	15	6	1	0.7
Pharyngotonsillitis	51	19	56	21	5	2	1.4
Respiratory tract infection	4	3	4	3	0	0	0.0
	344	159	396	175	52	16	11.1
*From ADAE , ADaM datasets							

Reviewer Comment: TEAE SOC groups and preferred terms are similar to those seen in the

adult brivaracetam long term follow up studies. The frequency of terms that capture infection and gastrointestinal disturbance is higher. These differences may reflect a greater vulnerability to gastric intolerance and the higher baseline frequency of respiratory infections seen in the pediatric population. Overall no new safety signal is emergent in the proposed pediatric treatment population.

7.5.6. **Laboratory Findings**

The sponsor examined mean change from baseline, shift from normal to abnormal (high/low) based on "possibly clinically significant treatment-emergent" (PCST) values and outliers for hematology parameters and clinical chemistry. The summary statement indicates the incidence of any PCST hematology, clinical chemistry, or urinalysis result was low, and few subjects met the Grade 3 or Grade 4 NCI CT criteria for any hematology or clinical chemistry parameter. There were no reports that met Hy's law criteria.

The reviewer evaluated six laboratory parameters of interest that may be associated with hepatic, renal, and hemopoietic dysfunction and association with hypersensitivity. These selected parameters were alanine aminotransferase (ALT), bilirubin, serum creatinine, leukocytes, neutrophils and eosinophils. Laboratory measurement from study 1266 were captured from the population age ≥4 to 16 years old with partial onset seizure and flagged as safety population, including 3 patients whose age exceeds 16 years but is less than 17.

Alanine Aminotransferase (ALT)

There were 9 entries from 5 (3.5%) patients for Alanine Aminotransferase (ALT) values > 3x ULN. The complete profile of ALT entries from these 5 patients including all study measurements (all study visits where laboratory values are obtained) are examined. Three of these patients had a single elevation to > 3x ULN with return to baseline or below by end of study participation.

One of these 5 patients (b) (6)) had a simultaneous elevation of total bilirubin to 1.4 x ULN (34.208 on study day 295). Both abnormal values were bracketed by normal range ALT and bilirubin values (3.4208 umol/L) on study days 202 and 395. The elevated bilirubin value was exactly 10 times the values entered at the samples from study days 202 and 395. This observation strongly suggests a laboratory recording error.

Two patients had multiple elevations >3 x ULN but neither had an elevation of total bilirubin. One patient had 3 values in a period of one month that were greater than 3 x ULN. These were obtained at unscheduled laboratory visits for safety follow up after the 1st value > 3x ULN was identified. Eight days later a value of 2 X ULN was identified. The ALT values continued to decline through the remainder of the study to below the baseline value. The second patient

(b) (6)) with multiple abnormal values was discontinued from the study. This patient had an ALT value of 6.4 x ULN identified on day 22 of brivaracetam treatment. This increased to 7.8 x ULN by day 43 of treatment. Study drug was discontinued with a return to baseline value in 20 days. There was no concurrent elevation of bilirubin noted.

Overall there was only a single instance of sustained increase in ALT identified although this was observed to be reversible after discontinuation of study drug.

Bilirubin

There were two instances from 2 patients (1.4%) with a bilirubin value greater than the upper limit of normal. The first of these patients (b) (6)) was captured in the discussion on elevations of ALT above.

In the remaining patient, a single elevation of 2.1 x baseline value (1.25 x ULN) occured on study day 1259. The subsequent value on day 1350 is within normal limits. No subsequent value through study day 1988 exceeds 0.67 x ULN. There is no concomitant elevation of alanine aminotransferase (ALT) or Alkaline Phosphatase (ALP).

The examination reveals no evidence of a Hy's law case and no sustained elevation of bilirubin.

Leukocytes

Low
There are 19 instances from 11 (7.6%) patients where a leukocyte count occurs that is in the range of PCST low. The minimum value observed is 2.06 G/L. In 13 instances from 5 (3.5%) patients the baseline measurement was OORR low. Only the remaining 6 (4.2%) instances with a shift from normal baseline to a PCST low value will be examined in further detail, Figure 2.

Patient (b) (6) had a single entry for PCST low leukocytes on study day 81. All other entries to study day 1291 were in normal range. On the corresponding day 81 the patient had a marked change in neutrophils where a value of 0.46 G/L is observed. This patient had PT entries in the AE dataset (ADAE study 1266 ADaM) on days 76, and 77, of pyrexia, croup, infectious, otitis media.

Patient (b) (6) had a single entry of PCST low leukocyte count on study day 379. All but 3 of 11 leukocyte values after baseline were OORR low. The value at unscheduled visit on study day 507 revealed a normal range leukocyte value. The patient had 3 adverse events in the SOC "infections and infestations" occurring on study days 375, 378, and 485.

Patient (b) (6) had a single entry of PCST low leukocyte count on study day 22, visit

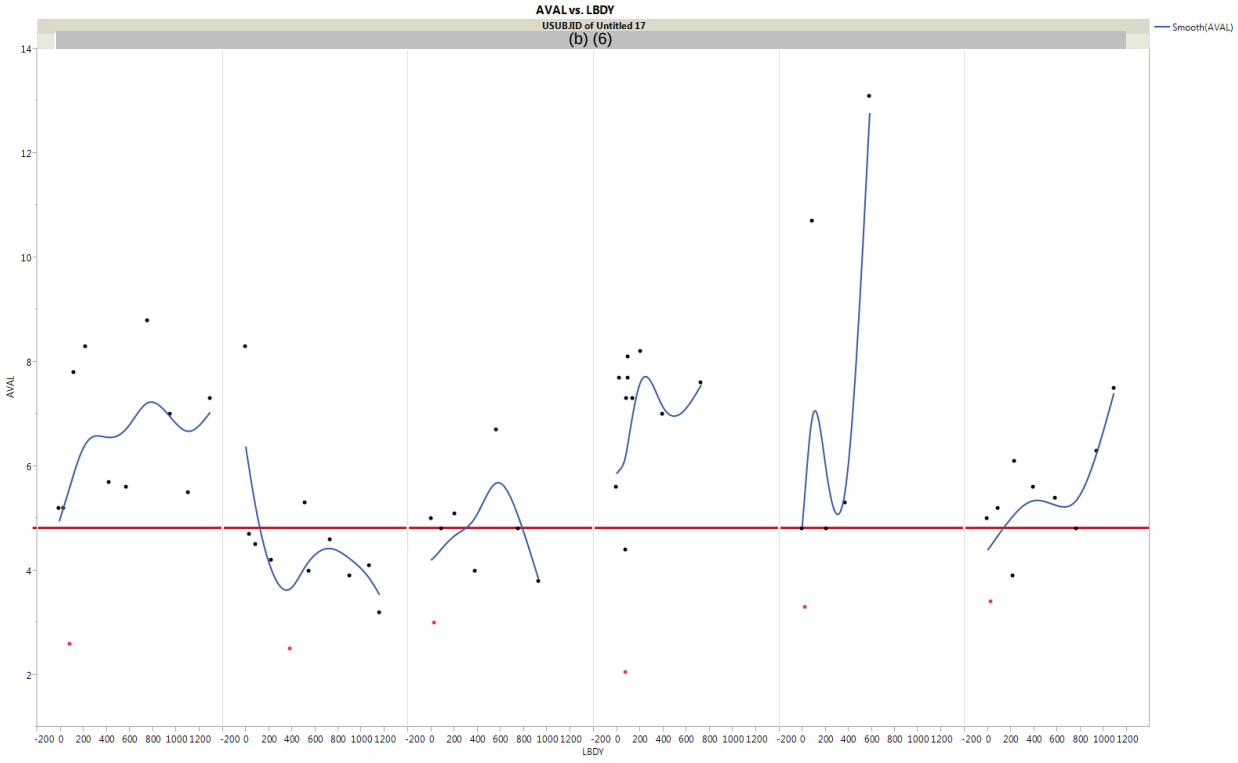
1. Four of the subsequent seven measurements were OORR low. None was less than 79% of RR (reference range). This patient had 7 entries in the SOC "infections and infestations", 2 for bronchitis and 5 for nasopharyngitis. None is entered as an SAE. These first of these "Infections and infestations" events were on study day 105.

