CLINICAL REVIEW

Application Type	NDA EFFICACY SUPPLEMENT, Prior Approval Efficacy Supplement
Application Number(s)	205836 (Tablet)-SD 289, 205837 (injection)-SD 122, 205838 (oral solution)- SD125
Priority or Standard	Standard
Submit Date(s)	10/28/2020
Received Date(s)	10/28/2020
PDUFA Goal Date	8/27/2021
Division/Office	DN2 / ODE1
Reviewer Name(s)	Steven Dinsmore
Review Completion Date	8/6/2021
Established/Proper Name	Brivaracetam
(Proposed) Trade Name	BRIVIACT
Applicant	UCB, Inc
Dosage Form(s)	Tablet, Oral Solution, Injection
Applicant Proposed Dosing Regimen(s)	Addition of a weight-based dosing strata for youngest pediatric cohort added in expanded pediatric population
Applicant Proposed Indication(s)/Population(s)	BRIVIACT is indicated for the treatment of partial-onset seizures in patients 1 month of age and older
Recommendation on Regulatory Action	approval
Recommended Indication(s)/Population(s) (if applicable)	BRIVIACT is indicated for the treatment of partial-onset seizures in patients 1 month of age and older

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Glossary

AE	adverse event
AR	adverse reaction
BRF	Benefit Risk Framework
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
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
LTFU	long term follow up
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NME	new molecular entity
OSI	Office of Scientific Investigation
OORR	Out of Reference Range
PCST	possibly clinically significant treatment-emergent
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
POS	partial onset seizures
PGS	primary generalized seizures
PREA	Pediatric Research Equity Act
SAE	serious adverse event
SAP	statistical analysis plan
SBP	Systolic Blood Pressure

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SOC	System Organ Class - MedDRA Hierarchy
TEAE	treatment emergent adverse event
TTO	time to onset
URI	upper respiratory infection

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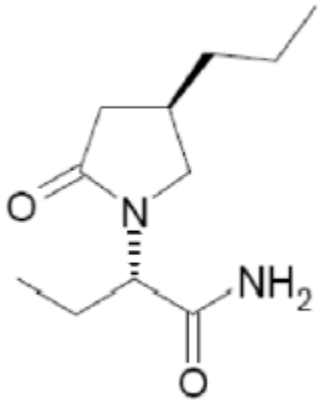
1. Executive Summary

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. Tablets are available in 10mg, 25mg, 50mg, 75mg, and 100mg strength. Oral solution is available in 10mg/ml solution. It is also available in an injectable (intravenous) formulation. All three forms share "Full Prescribing Information".

Current BRIVIACT (brivaracetam) Section 1 "Indication and Usage" Labeling from "Full Prescribing Information":

"BRIVIACT is indicated for the treatment of partial-onset seizures in patients 4 years of age and older.

As the safety of BRIVIACT injection in pediatric patients has not been established, BRIVIACT injection is indicated for the treatment of partial-onset seizures only in adult patients (16 years of age and older)."

Proposed Section 1 "Indication and Usage" Labeling from "Full Prescribing Information":

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"BRIVIACT is indicated for the treatment of partial-onset seizures in patients 1 month of age and older."

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 the pediatric population from the current labeling for the pediatric population where the lower age limit for treatment is age 4 years of age and older. The pediatric population will be expanded to add the younger segment of the population from 1 month to 4 years of age for use of the oral formulation. In addition, the application proposes expansion of the use of the intravenous formulation to the pediatric population age 1 month to less than 16 years where currently brivaracetam injection is indicated only in adult patients.

The requirements for extrapolation of efficacy as identified in Section 3.2, Summary of Presubmission/Submission Regulatory Activity, have been met based on examination of the sponsor's safety data for the expanded pediatric population in Studies N01263, N01266 and EP0065 as well as the Office of Clinical Pharmacology findings and recommendation for approval, see Section 4.5 Clinical Pharmacology.

1.3. Benefit-Risk Assessment

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Benefit-Risk Integrated Assessment

This expansion of indication for use of oral and intravenous brivaracetam will allow the full pediatric age spectrum to have access to this AED for treatment of partial onset seizures (POS). There are no apparent selective safety vulnerabilities in the expanded pediatric population 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.[1]	The large proportion of patients 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	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 ≥4 years and older. No new concerning signals have emerged in post marketing.

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

2. Therapeutic Context

"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."[2]

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

BRIVIACT tablets, injection, and oral solution (NDAs 205836, 205837 and 205838, (respectively) were approved 18 February 2016. BRIVIACT received approval for pediatric indication in treatment of POS on 10 May 2018 and is currently indicated for the treatment of POS 4 years and older (tablets and oral solution). BRIVIACT injection is currently indicated for the treatment of partial-onset seizures only in adult patients (16 years of age and older).

3.2. Summary of Presubmission/Submission Regulatory Activity

On 2/26/2021 the applicant was notified in a general advice letter that the Division of Neurology 2 determined that it is acceptable to extrapolate to pediatric patients 1 month of age and older the effectiveness of drugs approved for the treatment of partial onset seizures (POS) in adults. The letter notes that systematic and quantitative analyses conducted by FDA, using data from clinical studies of drugs approved for the treatment of POS in both adults and pediatric patients, have shown that the relationship between exposure and response (reduction in seizure frequency) is similar in adults and pediatric patients 4 years of age and older. These

[2] Kappes JA, Hayes WJ, Strain JD, Farver DK. 2017. Brivaracetam: An Adjunctive Treatment for Partial-Onset Seizures. Journal of Clinical Pharmacology 57:811-817.

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analyses and observations have allowed FDA to conclude that the efficacy of drugs approved for the treatment of POS can be extrapolated from adults to pediatric patients 1 month of age and older. Extrapolation based on these analyses applies only to POS, and not to other seizure types or forms of epilepsy.

The letter also states:

The following will be required to support an indication for the treatment of POS in patients 1 month and older that relies upon extrapolation:

• Approved indication for the treatment of POS in adults.

• A pharmacokinetic analysis to determine the dosing regimen that provides similar drug exposure (at levels demonstrated to be effective in adults) in pediatric patients 1 month of age and older and in adult patients with POS. This analysis will require pharmacokinetic data from both the adult and pediatric (1 month of age and older) populations.

• Long-term open-label safety study(ies) in pediatric patients 1 month of age and older.

To support extrapolation down to 1 month of age for drugs already approved for the treatment of POS in older pediatric patients, sponsors will be required to submit the relevant pharmacokinetic analysis and long-term safety data.

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

4.1. Office of Scientific Investigations (OSI)

There are no pediatric efficacy study data included in this application, therefore no inspections are requested to audit metrics that have potential influence on clinical efficacy outcomes.

4.2. Product Quality

There is no Product Quality review, Module 2, Section 2.3 of the eCTD indicates: The currently approved tablets, oral solution and injection are acceptable for pediatric use and cross references to the approved drug substance and drug product information are provided in this supplement.

This is no eCTD Module 3 present in the Application.

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4.3. Clinical Microbiology

This is no eCTD Module 3 present in the Application.

4.4. Nonclinical Pharmacology/Toxicology

There is no nonclinical review for this supplement

4.5. Clinical Pharmacology

From Section 2 Office of Clinical Pharmacology Recommendations, Integrated Clinical Pharmacology Review:

"Based on the information provided in this supplemental NDA applications (205836/s-009, 205837/s-007, 205838/s-006), the Office of Clinical Pharmacology review team recommends approval of BRV formulations for the treatment of POS in patients 1 month of age and older."

From Section 3.6. Summary of Key Conclusions, Integrated Clinical Pharmacology Review:

"Consistent with Agency's current policy for extrapolation of efficacy from adults, the applicant provided a pharmacokinetic analysis to determine a dosing regimen that would provide similar BRV exposure in pediatric subjects 1 months to < 4 years of age to BRV exposure levels demonstrated to be effective in adult subjects with POS. The applicant's proposed dosing recommendations for treatment initiation and maintenance regimen for BRV in patients 1 months to < 4 years of age (weighing 3 to < 11 kg) is acceptable, and the Agency recommends deletion of the lower weight bound of 3 kg."

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

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Clinical Study Reports for all studies, N01263, N01266, and EP0065, provide attestation of compliance with Ethical Conduct and Good Clinical Practice as follows:

"This study is conducted in accordance with the current version of the applicable regulatory and International Council for Harmonisation (ICH)-Good Clinical Practice (GCP) requirements, the ethical principles that have their origin in the principles of the Declaration of Helsinki, and the local laws of the countries involved."

Table 1 Table of Clinical Studies to Support Pediatric Safety, N01263, N01266, EP0065

Trial Identity	Trial Design	Regimen/ schedule/ route	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
N01263 (Oral)	Phase 2a/open-label, single-arm, fixed 3-step up-titration study	Oral Solution For subjects ≥8 years of age: ~0.4mg/kg bid for Week 1 ~0.8mg/kg bid for Week 2 ~1.6mg/kg bid for Week 3 For subjects <8 years of age: ~0.5mg/kg bid for Week 1 ~1.0mg/kg bid for Week 2 ~2.0mg/kg bid for Week 3	**21 days** treatment 14 days down titration, 14 days follow up	Total=99 Male 48 Female:51 ≥1mo to 2y=15/15 ≥2y to 12y=26/25 ≥12y to 16y=7/11	male or female between ≥1 month and <16 years of age at Visit 1 Localization-related, generalized, or undetermined whether focal or generalized epileptic syndrome (i.e., infantile spasms, Lennox Gastaut Syndrome, myoclonic astatic epilepsy, absence epilepsies [childhood absence epilepsy, juvenile absence epilepsy, and myoclonic absence epilepsy]), and other symptomatic generalized epilepsies, according to the ILAE classification.	29 Sites located in the US, Mexico, and the EU (Belgium, Czech Republic, Poland, and Spain).
N01266 (Oral)	Phase 3a/ongoing, open-label,	Each LTFU study participant begins treatment in N01266 at the	Interim exposures: From 0.043 to	Total=135/112 ≥1mo to 2y=12/15 ≥2y to <12y=88/66	male or female ≥4 years to <17 years of age. clinical diagnosis of POS	43 Sites Located in Belgium, Czech Republic, Hungary,

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Trial Identity	Trial Design	Regimen/ schedule/ route	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
	single-arm, long-term study	individualized BRV dose he/she was receiving at the completion of the core study. All directly enrolled (DE) study participants must be able to tolerate at least 1mg/kg/day during the Up-Titration Period prior to entering the Evaluation Period of N01266. For all study participants, the approximate doses to be administered are 0.5, 1, and 2mg/kg bid (1, 2, and 4mg/kg/day, respectively), with the daily doses not exceeding the maximums of 50mg/day, 100mg/day, and 200mg/day for Weeks 1, 2, and 3 of up-titration, respectively.	7.58 years. Mean = 3.1 years, Median = 1.7 years	≥12y to 17y=35/31 **33 / 39 patients enrolled from study N01263, 6 from EP0065**	according to the International League Against Epilepsy (ILAE) classification. have participated in a core study with a confirmed diagnosis of epilepsy and for whom a reasonable benefit from long-term administration of BRV was expected.	Italy, Mexico, Poland, Spain, and the US
Ep0065 (IV)	Phase 2, multicenter, open-label study with a primary	See Table 2 below		Total enrollment 50 >=1 month- 2 years 13 >=2 - <6 years 13 >=6 - <12 years 12	male or female from ≥1 month to <16 years of age. Diagnosis of epilepsy, Subject being	16 sites located in 7 countries including the Czech Republic,

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Trial Identity	Trial Design	Regimen/ schedule/ route	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
	objective of evaluating the pharmacokinetics (PK), safety, and tolerability of brivaracetam (BRV) administered as a 15-minute intravenous (iv) infusion and an iv bolus (up to 2-minute infusion) in subjects ≥1 month to <16 years of age with epilepsy.			>=12 - <16 years 12	treated with ≥1 AED (including BRV) without a change of dose regimen for at least 7 days prior to Screening.	Germany, Hungary, Italy, Mexico, Spain, and the US.