Patient (b) (6) had a single entry of PCST low leukocyte count on study day 71. Eight of 9 subsequent leukocyte counts over the next 317 days was within reference range.

Patient (b) (6) had a single entry of PCST low leukocyte count on study day 21. All but one of the remaining values to end of study on day 388 were within reference range. On study day 113 a value OORR high was identified.

Patient (b) (6) had a single entry of PCST low leukocyte count on study day 23. One additional value on study day 211 was OORR low while all remaining values were within reference range.

Figure 2 Leukocytes, Patients with One or More Leukocyte Values in PCST range. Scatterplot of All Leukocyte Measurements for Each Patient. (horizontal lines: Y axis Red at 4.8 G/L



High

Five patients (3.5%) had a PCST high value where there was a shift from normal baseline to the high value. The maximum value seen in the group was 1.5 x ULN (17.6 G/L). All subsequent measurements for this patient were within reference range.

Reviewer comment: The frequency of shift from normal to high and normal to low PCST values were very similar. There were no patients with a sustained declining trend in leukocyte values. There was one patient in the PCST shift from normal to low where all but one of the post baseline values were OORR low, patient (b) (6). These values had a scatter around 4 G/L, see Figure 2 . The examination does not reveal a signal for treatment induced low leukocyte count.

Neutrophils

The concern in evaluation of neutrophils is primarily a reduction to critical values. Only PCST Low neutrophil values are evaluated.

Low

There were 77 instances of PCST low neutrophil count from 24 (16.7%) patients. One patient had a value that was 30% of OORR lower limit of normal. The remaining 23 patients had values > 47% of the lower limit reference range. Patients with PCST low baseline values are excluded from further analysis. Forty-two (42) instances from 18 patients had a shift from normal to PCST low and are examined for neutrophil trend during over the entire long term follow up treatment interval. The mean and median laboratory study day of these PCST low events were 594 and 478 respectively with a range from 21 to 1623 days.

The full study timeline of neutrophil count entries for each patient with a PCST value is examined, shown as individual patient scatter plots by date in Figure 3 and Figure 4. Isolation of all neutrophil entries for these 18 patients yielded 171 neutrophil values. Examination of neutrophil values reveal 10 patients with a single PCST value with subsequent values in reference range. There were three patients with last study value at PCST level. These were preceded by a scatter of values in reference range. There were 5 patients with multiple PCST low values scattered among higher values and some in normal reference range. There was one patient (b) (6)) with a persistent declining trend in neutrophil values after study day 387, see Figure 4. The adverse event dataset for this patient is examined. There were three adverse events entered on days 1, 10 and 405. None were SAEs. The event entered on day 405 was preferred term “bronchitis”.

There were 4 patients with post baseline neutrophil values <1 G/L where 2 patients had OORR low at bassline and 2 patients (1.4%) had a “normal to low” shift. Examination of the complete

profile of measurements during the study timeline reveals all had a linear regression line of neutrophil values with a positive slope, see Figure 5. These events were scattered among a mix of measurements in the PCST low range and reference range. The examination of patients with values that decline below 1.0 G/L do not show sustained neutrophil decline, the events appear to be episodic transient reduction.

Reviewer Comment: The examination identifies 5 patients with multiple post baseline values in the PCST low range scattered without a trend among values in reference range and some OORR low values but not to PCST low. One patient had a trend of continuing decline in post baseline neutrophil values. These observations identify a trend toward treatment related low neutrophil values where 1 patient had a sustained declining trend.

The frequency of low neutrophil values and the single patient with a sustained negative trend suggests a brivaracetam treatment effect. The current brivaracetam label identifies "significant decreased neutrophil count (<1.0 x 10^9 /L)". This long term open label population has a much longer interval for accrual of low neutrophil events than the labeled clinical study data. Overall the neutrophil measurements in this pediatric study group is similar to the adult adjunctive therapy studies.

Figure 3 Patients 1 to 9 with One or More Neutrophil Values in PCST range. Scatterplot of All Neutrophil Measurements for Each Patient. (horizontal lines: Y axis Red at 1.5 G/L, Green at 3 at 2.0 G/L)

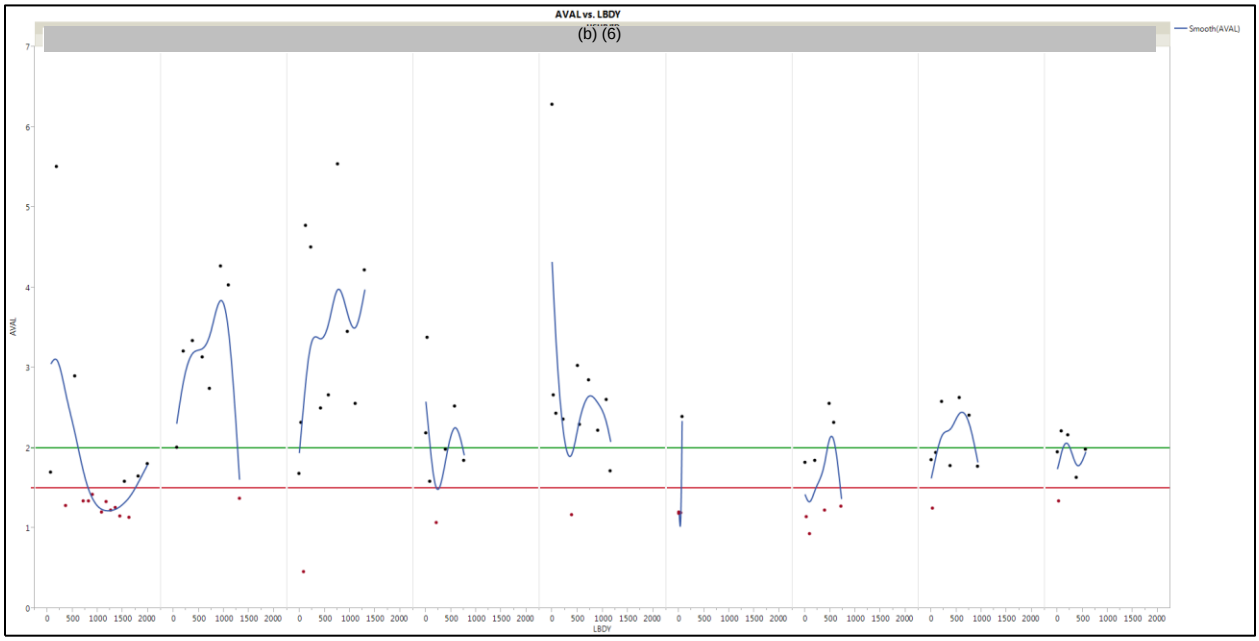


Figure 4 Patients 10 to 19 with One or More Neutrophil Values in PCST range. Scatterplot of All Neutrophil Measurements for Each Patient. (horizontal lines: Y axis Red at 1.5 G/L, Green at 3 at 2.0 G/L)