Table 2 BRV dosing during the Screening, IOB Treatment, and iv PK Periods (from Applicant EP0065 CSR, Table 3-2, page 29**)**

	Screening (1-10 days)	IOB Treatment (2-10 days)[a]	iv PK (1-6 days)[b]		
Subjects	**Dose (oral)**	**Dose (oral)**	**First dose (iv)**	**Subsequent dose(s) (iv)**	**Maximum BRV Dose**
OLB (Open-label BRV)	Per Long-Term, Open-Label study	N/A	mg-to-mg equivalent to last oral dose	Equivalent to first iv dose until PK sampling is completed.	5mg/kg/day (rounded) nte. 200mg/day for body weight ≥40kg

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RxB (Prescribed-BRV)	As prescribed	N/A	mg-to-mg equivalent to last oral dose	Equivalent to first iv dose until PK sampling is completed.	5mg/kg/day (rounded) nte. 200mg/day for body weight ≥40kg
IOB (Initiating Oral BRV)	Not receiving BRV	Subjects <50kg: 2mg/kg/day Subjects ≥50kg: nte. 100mg/day	mg-to-mg equivalent to last oral dose	Equivalent to first iv dose until PK sampling is completed.	4mg/kg/day nte. 200mg/day for body weight ≥50kg
IIB (Initiating iv BRV)	Not receiving BRV	N/A	Subjects <50kg: 1mg/kg Subjects ≥50kg: 50mg	Equivalent to first iv dose until PK sampling is completed.	4mg/kg/day nte. 200mg/day for body

bid=twice daily; BRV=brivaracetam; IIB=Initiating iv BRV; IOB=Initiating Oral BRV; iv=intravenous; LT=Long-term; N/A=not applicable; nte.=not to exceed; OL=Open-label; OLB=Open-label BRV; PK=pharmacokinetic; q12h=every 12 hours; RxB=Prescribed BRV

Note: Oral BRV will be administered in equally divided doses bid as either tablets or oral solution. Tablets will be administered orally, and oral solution will be administered either orally or by enteric administration (e.g., feeding tube) based on subject need.

Note: Intravenous BRV will be administered as a 15-minute (±3 minutes) infusion or bolus (up to 2-minute infusion), as assigned and will be administered q12hours ± 2 hours.

[a] Dose adjustment is allowed at the Investigator's discretion provided the adjusted dose does not exceed the maximum dose indicated in the rightmost column of this table and does not occur within 2 days of entry into the iv PK Period.

[b] Dose adjustment is allowed at the Investigator's discretion provided that PK sampling has been completed for 2 doses and the adjusted dose does not exceed the maximum dose indicated in the rightmost column of this table and does not occur within 2 days of entry into the iv PK Period.

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5.2. Review Strategy

Safety data will be examined for the patient cohort age < 4 years for studies N01263 and N01266 to cover the expanded age indication for the oral formulation while the review of study EP0065 will examine all patients for coverage of the expanded indication for the intravenous formulation, 1 month to< 16 years.

6. Review of Safety

6.1. Safety Review Approach

See section 5.2 above.

6.2. Review of the Safety Database

6.2.1. Overall Exposure

Study N01263

Exposure acquired in Study N01263 is short, restricted by the three week treatment duration of the study.

Table 3 Study N01263 Exposure to Brivaracetam

Exposure in Evaluation period- Days	# Patients
3	1
10	1
18	1
26	1

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Exposure in Evaluation period- Days	# Patients
27	1
28	1
21	2
24	2
25	2
23	5
22	21

Study N01266

Study N01266 is the primary source of patient exposure for the pediatric cohort. There were 29 patients less than 4 years of age with a treatment duration greater than 6 months with a mean modal dose and mean dose both of 3.8 mg/kg/day. Twenty-two (22) patients had exposure of ≥ 1 year with mean modal dose and mean dose of 3.8 and 4 mg/kg/day respectively. There were 18 patients with ≥ 2 years of exposure with a mean modal dose and mean dose of 3.8 and 4 mg/kg/day respectively, Table 4.

Exposures in the pediatric patient cohort greater than or equal to 4 years of age were also examined to provide a broader context of pediatric exposure that supports the expanded pediatric population. There were 133 patients with exposure ≥ 1 year with a mean modal dose and mean dose of 3.3 and 3.7 mg/kg/day respectively and 115 patients with exposure ≥ 2 years that had a mean modal dose and mean dose of 3.4 and 3.8 mg/kg/day respectively, see Table 5.

Reviewer Comment: The exposure supporting the expansion of pediatric treatment to the range of 1 month to less than 4 years of age is adequate.

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Table 4 Study N01266, Age < 4 years, Patient Exposure; Duration of Exposure by Select Intervals with Corresponding Mean and Modal Dose

Duration of exposure	# Patients	Mean modal dose (mg/kg/day)	Mean Dose (mg/kg/day)
≥0.25 yrs.	33	3.76	4.8
≥ .5 yr.	29	3.79	3.97
≥ 1yr	22	3.77	4.02
≥1.5 yrs.	20	3.85	4.09
≥ 2 yrs.	18	3.83	4.07
≥2.5 yrs.	16	3.94	4.14
≥3 yrs.	16	3.94	4.14
≥4 yrs.	15	3.93	4.16
≥5 yrs.	13	3.93	4.16

Table 5 Study N01266, Age ≥ 4 Years, Duration of Exposure by Select Intervals with Corresponding Mean and Modal Dose

Exposure Duration Cohort	# patients	Mean Modal Dose (mg/kg/day)	Mean Dose (mag/kg/day)
≥ 1 year	135	3.3	3.7
≥ 2 year	115	3.4	3.8
≥ 3 year	96	3.4	3.8
≥ 4 year	72	3.3	3.8
≥ 5 year	49	3.3	3.7

Study EP065

The contribution of duration of exposure from Study EP0065 is limited by the nature of the study where the primary purpose is to study PK and tolerability of the IV formulation. The daily exposures contributed by oral treatment and the IV treatment days are

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shown in Table 6. The primary contribution of Study EP0065 is the intravenous exposure. A count of the number of patients by iterative occurrence of IV infusion and infusion method, bolus or 15-minute infusion with associated mean brivaracetam dose and frequency of infusion by age cohort is shown in Table 7. There were 19 patients with a single 15-minute infusion and 21 patients with a single bolus infusion while the largest multiple infusion subset were those patients who received 3 intravenous infusions where 6 had a 15-minute administration and 2 had a bolus administration, Table 7.

Reviewer Comment: The intravenous exposure route including the bolus and 15-minute infusion administration are adequate to support expansion of intravenous treatment to the pediatric population.

Table 6 Study EP0065 Study Drug Exposure – number of days, (Safety Set-iv)†

	Age cohort				Infusion duration		All study participants
	≥1 month to <2 years	≥2 to <6 years	≥6 to <12 years	≥12 to <16 years	15-minute infusion	Bolus	
	N=13	N=13	N=12	N=12	N=26	N=24	N=50
Oral and iv BRV exposure duration (days)							
Mean (SD)	4.92 (4.07)	2.92 (2.60)	3.67 (2.87)	4.42 (3.20)	3.88 (3.09)	4.08 (3.45)	3.98 (3.24)
Min, max	1.0, 13.0	1.0, 8.0	1.0, 8.0	1.0, 9.0	1.0, 9.0	1.0, 13.0	1.0, 13.0

†From Applicant's "interim Clinical Study Report" July 31, 2020, Table 9-1, page 96

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Table 7 Study EP0065 Study Drug Exposure -number of infusions, during the iv PK Period (Safety Set-iv), by Age Cohort and Infusion Method (bolus vs 15-minute)

iv BRV exposure	Age cohort				Infusion duration		All study participants
	≥1 month to <2 years	≥2 to <6 years	≥6 to <12 years	≥12 to <16 years	15-minute infusion	Bolus	
	N=13	N=13	N=12	N=12	N=26	N=24	N=50
Number of infusions received during the iv PK Period, n (%)							
1 infusion	10 (76.9)	10 (76.9)	8 (66.7)	12 (100)	19 (73.1)	21 (87.5)	40 (80.0)
2 infusions	0	0	1 (8.3)	0	1 (3.8)	0	1 (2.0)
3 infusions	2 (15.4)	3 (23.1)	3 (25.0)	0	6 (23.1)	2 (8.3)	8 (16.0)
10 infusions	1 (7.7)	0	0	0	0	1 (4.2)	1 (2.0)
Mean iv BRV dose (mg/kg), n	13	13	12	12	26	24	50
Mean (SD)	1.11 (0.38)	1.17 (0.38)	1.02 (0.09)	1.13 (0.32)	1.08 (0.24)	1.14 (0.38)	1.11 (0.31)
Min, max	0.8, 2.2	1.0, 2.3	0.9, 1.3	1.0, 2.0	0.8, 2.0	0.9, 2.3	0.8, 2.3
iv BRV exposure duration (days), n	13	13	12	12	26	24	50
Mean (SD)	1.49 (1.23)	1.23 (0.43)	1.28 (0.44)	1.00 (0.00)	1.24 (0.42)	1.27 (0.92)	1.25 (0.70)
Min, max	1.0, 5.4	1.0, 2.0	1.0, 2.0	1.0, 1.0	1.0, 2.0	1.0, 5.4	1.0, 5.4

†From Applicant's "interim Clinical Study Report" July 31, 2020, Table 9-2, page 98

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6.2.2. Relevant characteristics of the safety population:

The patient age distribution and sample size for studies N01263, N01266 and EP0065 are presented separately from the study demographics because assessment of the correspondence of the study sample age distributions informs the support for the proposed expanded pediatric age range indications. The distribution of participant inclusion across the age range of Studies N01263 and N01266 adequately supports the expanded pediatric population of 1 month to less than 4 years for treatment with the oral formulation, see Figure 1 and Figure 2. Study EP0065 likewise provides adequate support for the expanded pediatric population age 1 month to less than 16 years of age for treatment with the IV brivaracetam formulation, see Study EP0065, Age 1mo to <16 years, n=50 see, Figure 3.

Age: Sample Size and Distribution

Study N01263, n=38

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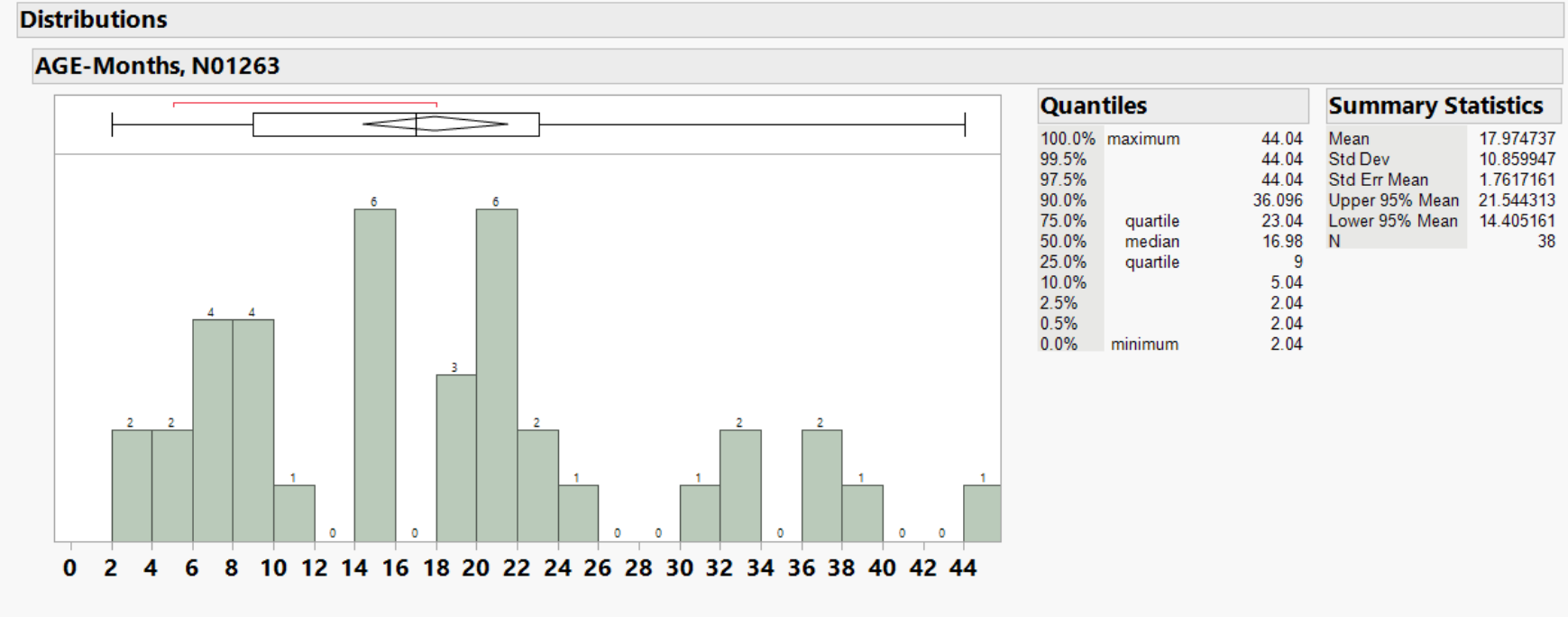
Figure 1 Study N01263 Age Distribution, n =38



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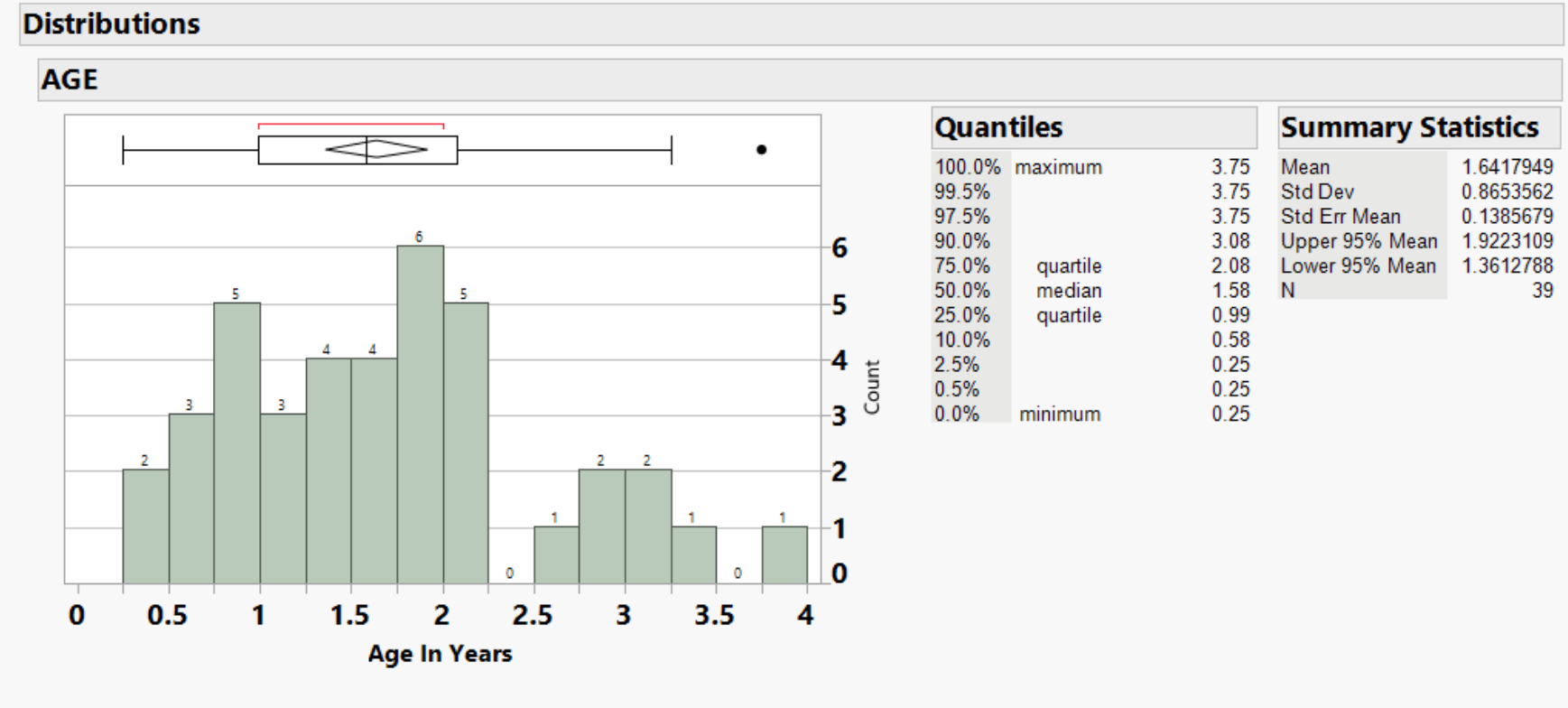
Study N01266, Age <4yrs, n= 39

Figure 2 Study N01266, Age Distribution Patients < 4 Years of Age, n=39



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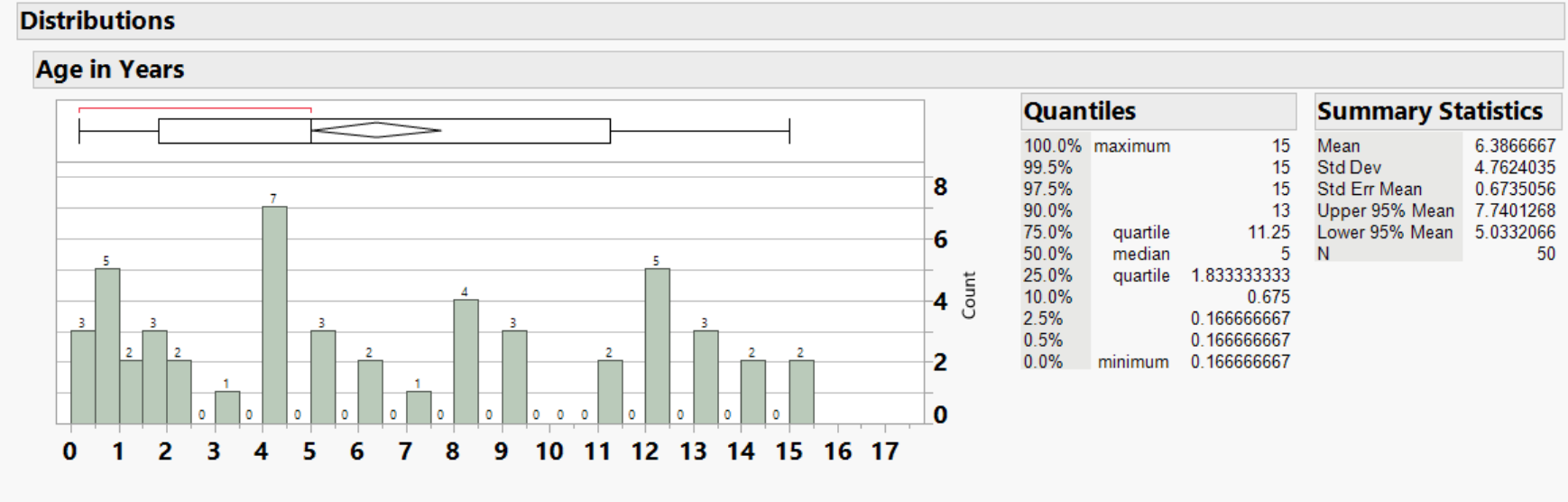
Study EP0065, Age 1mo to <16 years, n=50

Figure 3 Study EP0065 Distribution of Patient Age, n= 50



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Demographics

The demographics of Study N01266 are presented to inform assessment of the safety support for the oral formulation. The demographics for study N01263 are not presented for two reasons: first, the study did not contribute substantively to the overall brivaracetam exposure, and, second, all patients continued from study N01263 into long-term follow-up (LTFU) in Study N01266 unless discontinued and tapered from brivaracetam.

Patient participants in Study N01266 had either a diagnosis of PGS or POS because inclusion of LTFU patients allowed both POS and PGS inclusion. There was a 41% representation of POS patients in the less than 4-year-old age group. This is adequate to support safety in conjunction with the PGS patient and the larger population of patients in Study N01266 previously review for addition of the older pediatric age range age 4 years to less than 16 years that was approved in May of 2018. The study had an even mix of male and female patients. There were a predominance of white patients. The distribution of patients by country reveals the US cohort was number 2 (39%) in contribution to the less than 4-year-old patient cohort.

Study N01266
Age < 4 Years (n= 39), Inclusion: LTFU Entry- Diagnosis of Epilepsy, Direct Entry- Diagnosis of POS

Table 8 Study N01266 Population Distribution by Seizure Type

Seizure Type	# Patients	% Patients
POS	16	41
PGS	21	54
No Entry	2	5

Table 9 Study N01266 Population Demographic characteristics

SEX	# Patients		COUNTRY	# Patients
F	20		Poland	12
M	19		United States	9
			Mexico	8
RACE			Spain	5
Non-White	9		Hungary	3
WHITE	30		Belgium	1
			Italy	1
ETHNICITY (9 non-White Entries)				

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No Entry	1
HISPANIC OR LATINO	6
NOT HISPANIC OR LATINO	2

Study EP0065
Age: 1 mos to <16 years, (n=50), inclusion: Study participant had a diagnosis of epilepsy

Examination of the demographic characteristics of the EP0065 study population reveals a close to even mix of male and female patients. There is a predominance of white patient participants. The Country contribution has a Hungarian (60%) majority with small contributions from 6 additional countries, including 4 (8%) patients from the United States.

SEX	**# Patients**
F	24
M	26
Race	
American Indian or Alaska Native	2
Black	1
White	47
Ethnicity	
HISPANIC OR LATINO	4
NOT HISPANIC OR LATINO	46

COUNTRY	**# Patients**
Hungary	30
Spain	5
Czech Republic	4
Italy	4
United States	4
Mexico	2
Germany	1

6.2.3. Adequacy of the safety database:

The safety database is adequate to support the population expansion.

6.3. Adequacy of Applicant's Clinical Safety Assessments

6.3.1. Issues Regarding Data Integrity and Submission Quality

No Clinical OSIS consult was requested for this application

6.3.2. Categorization of Adverse Events

Characterization of Adverse Events is Acceptable

6.3.3. Routine Clinical Tests

Routing Clinical Testing is Acceptable

Reference ID: 4845026

6.4. Safety Results

6.4.1. Deaths

There were 4 deaths in the pool of study patients < 4 years of age from study N01263 and N01266. All deaths occurred during treatment with the oral formulation in the open label LTFU Study N01266 for the oral formulation. Among the 4 deaths, none are judged by the reviewer to have a causal relationship to brivaracetam treatment. There were two deaths due to an aspiration pneumonia event, one due to pneumonia, and one due to respiratory failure and apnea 5.8 years after beginning brivaracetam treatment, see Table 10.