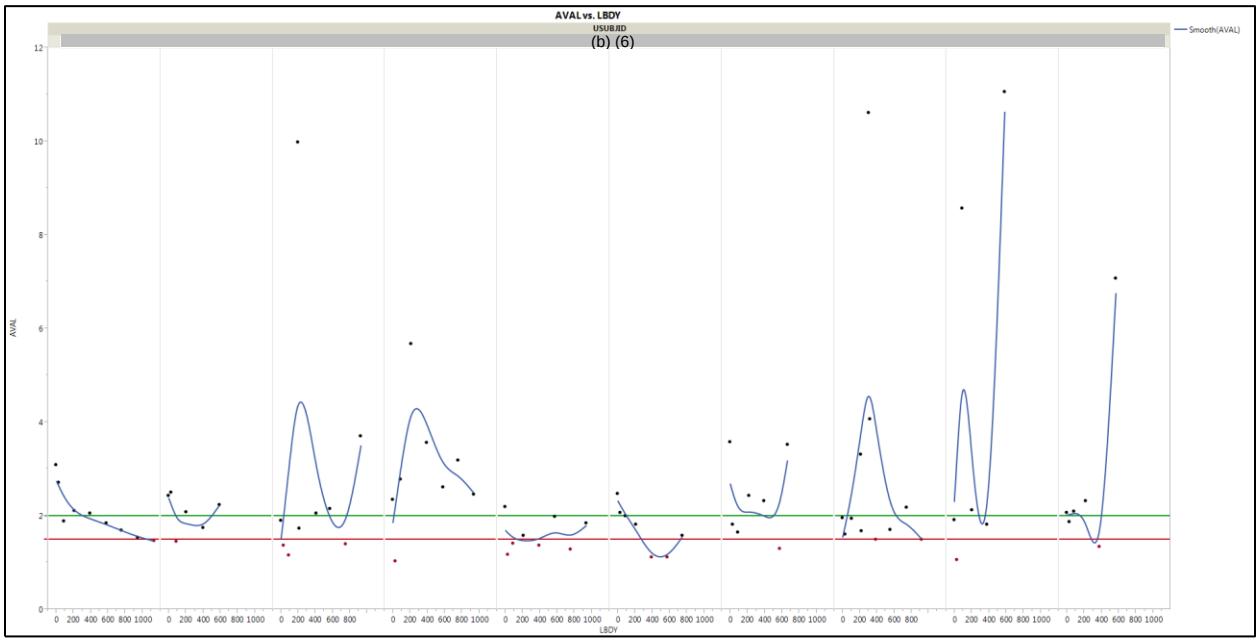
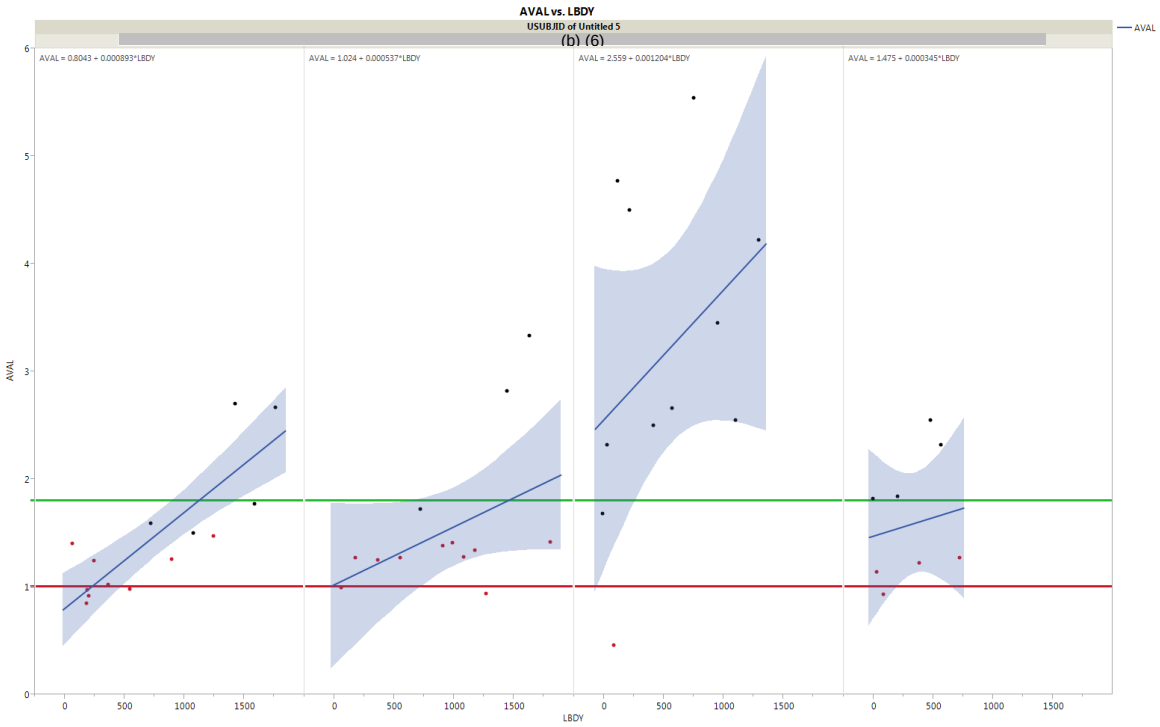


Figure 5 Patients with 1 or More Neutrophil Values <1 G/L, Linear Regression Line over Entire Study Timeline



Eosinophils G/L

There were no PCST values for eosinophil count

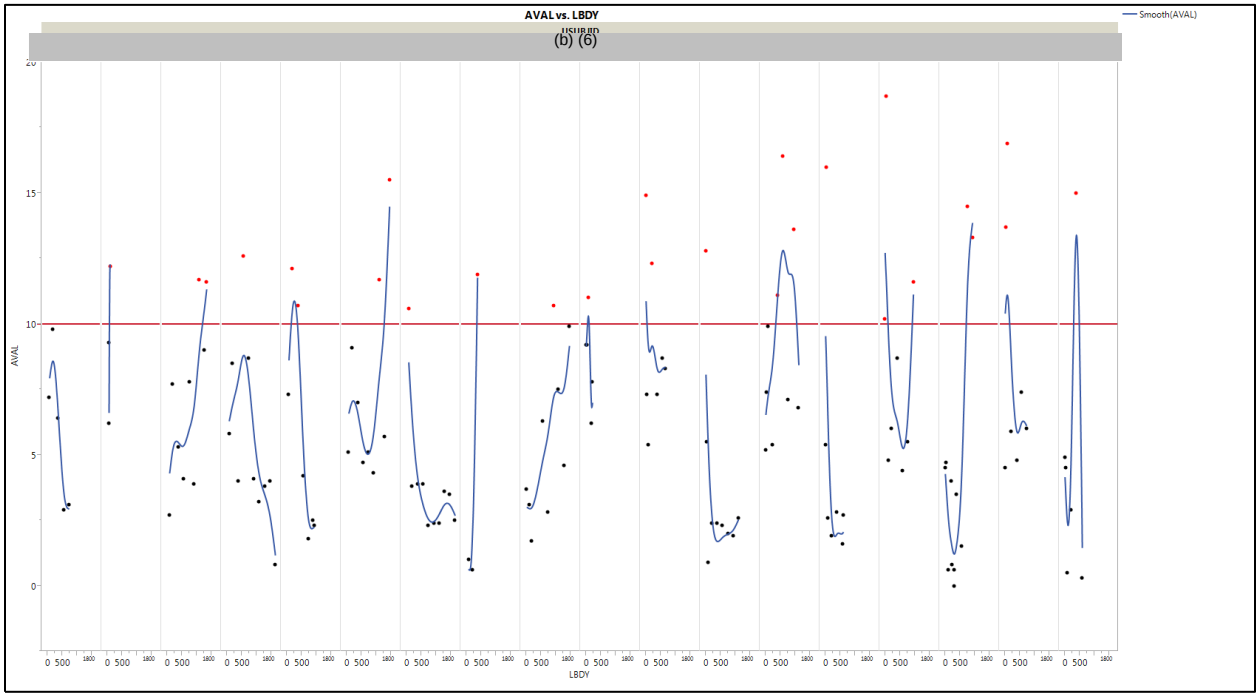
Eosinophils %

There were 35 instances of PCST values (≥10%) for eosinophils from 18 patients. The trendlines for all eosinophil measurements across the long term follow up were examined for each of the 18 patients. A best fit linear regression line was created from the eosinophil % value and the laboratory sampling day for each patient. The slope and maximum eosinophil % were examined, Figure 6. The maximum slope was +0.119 with a maximum eosinophil % value of 12.2% on day 90. The greatest percent eosinophil measurement was 18.7% on study day 29 with an associated trendline slope of -0.0013 through study day 939. There were eight patients with a positive regression line slope and 10 patients with a negative regression line slope. The overall mean slope was +0.0073 while the mean slope from patients with a positive slope regression line was +0.025. The was no consistent trend for increasing percent eosinophils. No patient had consistently increasing values. Elevated values were scattered among values below the range of PCST high.