There were no deaths in the intravenous formulation study EP0065 that included patients 1 month to 16 years of age.

Reviewer Comment: None of the deaths identified in the safety dataset under review were related to the study drug. There was no temporal relationship or mechanistic relationship to support a causal relation to brivaracetam.

Reference ID: 4845026

Table 10 Adverse Events with Fatal Outcome that Occurred in Studies N01263, N01266 Cohort < 4 years and Study EP0065. All Occurred in Open Label Long Term Follow up Study N01266

Subject ID	Age in years at treatment onset	Preferred Term	Duration of brivaracetam Treatment	Dose at time of event (mg/kg/day)	brief summary of event narrative	Comment on Causality
(b) (6)	0.61	Pneumonia	167	4	medical history included cerebral palsy (b) (6) -ongoing), malnutrition (b) (6) -ongoing), microcephaly (b) (6) -ongoing), and pharyngotonsillitis (b) (6)).The subject experienced an event of pneumonia on (b) (6) , during the Evaluation Period. The event occurred 167 days after the first study drug dose in N01263, and 146 days after the first study drug dose in N01266. At the time of the pneumonia, the subject was taking BRV 4mg/kg/day and had been at this dose for 146 days in this study. Per CIOMS# (b) (6) , the subject was hospitalized with pneumonia symptoms and presented with cardiopulmonary arrest	No causal relationship, patient has predisposing condition for deglutition difficulty as well as no temporal relationship to the adverse event
	1.77	Acute respiratory failure, Aspiration, Circulatory collapse	385	4	Per CIOMS# (b) (6) 2, on the evening of (b) (6) , the study participant had aspiration of food while eating. He then had breathing problems and experienced heart failure. The study participant experienced events of acute respiratory failure, aspiration, and circulatory collapse on (b) (6) . The events occurred 385 days after the first study drug dose in N01263, and 363 days after the first study drug dose in N01266. At the time of the acute respiratory failure, aspiration, and circulatory collapse, the study participant was taking BRV 4mg/kg/day and had been at this dose for 105 days in this study.	No causal relationship. The was no temporal relationship to the extrinsic event of aspiration as well as no likely mechanistic relationship to study drug
	2.2	Apnoea	2127	4	The study participant experienced a nonserious AE of apnoea on (b) (6) . The event occurred 2148 days after the first study drug dose in N01263, and 2127 days after the first study drug dose in N01266. The study participant received BRV 4mg/kg/day from 14 Nov 2017 to 06 Jan 2018. On 07 Jan 2018, the participant experienced apnea and died at home on the same day. He had no seizures on the day of his death. The emergency services were not activated after the apnea.	No causal relationship. The patient has an extensive history of respiratory insufficiency. There was no temporal relationship to study drug.

Reference ID: 4845026

(b) (6)	2.27	Pneumonia aspiration	177	2	The patient entered study N01266 from the IV study EP0065. The study participant experienced an SAE of aspiration pneumonia on (b) (6). The event occurred 177 days after study drug initiation in N01266. On (b) (6), in the morning, after a seizure episode, the participant's mother decided to bathe him, and she later gave him yogurt. While eating the yogurt, he experienced difficulty in breathing which led to cardio-respiratory arrest. An emergency service was called, and resuscitation was performed. He was then transferred to an intensive care unit. An electroencephalogram showed diffused hypovolted activity corresponding with a severe diffused cerebral hypoxia. On the same day, the participant died.	No causal relationship. The was no temporal relationship to the extrinsic event of aspiration as well as no likely mechanistic relationship to study drug

Reference ID: 4845026

6.4.2. Serious Adverse Events

Study N01263 (age < 4 years)

There were 10 SAE's that occurred in 6 (16%) patients during the treatment period of Study N01263. The two most frequent SAE's were "Convulsion" that occurred in 2 (5%) of patients and "dehydration" in 2 (5%) of patients, Table 11. One patient had drug withdrawn due to the SAE. This patient experienced "convulsions aggravated" and was hospitalized. The patient was discharged from the hospital without dizziness and sequelae, see Table 12.

Patient (b) (6), a 6-month-old male patient, had a fever of 38.5 degrees Celsius (101.3F) and was subsequently hospitalized. The patient's mother reported intolerance to oral intake. The patient was lethargic, dehydrated, and in hypovolemic shock on admission. Results of lumbar puncture and chest x ray were normal. The results of his complete blood count, chemistry, and liver function tests remained unaltered. Five days after admission the results of his blood, urine, and CSF cultures were negative. Study drug was discontinued 7 days after the SAE onset. Twenty-nine days after admission, the subject was discharged afebrile from the hospital.

Table 11 Study N01263 SAE by Preferred Term and Frequency

Preferred Term	# Patients < 4 years n=38	% Patients
Convulsion	2	5.3
Dehydration	2	5.3
Cytomegalovirus test positive	1	2.6
Diarrhoea	1	2.6
Otitis media	1	2.6
Pyrexia	1	2.6
Respiratory tract infection	1	2.6
Toxoplasmosis	1	2.6

Reference ID: 4845026

Reviewer Comment: The most frequency SAE preferred term was "convulsion". Examination of the narrative report did not reveal a clear causal relationship to brivaracetam treatment. There was no relationship between patient age and the frequency of the SAE preferred term "convulsion". The next most frequent SAE preferred term was "dehydration". In one case there may have been an underlying decrease in oral intake preceding the event of dehydration, and in the second there was an association with an underlying otitis media. Overall, the profile of serious adverse events in the pediatric population does not identify a safety profile that differs from the older pediatric and adult patients except for the age-associated higher frequency of infection related events.

Table 12 Study N01263 SAE by Individual Patient and Key Features of Event Narrative with Age, Preferred Term, Day of Onset and Action Taken with Study Drug

Patient ID	Age in Years	Age in Months	Preferred Term	Study day of SAE onset	Severity Reported by Investigator	Causality Judgement	Action Taken with Study Treatment	Key Summary Point
(b) (6)	0.75	9.0	Dehydration	9	Moderate	Not Related	DOSE NOT CHANGED	dehydration associated with otitis media on day 9 of treatment
	0.75	9.0	Otitis media	9	Moderate	Not Related	DOSE NOT CHANGED	
	1.33	16.0	Convulsion	20	Moderate	Not Related	DOSE NOT CHANGED	2 days after TEAE of nausea and vomiting patient had a convulsion, on the same day as convulsion a TEAE of dehydration was entered.
	2.08	25.0	Respiratory tract infection	4	Moderate	Not Related	DOSE INCREASED	The subject experienced an event of respiratory tract infection. the subject experienced RTI and was hospitalized. On the same day, a surgery was scheduled for gastrostomy tube replacement. A prolongation of scheduled hospitalization occurred after anesthesia, respiratory distress, and many other respiratory reactions. His oxygen need was increased. His condition was diagnosed as respiratory infection. He remained hospitalized for postsurgery monitoring. Patient also developed mild left pneumonia

Reference ID: 4845026

Patient ID	Age in Years	Age in Months	Preferred Term	Study day of SAE onset	Severity Reported by Investigator	Causality Judgement	Action Taken with Study Treatment	Key Summary Point
(b) (6)	0.42	5.0	Cytomegalovirus test positive	11	Mild	Not Related	DOSE NOT CHANGED	The subject experienced events of Cytomegalovirus (CMV) test positive and toxoplasmosis on (b) (6), 11 days after study drug initiation
	0.42	5.0	Toxoplasmosis	11	Mild	Not Related	DOSE NOT CHANGED	
	0.75	9.0	Convulsion	18	Severe	Not Related	DOSE REDUCED	diarrhea began in association with a new milk formula, the patient also had an SAE of seizure. No change in study drug treatment.
	0.75	9.0	Dehydration	8	Moderate	Not Related	DOSE NOT CHANGED	
	0.75	9.0	Diarrhoea	8	Moderate	Not Related	DOSE NOT CHANGED	
	0.5		Pyrexia	5	Moderate	Not Related	Study withdrawal 7 days after SAE due to protocol violation of study drug compliance < 80%, incorrect dose during evaluation period, PK sampling not performed at visit 3.	5 days after study drug administration the patient developed fever of 101.3 and taken to ER. In the ER patient was lethargic and dehydrated. The patient's mother reported intolerance to oral feeding. The patient was reported to be in hypovolemic shock. The patient remained sedated with mechanically assisted ventilation. No infectious etiology was identified. The patient was hospitalized for 28 days and progressed satisfactorily.

Study N01266 (Age < 4 Years)

There were 63 Adverse events flagged as SAE from 17 (44%) patients with a mean and median TTO of 699 and 365 days respectively. The SAE that occurred in more than one patient were “pyrexia”, “seizure”, “Gastrooesophageal reflux disease”, and “pneumonia” in 3 (7.7%),3 (7.7%),2 (5.1%), 2 (5.1%) patients respectively. There were 5 patients with an SAE where brivaracetam was discontinued. Four of these five patients had a fatal outcome and were captured in Section 6.4.1 “Deaths”. The remaining patient was a 1.81-year-old female with an SAE preferred term of “weight decreased” that began on study day 91. There were 9 (23%) patients with an SAE in the SOC “infections and infestations” or the preferred term “pyrexia”. This

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represents 53% of all patients with an SAE entry. The minimum time to onset was 31 days for an SAE of viral infection that occurred in a 1-year-old female. The patient recovered and brivaracetam was not discontinued.

There were seven (18%) patients with seven unique SAE preferred term entries that occurred within the first 90 days of study N01266. These are shown in Table 13. None are judged by the investigator as causally related. Four of seven events are infection or fever while one adverse event is a seizure, one dehydration and one event of spina bifida.

Table 13 Study N01266 SAE Occurring During the First 90 Days of Treatment

Subject ID	Age in Years	SEX	Preferred term	Time to Onset	Severity assessment	Causality Assessment	Dose at onset
(b) (6)	1.03	F	Viral infection	31	Severe	Not Related	7
	2.09	M	Generalised tonic-clonic seizure	38	Moderate	Not Related	4
	2.87	M	Spina bifida	55	Severe	Not Related	3.2
	1.6	M	Dehydration	72	Moderate	Not Related	4
	0.8	F	Viral upper respiratory tract infection	77	Moderate	Not Related	3.5
	0.57	F	Urinary tract infection	78	Mild	Not Related	4
	2.27	M	Pyrexia	78	Mild	Not Related	2

Reviewer Comment: Examination of the SAEs that occurred during study N01266 reveal a high frequency of infection related events. Infections are more common in the 1 month to 4-year age range. The overall time to onset of SAEs does not support a causal relationship. There is no evidence of a new safety signal or worsening of a known safety issue associated with brivaracetam treatment.

Study N01266 (Age ≥ 4 Years)

There were 127 SAEs reported from 54 (26%) patients with a mean and median TTO of 755 and 554 days respectively. Among these SAEs there were two (1%) fatal outcomes associated with the preferred terms “pneumonia” and “circulatory collapse”. These events occurred at 887 days and 188 days after the start of study N01266. The patient with a fatal outcome at day 188 was treated with 200mg/day of brivaracetam. The patient had an underlying history of aortic stenosis and collapsed while on a walk and then found by first responders to be in ventricular fibrillation. Concomitant medications were gabapentin, lamotrigine and copper and zinc supplement. There were 12 (5.8%) patients where brivaracetam was discontinued due to

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the SAE where the time to onset ranged from 21 days to 996 days with a mean and median of 518 days and 708 days respectively. Examination of time to onset of all 63 SAE entries reveals a mean and median of 699 and 365 days respectively. The event with the shortest TTO was associated with the preferred term "Homicidal ideation" while the event with a TTO of 34 days was associated with the preferred term "Nonconvulsive status epilepticus". All remaining brivaracetam discontinuations occurred greater than 2 months after start of open label brivaracetam.

Reviewer comment: The death events in the older population (≥4 years) do not show evidence of a causal relation to brivaracetam treatment due to the absence of temporal relationship. In one of two reports, there is no plausible mechanism and a medical comorbidity of an underlying history of moderate aortic stenosis.

Study EP0065

There were two (4%) patients that had a SAE entered during Study EP0065. This included one patient with cough and one patient who experienced aggression. There was no change in brivaracetam dosing in either case. The event of aggression occurred on day 1 of intravenous dosing in a 4-year-old female treated with an intravenous bolus of 25mg who was on prior oral treatment with 50mg / day.

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6.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Study N01263, Age < 4 years

There was a single withdrawal due to adverse event in Study N01263. A 6-month-old male patient (b) (6)) had a non-serious adverse event of "decreased appetite" on day 2 of brivaracetam treatment. Brivaracetam dose at the time of the event was 1.0mg/kg/day. The event of "decreased appetite" resolved the day after brivaracetam discontinuation. This may have been acute gastrointestinal intolerance of the study drug with rapid resolution and no sequala after discontinuation.

Study N01266, Age < 4 years

There were three patients that had adverse events, see Table 14. One patient (b) (6) had an SAE associated with study drug withdrawal, discussed above in Section 6.4.2 Serious Adverse Events. From among the remaining two patients one, patient (b) (6) had three TEAE associated with study drug withdrawal, these included "fatigue", "hypotonia", and "somnolence". The events are all entered on study day 135. The event narrative indicate the patient was on 3.4mg/kg/day at the time of the adverse events and had advance from a dose of 3.2mg/kg/day two days preceding the CNS adverse effect. These CNS adverse events may have been associated with dose escalation. Patient (b) (6) had the remaining study drug withdrawal that occurred on N01266 study day 277; however, the event occurred on day 298 after the first dose of brivaracetam in study N01263. The study timeline presented in the narrative report reveals a maximum elevation of ALT of 168 U/L on 9/26/2013 that had declined to 29 U/L at a follow-up visit of 10/14/2013. Brivaracetam was not discontinued until 11/7/2013 with a final ALT value of 20 U/L on 11/21/2013. The ALT had a sharp decline before study drug was discontinued while the TTO was 298 days. These characteristics of the AE do not support a causal relationship to the brivaracetam treatment.

Table 14 Study N01266 Discontinuations due to Adverse Events

Subject ID	SEX	Age	Preferred term(s)	Study Day
(b) (6)	M	0.84	Hepatic enzyme increased	277
	F	1.82	Weight decreased	91
	F	3.08	Fatigue	135
	F	3.08	Hypotonia	135
	F	3.08	Somnolence	135

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Study EP0065

No study participants discontinued due to an AE or discontinued for any other reasons. All 50 participants completed the study.

Reviewer Comment: The profile of study drug discontinuations due to adverse events is consistent with deceased appetite which may be more prominent in the younger population and known CNS adverse effects associated with brivaracetam. The event of elevation of ALT was non-serious with no associated elevation of AST or Bilirubin. This was an episodic event of uncertain significance.

6.4.4. Significant Adverse Events

No significant adverse events were identified in the safety review of the pediatric populations of Studies N01263, N01265 and EP0065.

6.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Study N01263, Age < 4 years

There were 99 TEAE from 29 (76%) patients. The most frequency TEAE preferred term was "pyrexia". This occurred in 18.4% of patients. Events that occurred in greater than 6% of patients were "pyrexia", "convulsion", "irritability", "dehydration", "pharyngotonsillitis", "decreased appetite", "diarrhoea", and "otitis media", see Table 12. All patients with a TEAE of pyrexia were ≤1.5 years of age.

There was a single TEAE associated with brivaracetam withdrawal; this occurred due to "decreased appetite". Twenty-five patients (66%) of patients had a TEAE entry of "pyrexia" or an entry from the SOC "infections and infestations". There were two patients with "metabolic acidosis" that occurred after the 3rd week of treatment; these are entered as "mild" and "moderate". Brivaracetam treatment was continued. In both of these patients, there were TEAE entries of "otitis media" and in one of these patients there was an entry for "dehydration.

Table 15 Study N01263 TEAE by Frequency and Percent of Patients.

Preferred term	# Patients	% Patients
Pyrexia	7	18.4
Convulsion	5	13.2
Irritability	5	13.2
Dehydration	4	10.5
Pharyngotonsillitis	4	10.5
Decreased appetite	3	7.9
Diarrhoea	3	7.9

Preferred term	# Patients	% Patients
Otitis media	3	7.9
Conjunctivitis	2	5.3
Constipation	2	5.3
Ear infection	2	5.3
Gastroenteritis	2	5.3
Metabolic acidosis	2	5.3
Oral candidiasis	2	5.3
Respiratory tract infection	2	5.3
Somnolence	2	5.3
Vomiting	2	5.3

Reviewer Comment: The profile of TEAE entries reveals a predominance of events related to infection. This observation is in alignment with the young age of patients and expectation of a higher frequency of infection. Overall, the profile of adverse events in the pediatric population does not identify a safety profile that differs from the older pediatric and adult patients except for the higher frequency of events related to infection.

Study N01266 (Age < 4 Years)

There were 820 TEAEs recorded from 35 (17%) patients while on brivaracetam treatment. The mean and median TTO were 755 and 462 days respectively. The most frequently occurring events seen in greater than 25% of patients were "Nasopharyngitis", "Pyrexia", "Vomiting", "Upper respiratory tract infection", and "Bronchitis", see Table 16.

Table 16 Study N01266 TEAE in > 10% of Patients < 4 Years of Age

Preferred Term	# patients	% Patients	Preferred Term	# patients	% Patients
Nasopharyngitis	15	38.5	Rhinitis	6	15.4
Pyrexia	15	38.5	Asthma	5	12.8
Vomiting	15	38.5	Gastrooesophageal reflux disease	5	12.8
Upper respiratory tract infection	13	33.3	Irritability	5	12.8
Bronchitis	10	25.6	Otitis media	5	12.8
Pharyngitis	9	23.1	Pharyngotonsillitis	5	12.8
Gastroenteritis	8	20.5	Seizure	5	12.8
Constipation	7	17.9	Urinary tract infection	5	12.8
Diarrhoea	7	17.9	Abdominal pain	4	10.3
Pneumonia	7	17.9	Insomnia	4	10.3
Conjunctivitis	6	15.4	Nausea	4	10.3
Cough	6	15.4	Varicella	4	10.3
Decreased appetite	6	15.4	Viral infection	4	10.3
Influenza	6	15.4	**All TEAE**	**35**	**90**

Reference ID: 4845026

Study N01266 (Age ≥ 4 Years)

The most frequent TEAEs greater than 15% are "Nasopharyngitis", "Pharyngitis" "Pyrexia", "Vomiting", "Headache", and "Seizure", see Table 17. Seventeen of the 25 most frequent TEAEs preferred terms from the age group ≥ 4 Years overlap with the 25 most frequent TEAEs preferred terms in the age group< 4 years of age.

Table 17 N01266 Study N01266 TEAEs in > 5% of Patients ≥ 4 Years of Age

Preferred Term	# Patients	% patients	Preferred Term	# Patients	% patients
Nasopharyngitis	53	25.5	Rhinitis	18	8.7
Pharyngitis	44	21.2	Abdominal pain upper	17	8.2
Pyrexia	43	20.7	Irritability	17	8.2
Vomiting	38	18.3	Bronchitis	15	7.2
Headache	37	17.8	Dizziness	15	7.2
Seizure	32	15.4	Abdominal pain	14	6.7
Pharyngotonsillitis	30	14.4	Ear infection	14	6.7
Diarrhoea	28	13.5	Fall	14	6.7
Upper respiratory tract infection	26	12.5	Aggression	13	6.3
Cough	22	10.6	Tonsillitis	13	6.3
Decreased appetite	22	10.6	Constipation	12	5.8
Gastroenteritis	20	9.6	Fatigue	12	5.8
Influenza	20	9.6	Oropharyngeal pain	11	5.3
Somnolence	20	9.6	Weight decreased	11	5.3
			All TEAE	**185**	**89**

Reviewer Comment: The overall frequency of TEAEs in the cohort < 4 years of age is similar to the proportion of patients that experienced TEAEs in the cohort of patients ≥ 4 years of age. The profile of preferred terms is also similar. The most notable difference between the age cohorts is seen in the high frequency TEAEs. For example, the preferred term "nasopharyngitis" occurs in 38.5% of the < 4-year-old cohort compared to 25.5% of the ≥4-year-old cohort. This is also true for the terms "vomiting" and "upper respiratory tract infection". This over representation of these terms in the younger group is likely related to a predisposition to URI and gastrointestinal viral syndromes in this age group as well as a smaller sample size in the younger cohort.

Study EP0065

There were 23 TEAEs that occurred from among 16 (32%) patients. The most frequent TEAE preferred terms were "somnolence", "dizziness", "ear infection", "fatigue", "pyrexia", and "rash", see Table 18.

Reference ID: 4845026

Table 18 Study EP0065, TEAE

Preferred Term	# Patients	% Patients
Somnolence	3	6
Dizziness	2	4
Ear infection	2	4
Fatigue	2	4
Pyrexia	2	4
Rash	2	4
Aggression	1	2
Conjunctivitis	1	2
Cough	1	2
Insomnia	1	2
Nasopharyngitis	1	2
Pharyngitis	1	2
Pruritus	1	2
Upper respiratory tract infection	1	2
Vessel puncture site haemorrhage	1	2
Vomiting	1	2

Reviewer Comment: There are a higher proportion of central nervous system TEAEs in this study due to the intravenous formulation delivery. There are TEAEs from the "Infection and Infestation" SOC, as seen in the longer-term treatment studies; however, these events likely represent background occurrences due to the short duration of the intravenous brivaracetam exposure in this study. TEAEs occur with higher frequency at age 9 years and below with the maximum frequency at age 5 years. This pattern does not reveal a higher frequency below the age of 4 years.

6.4.6. Laboratory Findings

Laboratory safety assessments were performed at V1 (day -7), V5 (day 21), and V7 (day 49).