One patient (b) (6)) had a notable upward trend in percent eosinophils from study day 1090 to 1440. The study 1266, ADaM- ADAE 120 day update dataset is examined. The patient had 30 adverse event entries but none in the "Immune system disorders" SOC. There were entries for pyrexia, nasopharyngitis and rhinitis. A second patient (b) (6) with only 3 measurements between day 2 and 366 had an appearance of a sharp post baseline rise, although slope was +0.0404. This is less than the observed maximum slope in the group, discussed above. The adverse event dataset, as noted previously, was examined and there were no entries in the "Immune system disorders" SOC. The patient did have entries for "nasopharyngitis and Otitis media acute" in the latter portion of the study.

Reviewer Comment: Overall, there is no trend of eosinophilia.

Figure 6 18 Patients with One or More eosinophil % Values in PCST range ≥ 10%. Scatterplot of All eosinophil % Measurements for Each Patient. (horizontal lines: Y axis Red at 10%)



Creatinine

High

One patient, (b) (6) , developed a marked elevation of creatinine at final study visit, 8 days after last brivaracetam dose. Further examination revealed concurrent abnormalities in creatinine clearance and serum potassium. Measurements were normal at end medication date just 8 days before the final study visit. This patient was withdrawn from study drug due to an

elevation of GGT but there was no narrative provided. There is discordance between the reported date of study termination and the date of the adverse event that resulted in drug withdrawal. The GGT of clinical concern (just over 3x ULN) occurred at screening, date 1/27/14 and persisted through all subsequent study visits. The patient continued treatment until 3/24/14 before withdrawal of medication. Relevant data points are summarized in Table 20 below.

On a subsequent information request the sponsor was able to provide an additional follow up laboratory value obtained from the investigator on 4/16/2014 that showed resolution of the elevated creatinine and urea. Upon inquiry, the investigator also reported no clinical symptoms suggestive of renal impairment at the time the increased creatinine, urea, and potassium values.

Table 20 Patient (b) (6), Post Study Elevation of Creatinine. Relevant Laboratory Measurement, Dose and Adverse Event Timeline

Patient (b) (6)										
visit type	screening	titration	Titration visit 2			Early D/C		Final Medication date	Follow up Safety Visit	Last available renal function values
DATE 2014 (month/day)	1/27	2/3	2/3	2/10	2/17	3/10	3/11	3/24	4/1	4/16
LAB PARAMETER										
Gamma Glutamyl Transferase (U/L)	55	61	67			55			55	
Creatinine (umol/L) (mg/dl)	--	42				43			375	37.5
		0.46				0.49			4.2	0.42
Urea (mmol/L)	4.28	5.71				5.36			17.14	9.07
Creatinine Clearance (mL/s)	159	146				143			16	
Potassium (mmol/L)	4.7	4.9				5.2			6.0	
Age		11.7 years								
Weight kg		39								
Dose			0.8	1.6	3.2		1.6	0.8		
Adverse Event Data										
Entries PT	AE Onset Date (variable AESDTL)	SAE	Action taken (Variable AEACN)							
Gamma-glutamyltransferase increased	1/27/14	No	Drug Withdrawn							
Upper respiratory tract infection	2/8/14	No	No change							

Diarrhoea	2/10/14	no	No change					1.6mg/kg/day		

Reviewer Comment: This single value of elevated creatinine with concurrent decline in creatinine clearance and elevated potassium are consistent with renal failure; however, there were no clinical features suggestive of renal impairment concurrent with these values. The event occurred in the post treatment interval observed 8 days after last study medication. This close proximity to end of brivaracetam treatment raises the possibility of a causal relationship to study drug. However, resolution of the elevated creatinine and urea values within 15 days and no other renal laboratory trends or adverse events do not support a signal for renal toxicity with Briviact.

***Conclusion:* Examination of the six laboratory parameters of interest reveals no new safety signal among the data from ALT, creatinine, bilirubin, leukocytes, neutrophils and eosinophils.**

7.5.7. Vital Signs

Weight

Increase in post baseline weight predominated over weight loss. There were 3 patients with a weight loss of 5% or greater at any value post baseline. None of these patients had sustained weight loss across their study timeline.

Systolic Blood Pressure

Visit number 80 (mean visit day # 471) was examined for change from baseline systolic pressure. There were 67 (61%) patients with a higher systolic pressure than baseline and 43 (39%) with a systolic blood pressure lower than baseline. There were no severe changes to high or low systolic pressure. The scatterplot of each patient profile of systolic blood pressure measurements across their study timeline is examined. There were no patients with a sustained decline in systolic blood pressure.

One patient was noted to have a systolic blood pressure of 72mmhg at the final two study visits at days 456 and 538. The adverse event dataset was examined for terms that may be related to low blood pressure. This patient had 30 adverse event entries but only three had a temporal relationship to the low systolic pressure values. These were three AEs, one each at study day 441, 452 and 482 with preferred terms “toothache”, “upper respiratory infection” and “rhinitis”.

There was a single site were data quality is an issue. Site 402 (17 patients), Poland, Dr. B.

Senkowska. Patients at this site were noted to have a predominance of systolic blood pressure values of 120 or 125 mmhg. From 285 measurements, there were 130 (46%) where systolic blood pressure is entered as 120 and 88 (31%) of 125mmhg.

Temperature

The distribution of temperature values from all entries in the dataset are examined for high or low outliers are examined.

Low

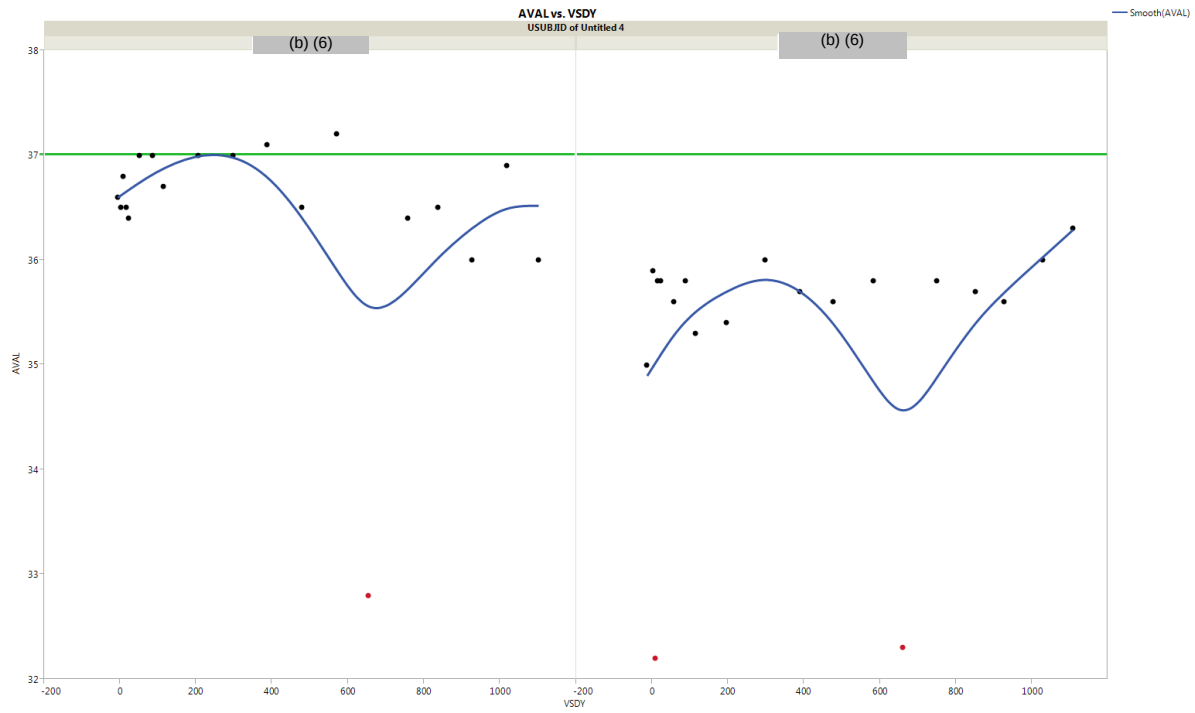
There were 57 entries from 17 patients with temperature entries <35.5. The study 1266 ADAE, ADaM dataset was examined for possibly related adverse events. The adverse event search identifies 146 AE entries. The two most frequently occurring SOCs are “Infections and Infestations” and “nervous system disorders” with 49 and 28 entries respectively. Four of the 146 entries were SAEs from 3 patients. There were three preferred terms from among the SAEs, these were “Partial seizures with secondary generalization” in 2 entries then “clavicle fracture” and “phimosis” in one entry each. These SAEs are not related to hypothermic temperature measurements.

There were two patients with entries below 32.9 C. An examination of the complete array of temperature values for these patients is examined. The exam reveals the readings to be sporadic where the remaining body temperature readings are closer to normal limits, see Table 21 and Figure 7 . A value of 32.8 C was captured from patient (b) (6) on laboratory day 653 while values of 32.2 and 32.3 were identified from patient (b) (6) on laboratory days 7 and 659 respectively. The basis for the extreme values of 91F and 90F is uncertain.

Table 21 Two Patients with Extreme low Body Temperature Values, Mean, Median, Minimum and Maximum of all Measurements During Study 1266 with Scatter Plot of Temperature values.

USUBJID	scale	measurements	# study days	Mean	Median	Min	Max
(b) (6)	C	19	1102	36.5	36.7	32.8	37.2
		38	1108	35.4	35.8	32.2	36.3
	F	19	1102	97.7	98.1	91.0	99.0
		38	1108	95.7	96.4	90.0	97.3
Scatter Plot Key (Figure 7)	Red Markers are Minimum Temperature measurements, Green Horizontal line at 37 C. Blue Smoother curve of scatter plot values						

Figure 7 Patients (b) (6) (left) and (b) (6) (right), Scatterplot of all Study Temperature Measurements



High

The highest temperature entry is 38.3. No further examination of this entry was done.

Reviewer Comment: Examination of weight, systolic blood pressure, and temperature reveals some unusual outliers but do not reveal a new safety signal.

7.5.8. Electrocardiograms (ECGs)

ECG data is provided with a binary normal / abnormal result as well as a field for "findings". The sponsor's summary of abnormal – normal shifts over the course of the study is examined. The shift from abnormal to normal at each yearly count reveals an excess of abnormal to normal shifts compared to shifts from normal to abnormal.

The study 1266 ADaM, ADEG dataset "findings" field is examined. There is 1 finding of "premature ventricular contractions". The most frequent finding is an entry of "OTHER INTERPRETATION NOT LISTED, PLEASE SPECIFY". There are 18 patients with a finding of

"T wave inversion" where in 11 patients the finding was present at baseline. There were 4 patients with findings of "incomplete right bundle branch block" where in 4 of these patients the finding was present at screening or baseline. One patient had a finding of "left bundle branch block". This patient had a finding of sinus tachycardia and T wave inversion at baseline. One patient had a finding of "T wave depression" at last value on study day 386. This an absence of temporal relationship between brivaracetam and the "T wave depression" which weakens the causal relation to study drug. There are no entries for malignant ventricular dysrhythmias.

Reviewer Comment: Overall, there is no signal for development of serious electrocardiographic disorders over the long term follow up of study 1266.

7.5.9. QT

The Applicant's NDA submission included results from a formal QT study that examined the effect of BRV on cardiac repolarization. The FDA Interdisciplinary Review Team (IRT) for QT studies reviewed Study N01233 in a review dated March 5, 2009. The IRT reported the following[13]:

- No significant prolongation effect of BRV was detected in this TQT study.
- No clinically relevant effects on the PR and QRS intervals.

There were no ECG findings of QT prolongation and no adverse events with preferred terms concerning the QT interval.

7.5.10. Immunogenicity

N/A small molecule therapeutic

7.6. Analysis of Submission-Specific Safety Issues

Section 5.3 of the brivaracetam label prior to this submission contains a warning for "Psychiatric Adverse Reactions". The labeled language states that psychiatric events included both non-psychotic and psychotic symptoms. There are 24 adverse event terms identified in the labeling, Table 22. The pooled pediatric adverse event dataset is examined to determine if there is a change in the signal for these adverse event terms in the "Pool Pediatric Studies".

7.6.1. Psychiatric Events Analysis

[13] Brivaracetam NDA Safety Review, Mary Doi MD, MS, 11/5/15 section 7.4.4, p147.

Table 22 Psychiatric Terms from Section 5.3 BRIVIACT Label*

ALL PSYCHIATRIC PREFERRED TERMS IN EXISTING LABEL	
1. abnormal behavior	2. depression
3. acute psychosis	4. hallucination
5. adjustment disorder	6. Irritability
7. affect lability	8. mood swings
9. aggression	10. Nervousness
11. agitation	12. paranoia
13. altered mood	14. psychomotor hyperactivity
15. anger	16. psychotic behavior
17. Anxiety	18. psychotic disorder
19. apathy	20. psychotic symptoms
21. belligerence	22. restlessness
23. depressed mood	24. tearfulness
* Drugs at FDA 9/14/2017	

Examination of the pooled pediatric AE dataset[14] revealed 13 of these 24 terms were present. The ADAE ISS safety dataset from the initial brivaracetam NDA submission, section 5.3.5.3 "*Analysis of Data from more than one Study*" is used as a comparator to examine the frequency difference between the adult and pediatric populations. The S4 pool of the ADAE safety dataset contains long term follow up data from brivaracetam controlled trials where mean, median and maximum duration of treatment was 39, 30 and 133 months[15]. Brivaracetam doses ranged from 5mg to 400mg with a mean and median of 152mg/day and 150mg/day respectively.[16] The overall exposure of patients with partial onset seizures in the pediatric safety pool, age range from 4 years to <16 years was a maximum of 5 years with a minimum of 1 months with where mean and median duration of treatment was ≥ 2 years.

The temporal profile of adverse event occurrence of the 13 events of interest is examined for the pediatric pool and the S4 pool. The S4 pool duration of treatment was about three (3) times as long as the timeline of the pediatric pool. The S4 pool had a combined mean study day of onset for the 13 preferred terms of 527 days with a median of 219 and a range of 1 to 3806 days. The pediatric pool had a mean study day of AE onset of 169 days with a median of 32 days with a range of 1 to 1105 days. In the S4 AE dataset, 50% of the events occurred by study day 218 while in the pediatric pool 76% of events occurred by day 214. Although the S4 pool has a much longer brivaracetam exposure timeline the clustering of adverse events during the first 60% of a year in both studies allows some comparability of the data.

[14] concatenated 1263 -1266 ADSL with POS and SAFETY flag joined to concatenated ADaM ADAE sets from 1263-1266 with all 1266 patients plus 24 1263 patients who did not move forward into 1266 LTFU
[15] NDA 205836, ISS section 5.3.5.3, ADSL Analysis Dataset. Variables TRTEDT-TRTSDT.
[16] NDA 205836, ISS section 5.3.5.3, ADAE Analysis Dataset-from 120-day safety update. Variables DOSEAEON and TR99AG4.

The results of the examination of adult safety dataset S4 compared to the "Pooled Pediatric Studies" dataset reveal an excess of adverse events among pediatric patients greater than 1% over the percent occurrence in the adult long term follow up dataset for 5 preferred terms. These are the preferred terms "irritability", "psychomotor hyperactivity", "aggression", "suicidal ideation", and "abnormal behavior". The maximum frequency over the adult dataset is 4.9% for the term "irritability". The frequency of overall serious adverse events occurring in both groups reveals a small, 0.7% excess in the pediatric pool over the adult long term follow up group. Some terms had higher frequencies in the adult Pool S4 compared to the pediatric patient pool. These preferred terms were "depressed mood", "insomnia", "anxiety" and "depression", shown in Table 23.