Means

Study N01263, Age < 4 years

Group Change from Baseline, Mean Analysis

Reference ID: 4845026

Table 19 Study N01263 Analysis of Hematology Values, Change from Baseline

Parameter	# Patients with Measurements	Baseline Mean	Baseline SD	Change from Baseline Mean	Change from Baseline SD	% Change from Baseline, Mean (absolute value)	% Change from Baseline, SD
Basophils (G/L)	35	0	0	0	0	57.8	230.1
Basophils/ Leukocytes (%)	35	0.4	0.3	0	0.4	63.1	184.3
Eosinophils (G/L)	35	0.3	0.2	-0.1	0.2	66.8	432.8
Eosinophils/ Leukocytes (%)	35	2.9	2.4	-0.5	2.9	98.9	569.8
Hematocrit (%)	37	36.6	2.3	-0.3	2.9	0.7	7.8
Hemoglobin (g/L)	37	121.1	8.7	-0.9	10.3	0.5	8.3
Leukocytes (G/L)	37	10.1	3.5	-1.3	2.6	10	22.9
Lymphocytes (G/L)	35	5.2	2.2	-0.5	1.5	4.7	28.4
Lymphocytes/ Leukocytes (%)	35	51.2	13	2.1	13.6	9.5	37.1
Monocytes (G/L)	35	0.7	0.4	-0.1	0.5	19.9	115.9
Monocytes/ Leukocytes (%)	35	7.2	3.6	0.6	5.2	34.4	108.1
Neutrophils (G/L)	35	4	2.1	-0.7	2.3	7.8	45.1
Neutrophils/ Leukocytes (%)	35	38.3	12.4	-2.3	13.8	0.7	33.4
Platelets (G/L)	32	339	101.7	-24.4	75.5	3.8	26.1

Table 20 Study N01263 Analysis of Clinical Chemistry Values, Change from Baseline

Parameter	# Patients with Measurements	Baseline Mean	Baseline SD	Change from Baseline, Mean	Change from Baseline, SD	% Change from Baseline, Mean (absolute value)	% Change from Baseline, SD
Alanine Aminotransferase (U/L)	32	22	16.5	6.5	23.1	34.8	78.9
Albumin (g/L)	35	44	3.9	-0.5	3.7	0.9	8.2

Reference ID: 4845026

Parameter	# Patients with Measurements	Baseline Mean	Baseline SD	Change from Baseline, Mean	Change from Baseline, SD	% Change from Baseline, Mean (absolute value)	% Change from Baseline, SD
Alkaline Phosphatase (U/L)	35	273.2	111.9	-6.8	64.1	2.9	28.2
Aspartate Aminotransferase (U/L)	32	38.1	14.4	3.3	26.4	10.9	58.9
Bicarbonate (mmol/L)	35	17.6	2.7	0.9	2.9	6.2	18.2
Bilirubin (umol/L)	35	2.4	0.8	0.1	0.9	8.4	39.4
Blood Urea Nitrogen (mmol/L)	35	4.2	2.1	-0.2	1.7	2.5	39.7
Calcium (mmol/L)	35	2.5	0.2	0	0.2	0.5	6.4
Chloride (mmol/L)	35	105.7	3.3	0	3.6	0.1	3.4
Cholesterol (mmol/L)	35	4	0.7	-0.2	0.7	4.2	16.3
Creatinine (umol/L)	35	26.7	8.2	-1.5	7.7	0.6	29.4
Gamma Glutamyl Transferase (U/L)	35	41.2	42	-1.2	12.6	5	29.5
Glucose (mmol/L)	35	5	0.5	-0.2	1	3.2	19.7
Phosphate (mmol/L)	35	1.8	0.3	0	0.2	0.2	14.7
Potassium (mmol/L)	35	4.8	0.5	-0.1	0.4	1.3	8.9
Protein (g/L)	35	65.5	5.4	-1.5	5.9	1.9	8.6
Sodium (mmol/L)	35	143	3.5	-1.1	4.4	0.7	3
Triglycerides (mmol/L)	35	1.4	0.5	0	0.6	5.3	49.1

Reviewer Comment: The metric that best identifies the divergence from baseline value at visit five is the percent change from baseline.

Examination of the Hematology mean change from baseline analysis reveals the most prominent change from baseline is identified by the percent change from baseline. The parameters with the greatest percent change from baseline are *Basophils (G/L), Basophils/Leukocytes (%), Eosinophils (G/L), Eosinophils/Leukocytes (%), Hematocrit (%), Hemoglobin (g/L), Leukocytes (G/L), Lymphocytes (G/L),Lymphocytes/Leukocytes (%), Monocytes (G/L), and Monocytes/Leukocytes (%).* These parameters also have the largest variation in their percent change from baseline. This large variability reduces the likelihood of a consistent sustained trend due to an underlying drug effect. The hematologic metrics of hemoglobin, WBC count, lymphocytes, neutrophils, and platelets have smaller mean percent changes from baseline, none > 10%.

Examination of clinical chemistry mean change from baseline reveals the greatest mean change present in the measurement of ALT and AST where the values are 6.5 U/L and 3.3 U/L respectively. These values were not reflective of a large number of high outlier values. Overall, the clinical chemistry values do not identify a safety single in the population < 4 years of age.

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Study N01266, Age < 4 years

Clinical Chemistry: Examination of the mean change from baseline of clinical chemistry parameters does not reveal a systematic or consistent trend of increase or decline across measurements from visit 5 (6 months), visit 7 (12 months), Visit 9 (18 months) and Visit 15 (36 months), see Table 27.

Hematology: Examination of the mean change from baseline of Hematology parameters does not reveal a systematic or consistent trend of increase or decline across measurements from visit 5 (6 months), visit 7 (12 months), Visit 9 (18 months) and Visit 15 (36 months) in any parameter except Platelets, see Table 26.

Individual patient values for platelets are examined at Visit 3 (2 months), Visit 5 (6 months), Visit 7 (12 months) and Visit 9 (18 months). This examination reveals a single OORR low entry for patient (b) (6). This patient has a platelet measurement of 119 x 10^3/µL at visit 5 on study day 190. No baseline measurement was obtained (or is available). All subsequent platelet values are greater and the measurement at Visit 6 day 280 was 181 x 10^3/µL. Examination of individual patient platelet values over time does not reveal a systematic directional trend.

Sponsor Focused Statement Concerning Endocrinology Values:
"Mean values for the endocrinology parameters remained within the normal ranges for the duration of the study overall and for each age group. Mean and/or median endocrinology values occasionally were outside the normal range overall and for individual age groups at visits where the number of study participants for that visit was small or where values for the given parameter were already outside the normal range at Baseline. These changes were not deemed to be clinically significant ", see Table 21.

Table 21 Mean change from Baseline to the Last Value for endocrinology parameters during the Evaluation Period by age group. (from N01266 CSR, P136, Table 8-19)

		≥1 month to <2 years		≥2 to <12 years	
Parameter	**Descriptive statistic**	**n**	**Mean (SD)**	**n**	**Mean (SD)**
Follicle stimulating hormone (U/L)	Baseline	17	4.58 (4.94)	101	1.76 (1.49)
	Mean change from Baseline	17	-1.27 (4.39)	101	1.92 (3.31)
Luteinizing hormone (U/L)	Baseline	17	0.21 (0.24)	102	0.36 (0.89)
	Mean change from Baseline	17	-0.03 (0.33)	102	1.83 (3.71)
Thyrotropin (mU/L)	Baseline	17	2.25 (0.96)	102	2.77 (2.05)
	Mean change from Baseline	17	-0.61 (1.22)	102	-0.33 (1.35)

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		≥1 month to <2 years		≥2 to <12 years	
Parameter	**Descriptive statistic**	**n**	**Mean (SD)**	**n**	**Mean (SD)**
Thyroxine, free (pmol/L)	Baseline	16	13.65 (2.27)	99	13.17 (2.22)
	Mean change from Baseline	16	2.21 (3.25)	99	0.46 (2.60)
Triiodothyronine, free (pmol/L)	Baseline	16	5.61 (1.01)	99	5.47 (0.85)
	Mean change from Baseline	16	0.24 (1.07)	99	-0.03 (0.85)

N01263 Out of Reference Range (OORR) Analysis

Reviewer outlier examination of the following laboratory parameters is performed: ALT, AST, Bili, Creatinine, Eosinophils, Hemoglobin, Hematocrit, WBC, neutrophils, Sodium, Potassium and Calcium.

OORR High Study
Tested by reviewer: ALT, AST, Bili, Creatinine, Eosinophils, WBC, neutrophils, Sodium, Potassium and Calcium.

ALT
There was a single 1.8-year-old patient with a critical ALT value at visit 5. The ALT at baseline was 39 U/L with an increase to 158 U/L at visit 5 (day 21). The AST value at visit 5 was also elevated to 175 U/L. Bilirubin was 1.7 umol/L at visit 5, an OORR low value. This patient had no adverse event related to hepatic function, there were 3 adverse event entries that included "Herpes pharyngitis", "irritability", "Pharyngotonsillitis" and "somnolence". There was one other patient with a post baseline ALT value more than 2x ULN. This patient had an elevated baseline with a reduction of ALT value at visit 5.

AST
One patient had a post baseline value of ALT elevated greater than 2x ULN. This was a 1.8-year-old patient also with elevated AST, identified above, at visit 5. There was no adverse event related to hepatic function, there were 3 adverse event entries that included "Herpes pharyngitis", "irritability", "Pharyngotonsillitis" and "somnolence".

Bilirubin: there were no patients with a post baseline bilirubin value that was OORR high.

Creatinine
There was one patient with a normal creatinine value at baseline with an OORR high creatinine value at a post baseline measurement. There was a 13% increase from 0.38mg/dl baseline value to 0.43mg/dl value at visit 5 where the reference range high value is 0.41mg/dl.

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Eosinophils

There were no patients with both a normal baseline absolute eosinophil count and OORR high count. There were two patients with high baseline counts that were OORR high at the post baseline measurement. One of these patients had a decline from baseline count but remained elevated above reference range. The remaining patient ((b) (6)) had a further 78% increase from baseline to visit 5 where the absolute eosinophil count was 1280 eos/ul. This patient had 3 post baseline entries in the adverse event dataset. These events were "aggression", "ingrown toenail" and "otitis media".

WBC
There were no patients with a normal baseline value and subsequent elevation to OORR high value. There was one patient ((b) (6)) with a high baseline value with a 20% further post baseline elevation to 18.9 x 10^3 WBC/ ul at visit 5. This patient had 3 adverse event entries in the ADAE dataset. These events were "conjunctivitis", "Gastroenteritis rotavirus" and "Respiratory tract infection" where the "Respiratory tract infection" was entered as an SAE. Brivaracetam (study drug) was not discontinued and was increased at study day 4.

Neutrophils

One patient had a normal baseline neutrophile value with a post baseline OORR high value. This patient ((b) (6)) had a baseline value of 5260 neutrophil/ ul that increased to 11090 neutrophils/ul at visit 5. This patient was identified above under the discussion of WBC high outliers.

Sodium

There were 3 patients with OORR high sodium values that were normal at baseline. The percent change from baseline ranged from 3 to 4 percent while the percent change over reference range high was 3 to 4%.

Potassium
One patient with normal baseline potassium had an OORR post baseline value. This patient ((b) (6) 8) had a baseline potassium value of 4.7 mEq/L with a 21% elevation to 5.7 mEq/L at visit 5 where the reference range high value is 5.5 mEq/L. This patient had no post baseline entries in the ADAE dataset.

Calcium

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There were 2 patients with an OORR high post baseline calcium value where the baseline value was normal. From among these two patients the maximum % change from baseline was 3% and the maximum % over ULN was 3%. Neither of these patients had a post baseline adverse event entry in the ADAE dataset.

Reviewer Comment: examination of high outlier cases in the selected laboratory parameters did not reveal a safety signal in the < 4-year-old pediatric population.

OORR Low Study

Tested by Reviewer:
Hemoglobin, WBC, neutrophils, Glucose, Sodium, Potassium and Calcium

Hemoglobin

There were two patients with normal baseline hemoglobin values that had a post baseline OORR low value. The first case, patient (b) (6), had a baseline hemoglobin of 12.6 g/dl that declined to 9.4 g/dl at study day 14. The second case, patient (b) (6), had a baseline hemoglobin value of 12.0 g/dl that declined to 9.0 g/dl at study day 57, 1/8/2013. Patient (b) (6) has three entries in the adverse event dataset. These events are "decreased appetite", "skin injury" and "viral infection". None are entered as SAEs. This patient entered study N01266 where hemoglobin is observed to have recovered to a value of 12.1 g/dl on 2/5/2013 and was discontinued from study N01266 due to lack of efficacy.