To examine the frequency of psychiatric adverse events in shorter-term exposure, a controlled trial interval the pediatric pool dataset is compared to the brivaracetam treatment arm of study 1358. Study 1358 was a pivotal trial with 503 patients in the safety flag set of the brivaracetam treatment arm. The adverse event data from study 1358 was accrued during the 12-week double blind controlled trial interval. This represents a shorter interval for the occurrence of psychiatric adverse events. The comparison reveals a somewhat greater excess of events in the pediatric pool over the adult brivaracetam treatment population. The maximum difference was seen for the term "irritability" where there was a 3.2% frequency in the study 1358 population and 10.7% frequency in the pediatric pool for a difference of 7.6%. The remaining terms were not notably different from the comparison to the S4 safety dataset.

Table 23 Frequencies of Psychiatric Adverse Event Terms, Comparison of Adult Long Term Follow up Patient Population, Pivotal Trial 1358 12 Week DB Treatment Interval and Pooled Pediatric Studies. *

	S4 Adult Long Term Follow up safety dataset		Study 1358 controlled trial, BRV treatment arm. (SAFETY FLAG)		POOL Pediatric		Differences in frequencies between safety populations	
	N= 2388		N= 503		N= 149			
Preferred Term	Unique Patients and Percent of N							
Preferred Term	#	%	#	%	#	%	Δ PED-S4	Δ pediatric - 1358
Irritability	139	5.8	16	3.2	16	10.7	4.9	7.6
Psychomotor hyperactivity	7	0.3	0	0.0	7	4.7	4.4	4.7
Aggression	46	1.9	4	0.8	7	4.7	2.8	3.9
Suicidal ideation	51	2.1	2	0.4	7	4.7	2.6	4.3
Abnormal behaviour	17	0.7	0	0.0	3	2.0	1.3	2.0
Hallucination	11	0.5	0	0.0	2	1.3	0.9	1.3
Nervousness	42	1.8	2	0.4	3	2.0	0.3	1.6
Anger	17	0.7	3	0.6	1	0.7	0.0	0.1
Mood swings	17	0.7	3	0.6	1	0.7	0.0	0.1
Depressed mood	46	1.9	2	0.4	2	1.3	-0.6	0.9
Insomnia	169	7.1	13	2.6	7	4.7	-2.4	2.1
Anxiety	132	5.5	11	2.2	4	2.7	-2.8	0.5
Depression	186	7.8	4	0.8	2	1.3	-6.4	0.5
Combined total SAE	31	1.3	0	0.0	3	2.0	0.7	2.0

* sorted in descending order by Δ PED-S4 column

Reviewer comment: There is no notable excess in the pediatric population of the psychiatric adverse event terms present in the current brivaracetam label. The differences in frequency between the pediatric pool and the adult long term follow up patient pool do not exceed 5%. There is little difference in the combined frequency of SAEs in this panel of psychiatric preferred terms between the adult and pediatric population. Overall, the adverse reactions in pediatric patients age 4 to less than 16 years of age are similar to those seen in adult patients.

7.7. Safety Analyses by Demographic Subgroups

Demographics of the Safety Population

Patients age 4 to <16 with Partial onset seizures

There is a modest inequality of the proportion of male and female patients where 43.4% of patients are female and 56.4% are male. From among the sex groups the frequency of any adverse event was similar where 89.2% of females and 94% of males had any adverse event. There was a higher frequency of serious adverse events in males over females where 26.2% of males and 12.3% of females had a serious adverse event, Table 24, Table 26.

The racial composition of the Pool Pediatric was primarily white and other/mixed, where the content of other/mixed was not further defined in the submission or dataset. The Pool had 66% caucasian, 31% other/mixed, 0.7% other, and 2.7% black or African American. Examination of all adverse event entries reveals a high proportion for each group at 75%, 98% and 91% for Black or African American, Other/mixed and White respectively. The 75% value for "Black or African American" represents an adverse event for 3 of the 4 patients in the pool. The frequency of SAEs across the racial cohorts was similar at 25%, 19.6% and 20.4% in the Black or African American, Other/mixed and White subgroups, respectively, Table 25, Table 26.

Age strata reveal a mild disproportion from complete equality of distribution where the age 4 to <7 cohort contained a modestly higher percent of patient at 29.5% and the age 13 to 16 cohort had a smaller proportion of the total at 19.5%. This is a favorable skew because the 4 to <7 cohort is the most distant from the adult population age. Examination of all adverse entries reveals a modestly higher frequency in the 4 to <7 at 42% while the remaining age subgroup cohorts had a frequency of 29%, 36% and 30% for the 7 to < 10, 10 to < 13 and 13 to 16 age cohorts respectively. Serious adverse events (SAE) had a maximum of 27% in the 10 to 16 age group and a minimum of 6% in the 10 to < 13, Table 25, Table 26.

Table 24 Demographics, Male and Female Patients*

	patients	% of cohort
F	65	43.6
M	84	56.4
* Demographics derived from Pool Pediatric dataset 1263-1266		

Table 25 Demographics; Age Strata and Race*

age strata	patients	% of cohort	RACE	Patients	% of cohort
4 to <7	44	29.5	BLACK OR AFRICAN AMERICAN	4	2.7
7 to < 10	36	24.2	OTHER	1	0.7
10 to < 13	40	26.8	OTHER/MIXED	46	30.9
13 to 16	29	19.5	WHITE	98	65.8
Mean age	9.5				
Median age	9.6				
* Demographics derived from Pool Pediatric dataset 1263-1266					

Analysis of Adverse events by Subgroup

Table 26 Demographics; Adverse Events by Sex, Race and Age Cohort*

	TEAE			SAE		
Sex	instances	Patients	% Patients	instances	patients	% patients
Female	575	58	89.2	13	8	12.3
Male	744	79	94.0	47	22	26.2
RACE	instances	patients	% Patients	instances	patients	% patients
BLACK OR AFRICAN AMERICAN	24	3	75	3	1	25
OTHER/MIXED	452	45	97.8	21	9.0	19.6
WHITE	843	89	90.8	36	20.0	20.4
AGE Strata						
4 to <7	453	42	82.4	28	11	21.6
7 to < 10	261	29	69.0	14	6	14.3
10 to < 13	271	36	72.0	3	3	6.0
13 to 16	334	30	81.1	15	10	27.0
* Analysis of AE data on study 1266 ADaM, ADAE dataset, safety flag, +POS, n=144 patients compared to Pool Pediatric n= 149 for the same age/ POS composition.						

Reviewer Comment: The notable demographic characteristics are a small predominance of males over female patients, a racial mix of predominantly Caucasian with a large component of other/mixed and a very small proportion of Black or African American patients. Without further definition, it is unclear what group the "other/mixed" category of race may generalize to. The adverse event analysis reveals an SAE frequency in males that is twice that of females. Given the wide variation in clinical conditions, the open label data source and the long intervals of observation no conclusion may be drawn on the significance of this observation. Overall, the adverse event analysis does not identify any notably conclusive difference between demographic subgroups.

7.8. Specific Safety Studies/Clinical Trials

N/A

7.9. Additional Safety Explorations

7.9.1. Human Carcinogenicity or Tumor Development

No additional nonclinical studies were performed for this sNDA.

7.9.2. Human Reproduction and Pregnancy

No additional studies were performed for this submission. A pregnancy occurred in the Pool Pediatric study 1266, patient was 14.5 years old at entry. Study drug was discontinued and the subject delivered a normal, healthy baby via caesarian section.

7.9.3. Pediatrics and Assessment of Effects on Growth

This efficacy supplement proposes the use of BRIVIACT as monotherapy and adjunctive therapy in the treatment of partial onset seizures (POS) in patients 4 to younger than 16 years of age with epilepsy in accordance with PREA requirements. As indicated in section 6.1 there are no pediatric efficacy study data included in this Application. This sNDA proposes an expanded indication for adjunctive and monotherapy treatment of partial onset seizure in the population of patients aged 4 to less than 16 years of age as outlined in General Advice letters of 9/13/16 (monotherapy) and 11/12/15 (pediatrics).

TEAEs potentially associated with growth, endocrine function/sexual maturation, neurodevelopment, cognitive impairment, anxiety, and depression in the Pool Pediatric studies are examined for ages 4 to < 16 years with POS. Sponsor table 6-28 of the ISS page 164 reveals no events for the preferred terms “underweight” or “failure to thrive”. The most common event under the heading of neurodevelopment is from the “nervous system disorders” SOC, preferred term “psychomotor hyperactivity in 7 (4.7%) patients. This term is captured in the discussion of “Psychiatric Terms” in section 7.6.1. Additional terms captured in the sponsor table related to cognitive development in the SOC “psychiatric disorders” are “Attention deficit/hyperactivity disorder” identified in 3 (2.0%) patients, “Confusional State” in 3 (2.0%) of patients, “anxiety” in 6 (4.0%) patients and “nervousness” in 2 (1.3%) of patients. None of these psychiatric terms were identified as serious adverse events.

The reviewer examination (section 7.5.7) of vital signs dataset revealed 3 patients with a > 5% weight loss, however no patients had sustained weight loss over the study interval.

Reviewer Comment: No signal for drug related disorder of growth or cognitive development is identified in this long term open label dataset.

7.9.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Evaluated at NDA submission for initial approval. See CSS memorandum 2/17/16.

7.10. Safety in the Postmarket Setting

7.10.1. Safety Concerns Identified Through Postmarket Experience

Post Marketing Assessment based on FAERS Reporting

There are no reports in FAERS or Empirica Signal using “Trade” suspect drug, under the preferred terms “bilirubin abnormal”, “bilirubin increased”, “ALT abnormal”, “ALT increased”, “hepatitis”, “hepatitis fulminant”, “hepatitis acute”, “hepatitis toxic”. Also, there are no reports under “Drug reaction with eosinophilia and systemic symptoms” (DRESS). Search performed 12/6/17.

An Empirica Signal search for all preferred terms with an EB05 ≥ 2 is conducted. This search yields 19 terms. The highest frequency terms with more than 20 entries are “seizure”, “off label use” and “aggression”. The terms with highest EB05 of 216.5, 133.2, and 54.6 were “post ictal psychosis”, “mutism”, and “change in seizure presentation” respectively, Table 27.

The high frequency terms of “seizure” and “aggression” are not unexpected. The frequency of seizure or change in seizure presentation entered in spontaneous reporting are difficulty to differentiate from events seen as background due to the underlying disease state. Aggression is present in current labeling section 5.3 “psychiatric adverse reactions”. The events of very high EB05 have a low frequency. Post ictal psychosis and change in seizure presentation are again, difficult to differentiate from the frequency that may be seen due to the underlying epilepsy. The term “mutism” was unexpected and investigated further by individual case report examination. The 8 individual case reports of “mutism” appear to be duplicates of a single case. In each of the reports the patient is male, no age is provided for additional cross reference but the primary adverse event term is “aggression”. An additional term “dementia” is present in every report. The length of narrative varies but appears to describe the same incident. Therefore, the “mutism” has an n=1 rather than 8 and occurs in the context of dementia.

Table 27 Post Marketing; Empirica Signal Search, All Preferred Terms with EB05 ≥ 2

Preferred Term	Event Count	EB05
Seizure	71	29.5
Off label use	44	3.5
Aggression	22	20.7
Suicidal ideation	19	6.6
Generalised tonic-clonic seizure	16	35.1
Depression	16	3.0
Somnolence	15	3.4
Confusional state	11	2.9
Overdose	11	2.7
Balance disorder	10	3.7
Postictal psychosis	8	216.5
Mutism	8	133.2
Abnormal behaviour	8	3.2
Hypersomnia	6	2.8
Status epilepticus	5	2.6
Sedation	5	2.3
Change in seizure presentation	4	54.6
Partial seizures	4	2.5
Atonic seizures	3	2.2

Reviewer Comment: The post marketing event evaluation does not reveal a new safety signal.

Pediatric Post Marketing Experience, Age 4 to <16 years

Post marketing safety reports for pediatric use of brivaracetam are derived from off label use because brivaracetam is not currently approved in any country for use in pediatrics (<16 years)

The total amount of product distributed is (b) (4) mg for the time period 1/14/2015 to 10/14/2016, contributing to approximately 6,197 patient-years in the general population, however he postmarketing pediatric BRV exposure is very low and thereby interpretability of overall pediatric exposure is limited.

The adverse event pediatric postmarketing dataset captured from patients age 4 to <16 was examined. There were 82 adverse event entries containing 17 preferred terms from among 26 patients. The greatest percent preferred term identified from among these 26 patients was “no adverse event”. In descending order, all terms with greater than 2 instances included “off label use”, “aggression”, “intentional product misuse”, “seizure”, and “suicidal ideation” see . There was no completed suicide.

Table 28 Frequency of Preferred Terms From 26 Pediatric Patients with a Post Marketing Adverse Event Report*

preferred term	# patients	% Patients
No adverse event	18	69.2
Off label use	5	19.2
Aggression	2	7.7
Intentional product misuse	2	7.7
Seizure	2	7.7
Suicidal ideation	2	7.7
Brain operation	1	3.8
Decreased appetite	1	3.8
Depressed mood	1	3.8
Drug ineffective	1	3.8
Fatigue	1	3.8
Lacrimal disorder	1	3.8
Malaise	1	3.8
Mood swings	1	3.8
Petit mal epilepsy	1	3.8
Rash	1	3.8
Tonic convulsion	1	3.8

*from pm4_16y, Analysis Dataset Legacy, eCTD section 5.3.6 "Reports of Postmarketing Experience. Reports were identified in the UCB Global Safety database in patients ≥4 to <16 years of age.

Reports Characterized as Serious

Four of the 26 patients had events characterized as serious. There were 2 reports with preferred term "suicidal ideation", and one report each with preferred terms "brain operation" and "tonic convulsion".

The sponsor performed a literature search for publications relevant to the pediatric population. There were no articles identified during the search that reported on the use of BRV in the pediatric population.

The sponsor performed a comprehensive review of the fatal cases (including potential SUDEP), AEOIs relevant to BRV in pediatric population (suicidality-related events, behavior disorders, blood dyscrasias, potential worsening of seizure, potential abuse, DRESS and SCARs, hepatotoxicity-related events, renal injury, psychosis, depression, anxiety, fall and injuries, potential effects on growth, cognition, endocrine, sexual maturation and neurodevelopment, and malignancies), and other medically important events (lack of efficacy and pregnancy), did not show concerns specific to the use of BRV in patients ≥4 to <16 years of age.

Overall, there were a small number of pediatric post marketing adverse event reports. The most comment preferred term in the dataset (70% of patient reports) is found to be "no adverse event" a term used by the sponsor for data entry when no clinical event is associated with an off-label use. The second most frequent term in the post marketing reports is "off label use". When all entries for "no adverse event" and "off label use" are excluded there are 53 remaining preferred term entries from 8 reports. Examination of these preferred terms reveals there were 4 terms derived from 2 patient reports each with the remaining 11 terms occurring in 1 patient report each. The four terms associated with 2 patient reports were "aggression", "intentional product misuse", "seizure" and "suicidal ideation".

The 2 reports of "intentional product misuse" occurred in one patient where the brivaracetam tablet was crushed. In the second report, a patient of elementary school age was reported by a consumer as using brivaracetam off label.

Reviewer comment: there were a small number of post marketing reports associated with preferred terms that were not related to "off label use". These reports occur in a context where overall product use for the population of interest is not known. No new safety concerns have emerged out of this analysis of the post marketing reports of patients 4 to < 16 years of age.