Patient (b) (6) has 5 post baseline entries in the adverse event dataset. These adverse events were "bronchospasm", "convulsion", "muscle spasticity" and "pyrexia" where "pyrexia" is entered as an SAE. The patient subsequently withdrew from study N01263 due to the SAE of pyrexia.

WBC
There were 6 patients with normal WBC at baseline with an OORR decline at study day 21 or end of study visit.

A six-month-old patient with a high value at baseline that had a notable decline at visit 5 ((b) (6)). This patient had a baseline value of 15 x 10^3/ul that declined to 4.8 x 10^3/ul. This patient had an SAE of pyrexia and was discontinued from the study. The case is presented in Section 6.4.2. An 8-month-old patient had a low baseline WBC count of 5.2 x 10^3/ul with a further 34% decline to 3.4 x 10^3/ul at study day 21. This patient had a TEAE of diarrhea at baseline followed by additional TEAE of "pneumonia", and "pyrexia" during the study and an SAE of convulsion. Brivaracetam was continued and the patient completed the

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study. There is no clear causal relationship between brivaracetam treatment, and the low WBC counts in these two cases. Only an association is present.

The remaining 4 patients had decline from baseline to OORR low with a range of 5% to 8% below the reference range minimum.

Neutrophils

One patient had a normal baseline neutrophil value with an OORR low value at visit 5. There was a 43% decline from a baseline absolute neutrophil count of 1570/ul. This patient has a TEAE of "ear infection" on day 2 of brivaracetam treatment. This short temporal relationship does not support a causal relationship.

Glucose: One patient a 13.7 year old had a visit 5 (day 22) glucose low value of 53mg/dl from a baseline value of 86mg/dl. There was a single TEAE of "flushing" entered for this patient on study day 1.

Sodium: there were no patients with an OORR low sodium value while on brivaracetam treatment.

Potassium: there were no patients with an OORR low potassium value while on brivaracetam treatment.

Calcium: there were no patients with an OORR low calcium value while on brivaracetam treatment.

Reviewer Comment: Examination low outlier Hematology values reveals two patients with marked decline in Hb. Neither patient was discontinued from the study due to the laboratory finding and neither had an adverse event of anemia entered. In one patient the value was seen to recover to normal range in the long term follow up study N01266 where brivaracetam treatment was continued. From among the six patients with a decline in WBC count there were four where the shift below reference range was small. In the remaining two patients there were multiple medical confounders during the study. While one of these patients discontinued the study due to pyrexia the other continued brivaracetam unchanged. Overall, among the observed decline below reference range there were no clear causal relationships identified.

Critical Value Flags (N01263)

The critical value flagged laboratory parameters for study N01263 are shown in Table 22. The most medically significant of these are captured in the outlier discussion above while overall the profile of critical values does not identify a new safety signal in the under 4-year-old

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population.

Table 22 Study N01263 Frequency of Critical Value Entries in the Laboratory Dataset (ADLB)

CRIT1	N Rows
Alanine Aminotransferase (U/L) > 90 (U/L)	1
Cholesterol (mmol/L) > 250 (mg/dL)	1
Eosinophils/Leukocytes (%) >= 10.0 (%)	1
Gamma Glutamyl Transferase (U/L) > 66 (U/L)	4
Hematocrit (%) > 47 (%)	1
Hemoglobin (g/L) > 16.0 (g/dL)	1
Leukocytes (G/L) < 3.5 (10E9/L)	1
Leukocytes (G/L) > 15.0 (10E9/L)	2
Monocytes/Leukocytes (%) >= 20.0 (%)	1
Triglycerides (mmol/L) > 250 (mg/dL)	3

N01266 Critical Value Assessment

All laboratory entries flagged with a critical value report were captured from the Study N01266 ADLB dataset. There were 157 critical value entries from 23 patients. There were 17, 302 total results in the dataset of laboratory studies from patients < 4 years of age. The most frequent entries were for GGT studies where there were 44 entries from 10 patients.

GGT: Patient (b) (6) had the maximum recorded GGT value of 999 U/L, on study day 275. The patient had a mild elevation of baseline GGT at 1.6 x ULN (61 U/L) This value remained stable from study day -28 to study day 275 when the very high elevation was identified. Study Drug was discontinued and a decline of GGT to 188 U/L was seen after 18 days (study day 293). The patient had an elevation of ALT to 5 x ULN (168 U/L) on study day 275 with all preceding values found to be normal. The patient had a doubling of baseline bilirubin on study day 90 to 3.4 umol/L. This value remained in the reference range of 3.4 umol/L to 20.5 umol/L.

Patient (b) (6) had 15 entries of elevated GGT with a maximum of 308 U/L on study day 190 and an elevated baseline value of 204 U/L. The patient has 11 follow up GGT values from study day 281 to study day 2072 where only one entry, on study day 926 is elevated over baseline (value 208 U/L). From among the remaining 10 follow up values the maximum is 162 U/L, and none exceeds the baseline value of 204 U/L.

Patient (b) (6) had 3 entries of elevated GGT with a maximum of 366 on study day 554. The patient had an AE entry of "Gamma-glutamyltransferase increased" increase on study day 1100. The patient also had 54 adverse event entries including SAEs of "pneumonia", "pyrexia" and "Clostridium difficile colitis". Brivaracetam treatment was not discontinued.

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Patient (b) (6) had 5 entries of elevated GGT with a maximum of 171 on study day 181. The patient had an elevation of ALT to 2 x ULN on study day 285 with no elevation of bilirubin.

Patient (b) (6) had two entries of elevated GGT with a maximum value of 110 on study day 554, however this patient had a baseline value of 109 U/L.

The remaining 5 patients in the group with critical value elevations did not exceed 5 x ULN.

ALT: Two patients, (b) (6) had elevations of ALT to 159 U/L and 168 U/L respectively. These elevations occurred on study day 1 and 275 respectively. Patient (b) (6) is presented above in the discussion of GGT elevations. All ALT entries of patient (b) (6) are examined. All subsequent eighteen ALT values over 2340 days are less than 2 x ULN except an entry of 79 (2.6 x ULN) at study day 366, shown in Table 23.

Table 23 Study N01266 Patient (b) (6) All ALT Values Over Study Timeline

(b) (6)				
Visit	**Study Day**	**baseline value**	**Change from baseline**	**ALT value**
Baseline	-27	39		39
Visit 1 (EV)	1	39	119	158
Unscheduled [2] Visit [1.2]	8	39	12	51
Visit 3 (FEV Month 2)	76	39	8	47
Visit 4 (MEV Month 3)	93	39	2	41
Visit 5 (FEV Month 6)	181	39	-7	32
Visit 6 (MEV Month 9)	275	39	17	56
Visit 7 (YEV Month 12)	366	39	40	79
Visit 9 (FEV Month 18)	552	39	-9	30
Visit 11 (YEV Month 24)	730	39	-18	21
Visit 13 (FEV Month 30)	916	39	-16	23
Visit 15 (YEV Month 36)	1087	39	-20	19
Visit 17 (FEV Month 42)	1267	39	-22	17
Visit 19 (YEV Month 48)	1450	39	-20	19
Visit 21 (FEV Month 54)	1624	39	-8	31
Visit 23 (YEV Month 60)	1802	39	-22	17
Visit 25 (FEV Month 66)	1984	39	-12	27
Visit 27 (YEV Month 72)	2173	39	1	40
Visit 29 (FEV Month 78)	2348	39	-3	36
Last Value	2348	39	-3	36

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Lymphocytes: Lymphocytes are found to have sponsor-assigned critical values in five patients with an age range from 0.82 to 2.78 years. The reference range is reported as 0.5 to 5 x 10^3 lymphocytes/uL. Lymphocytes may be elevated by viral infections to account for this observation in this population. There was one patient (b) (6) with a maximum value of 13.37 x 10^3 cells/uL on study day 188, this case will be explored further. This patient has no baseline measurement in the dataset. There are 4 additional values from study day 1 to 366 with a range from 6.86 to 9.3 x 10^3 cells/uL. The patient is found to have 14 TEAE entries where 10 of the entries are from the SOC "infections and infestations" and the remaining 4 are related to a diarrhea syndrome.

Eosinophils: there were 6 entries from 4 patients with critical value eosinophil measurements. The adverse event dataset of these four patients is examined for entries related to allergic reactions. There were 172 adverse event entries identified that were linked to these four patients. There was one entry from the SOC "immune system disorders". This entry was "milk allergy" under patient (b) (6). There were three additional terms identified by the reviewer that may be associated with allergic phenomena, these included "asthma" and "dermatitis contact" under patient (b) (6) and "rash" listed under patient (b) (6) entries. These entries of elevated eosinophils do not appear to be causally associated with allergic phenomena, but parasitic disorders have not been excluded.

Chloride (reference range 98-107): There were five entries from 3 patients with critical value chloride measurements. Patient (b) (6) had a baseline chloride value of 112meq/L with a maximum increase to 113 meq/L. Patient (b) (6) had a maximum chloride value of 112 meq/L on study day 8. The three subsequent values were 108, 107 and 108 on study days 76, 181 and 366 respectively. An additional elevation to 116 meq/L is recorded on study day 552 but the subsequent 10 chloride measurements are within reference range through the final study day 2348. Patient (b) (6) had a single critical chloride value of 114 on study day 62 with the subsequent 5 values obtained between study day 62 and 725 found to be within reference range. There is no sustained hyperchloremia identified from among the 3 patients.

Leukocytes: There were 4 patients with five entries for leukocyte critical values. The range of values was 16.3 to a maximum of 19.8 x 10^3 cells/uL. One entry was on study day 1, a second on study day 67 while the remaining three were near study day 365. The adverse event dataset for these 4 patients were examined for the frequency of entries in the SOC "infections and infestations". All patients had entries in this SOC with a frequency ranging from a minimum of 13 to a maximum of 88. All leukocyte entries for these patients are examined. The critical values were single occurrences of outlier values for each patient. None of the patients had OORR high leukocyte values subsequent to the recorded critical value. The critical value is best explained as an episodic response to an infectious event.

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Neutrophils (RR = 1.5 to 8.5 x 10^3 cells/uL): There were 5 entries from five patients with neutrophil values below the designated critical value of 1.5 x 10^3 cells/uL. There were two patients with entries less than 1000 cell/ul, patient (b) (6) with a value of 470 cells/ul and patient (b) (6) with a value of 890 cells/ul. There remaining three patients had values > 1000 cells/ul.

Patient (b) (6) is identified in the Study N01266 ADSL dataset as discontinued with 38 days of exposure however there is no AE leading to withdrawal or an entry in the Study N01266 narratives. The Study N01263 narratives are explored and there is an entry for an SAE of increased seizures entered for this patient. The study drug was not discontinued. Examination of the Study N01263 laboratory dataset reveals a baseline value of 1570 cells/ul with a value of 890 cells/ul at end of study day 21 where there were adverse events of "Nausea", "Vomiting"," Convulsion", "Dehydration", "Hypophagia", and "Lethargy" on study days 18, 18, 20, 20, 22 and 22 respectively. The relationship of these adverse events to the low neutrophil count is uncertain. It is unclear if the events are causal to the adverse events or caused by the adverse events.

All neutrophil measurements obtained during participation in Study N01266 are examined for the remaining four patients. The profile of neutrophil values reveals that the critical low values are sporadic outlier events and do not indicate a systematic suppression of neutrophil count, see Figure 4.