7.10.2. Expectations on Safety in the Postmarket Setting

N/A

7.10.3. Additional Safety Issues From Other Disciplines

N/A

7.11. Integrated Assessment of Safety

The safety synthesis for this sNDA examines the findings for patients in the pediatric age range 4 to <16 years with POS. The objective is to address the potential for new safety signals in this pediatric population or identify an increased severity of signals seen in the initial safety review as brivaracetam was an NME in the 16 year or older population. The safety dataset for this application is the "Pool Pediatric Studies" derived from studies 1263 and 1266. The reviewer assembled this dataset for cross checking the sponsor results from the ADaM datasets provided individually for studies 1263 and 1266 where the methodology is explained in the section "Pool Pediatric Studies". The safety review relies primarily on the reviewer constructed datasets and in part on the sponsor presentation in the ISS and individual study reports.

<u>Deaths:</u>

There were four deaths identified in the Pool Pediatric studies, 3 were captured during initial

NDA safety review and 1 new event was identified in the sNDA dataset. In the new report, a patient suffered septic shock after 30 months of brivaracetam treatment. The event is unrelated to study drug.

Serious Adverse events (SAE)

An increase in the frequency of preferred terms categorized as an SAE was noted. The preferred terms are “convulsion” and “status epilepticus”. This increase is based on comparison to the adult S4 (long term follow up) pool. There was also a case report of severe behavioral disturbance identified as homicidal ideation in a single patient. This patient behavior occurred on a background of pretreatment severe aggressive behavior disturbance.

Discontinuations

The overall frequency of TEAE leading to discontinuation was lower in the pool pediatric studies compared to the pool monotherapy, pool ULD and Pool S4 patients of the initial brivaracetam NDA review. The profile of TEAE leading to discontinuation in pool pediatric studies was also similar to Pool S4 where the SOC “nervous system disorders” and “psychiatric disorders” were the most frequent TEAE leading to discontinuation. The composition of the individual preferred terms within these SOCs was also similar between the Pool Pediatric studies and Pool S4 / Pool monotherapy.

Unexpected adverse events

Seven case reports of unexpected adverse events are identified including "Acute respiratory failure", "deafness neurosensory", "spina bifida", "septic shock", "hypoxia", "hemodynamic instability" and “renal failure”. The finding of renal failure was identified from an examination of the study 1266 ADaM, ADLB laboratory dataset where patient entries revealed a rapid increase in serum creatinine over eight days from last administered study medication (brivaracetam) to final laboratory measurement with resolution 15 days later at a follow up measurement. This report is covered in additional detail in section 7.5.6, Laboratory Findings. Examination of the remaining six events revealed lack of temporal relationship, confounding by concomitant medications and underlying medical illness. The reports of “deafness neurosensory", "spina bifida", "hypoxia", "hemodynamic instability" do not appear related to study drug while "acute respiratory failure" resulted in discontinuation and "septic shock" resulted in death. The basis of the single spike in renal function parameters in the report noted above remains uncertain but appears to have resolved quickly or may have been laboratory error.

Treatment Emergent Adverse Effects (TEAEs) (common adverse effects)

Overview of TEAEs reveals lower frequencies of all events, related events, severe events and SAEs compared to the adult LTFU brivaracetam studies in all but the < 4yo subset of the "pool pediatric studies". Interpretability of this cohort is limited due to the small size of this subset with only 16 patients. Overall the TEAE SOC groups and preferred terms are similar to those seen in the adult brivaracetam long term follow up studies. The frequency of terms that capture infection and gastrointestinal disturbance is higher. These differences may reflect a greater vulnerability to gastric intolerance and the higher frequency of respiratory infections seen in the pediatric population. Overall no new safety signal is emergent in the proposed pediatric treatment population.

Laboratory findings

The sponsor did not identify any overall divergence in laboratory testing across the study timeline of Pool pediatric studies. The reviewer examined six core laboratory parameters interest that may be associated with hepatic, renal, and hemopoietic dysfunction and association with hypersensitivity. These selected parameters were alanine aminotransferase (ALT), bilirubin, serum creatinine, leukocytes, neutrophils and eosinophils.

Examination of the six laboratory parameters of interest reveals no new safety signal among the data from ALT, bilirubin, leukocytes, neutrophils and eosinophils. In the single finding of laboratory values consistent with renal failure, there is not sufficient information to conclude if this was true renal dysfunction or a laboratory inaccuracy

Vital signs: Examination vital signs did not identify a safety signal

ECG: Overall, there is no signal for development of serious electrocardiographic disorders over the long term follow up of study 1266.
Psychiatric adverse terms

There is no notable excess in the pediatric population of the psychiatric adverse event terms present in the current brivaracetam label. The differences in frequency from the adult long term follow up patient pool do not exceed 5%. There is little difference between the adult (S4) LTFU and pediatric population SAEs in this panel of psychiatric preferred terms. Overall, the adverse reactions in pediatric patients age 4 to less than 16 years of age are similar to those seen in adult patients.

Reviewer Summary Comment: The overall safety profile is not notably divergent from the findings in the adult population of the initial NDA.

8. Advisory Committee Meeting and Other External Consultations

NA

9. Labeling Recommendations

9.1. Prescription Drug Labeling

There are no clinical recommendations for labeling changes in addition to the proposed age expansion for the ages 4 to 16 years. There is a change in proposed dosage by weight. This is based on Clinical Pharmacology modeling, section 4.5. This change will add a modification to the dose for pediatric patients under 50kg.

Weight based dose labeling for patients 50kg or less will have tiered maintenance dose minimum and maximum recommendations to compensate for decreased exposure at body mass below 20 kg identified in simulations. The sponsors proposed language will be replaced by a tiered dose schedule displayed in tabular form, Table 29.

Table 29 Recommended Dosage for Adults and Pediatric Patients 4 Years and Older

Age and Body Weight	Initial Dosage	Minimum and Maximum Maintenance Dosage
Adults (16 years and older)	50 mg twice daily (100 mg per day)	25 mg to 100 mg twice daily (50 to 200 mg per day)
Pediatric patients weighing 50 kg or more	25 mg to 50 mg twice daily (50 mg to 100 mg per day)	25 mg to 100 mg twice daily (50 to 200 mg per day)
Pediatric patients weighing 20 kg to less than 50 kg	0.5 mg/kg to 1 mg/kg twice daily (1 mg/kg to 2 mg/kg per day)	0.5 mg/kg to 2 mg/kg twice daily (1 mg/kg to 4 mg/kg per day)
Pediatric patients weighing 11 kg to less than 20 kg	0.5 mg/kg to 1.25 mg/kg twice daily (1 mg/kg to 2.5 mg/kg per day)	0.5 mg/kg to 2.5 mg/kg twice daily (1 mg/kg to 5 mg/kg per day)

9.2. Nonprescription Drug Labeling

N/A

10. Risk Evaluation and Mitigation Strategies (REMS)

None Recommended

11. Postmarketing Requirements and Commitments

none

12. Appendices

12.1. References

Entered as footnotes

12.2. Financial Disclosure

The submission is supported by two clinical studies N01263 and N01266. Safety data is derived from both of the open-label pediatric studies (N01263 and N01266). Pharmacokinetic data from N01263 contributed to the PK and PK/PD modeling and simulation studies that support pediatric dosing recommendations. Study 1266 is an open label safety study that is an extension of study 1263 with allowance of direct enrollment (non-1263 participants) for patients age 4 to <16 years old. As noted in section 6.1 there is no pediatric efficacy study necessary to support this sNDA and expanded indication.

There is no notable conflict of interest from disclosable financial interest (DFI). One investigator, Dr. William Rosenfeld, who participated in in both studies 1263 and 1266 had DFI. Details of the DFI could not be obtained by the sponsor although a report of due diligence is provided in the submission.

Covered Clinical Study (Name and/or Number): 1263

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 94		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____		

Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 1266

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 166		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		

Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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/s/

STEVEN T DINSMORE
04/24/2018

TERESA J BURACCHIO
04/25/2018