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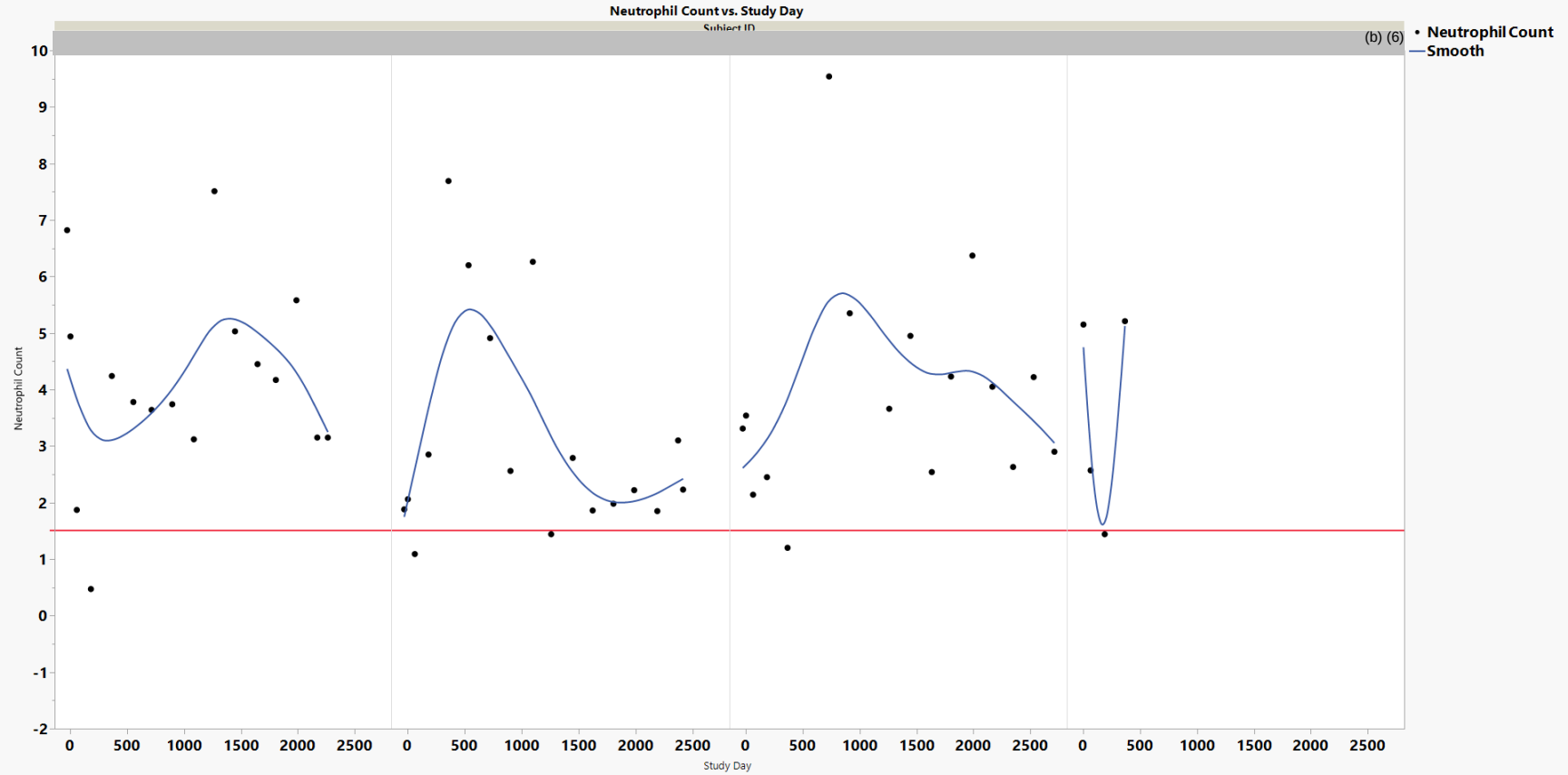
Figure 4 Study N01266, Critical Value Neutrophil Counts, Timeline of All Values During Study Participation ((b) (6))



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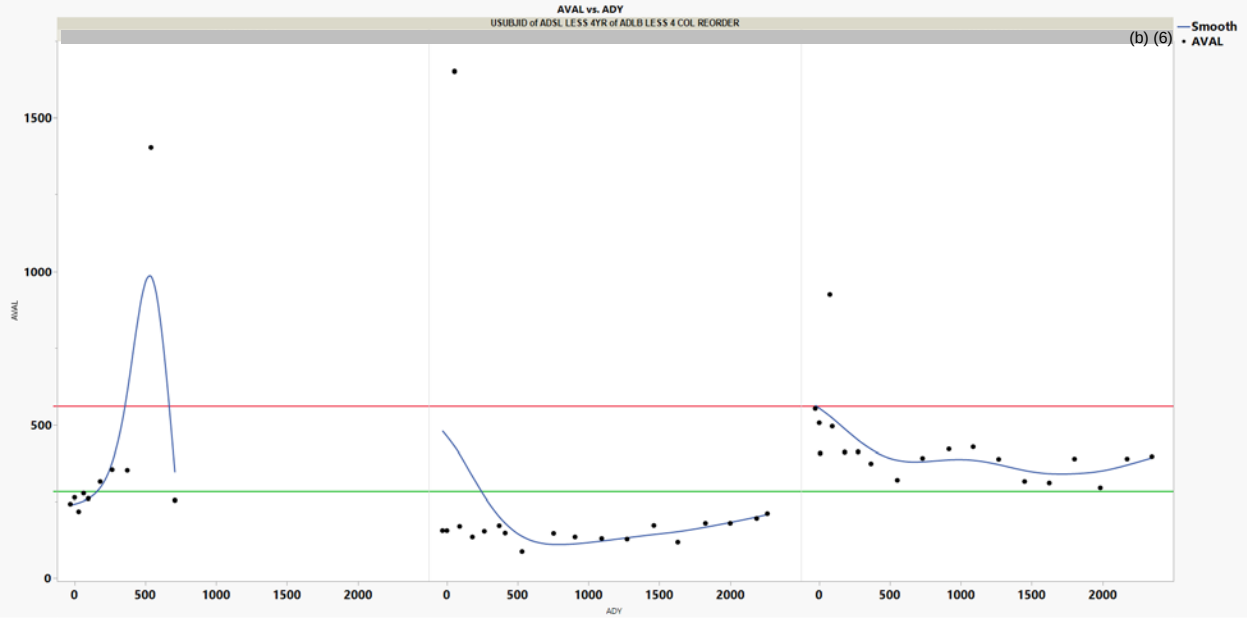
Triglycerides: Patient [redacted] (b) (6) had no baseline triglyceride measurement as a participant in Study N01263. This patient had an elevated value of 3.89 mmol/L at end of treatment, day 21 in Study N01263. The patient had 3 addition high values at day 55 and 534 of Study N01266. The significance of the high value is uncertain due to the absence of a baseline measurement.

Alkaline Phosphatase (RR = 0 to 281 U/L): there were 3 patients with three critical values for ALP. These patients, [redacted] (b) (6) had ALP values of 1651, 924 and 1403 on study days 55, 76 and 540 respectively. The adverse event dataset entries for these patients was examined. There were 71, 99, and 51 adverse event entries for patients [redacted] (b) (6) respectively. There were no entries under the SOC "hepatobiliary disorders". The complete profile of ALP values during the course of study N01266 is examined. From among the three patients there are single values for each that are greater than 2 x ULN, see Figure 5. It is likely the sporadic highly elevated ALP, greater than 2 x ULN was associated with one of the underlying medical events identified in the extensive list of adverse events associated with each of these patients.

Figure 5 Study N01266, Critical Value Alkaline Phosphatase Measurements, Timeline of All Values During Study Participation (Patients [redacted] (b) (6))



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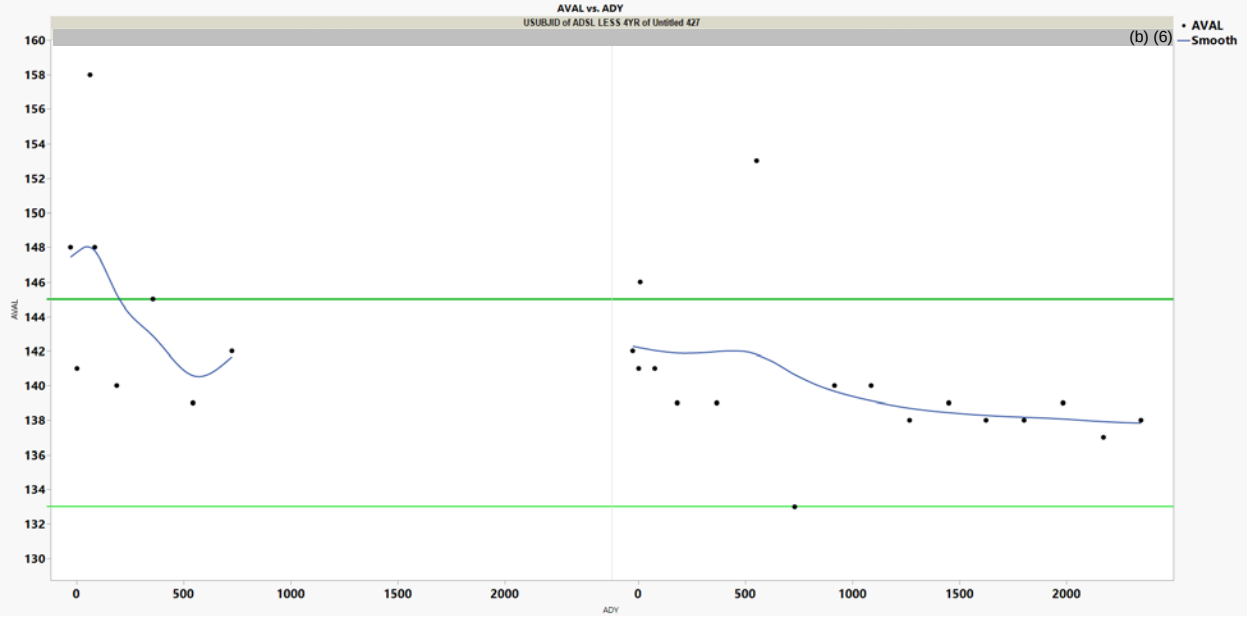
Cholesterol (RR= 1.4 to 3.91 mmol/L): A single patient, (b) (6) had three cholesterol measurements of 7.72, 6.76, and 7.85 mmol/L on study days 1, 55 and 190. There was no baseline value obtained. The significance of this elevation is uncertain. This patient also had elevated triglycerides thus an underlying disorder of hyperlipidemia is possible.

Hematocrit (RR = 28 to 42%): There were three high critical value entries from two patients. These events represented a 25% increase over baseline but a small increase over reference range. These events do not represent a serious physiologic threat.

Sodium (RR=133 to 145meq/L): There were two patients with one each critical high sodium value. Patients (b) (6) with values of 158 and 153 meq/L respectively on study days 62 and 552. The full profile of sodium values during participation in study N01266 are examined. There is one very high OORR elevation of sodium for each patient while the majority of values remain within reference range, see Figure 6.

Figure 6 Study N01266, Critical Value Sodium Measurements, Timeline of All Values During Study Participation (Patients (b) (6))



Urate (highest reference range = 327 umol/L, critical value 386 umol/L): There were two patients (b) (6) with critical value urate elevations, the values were 482 umol/L and 399 umol/L respectively on study days 543 and 557, again respectively. The complete profile of urate values during Study N01266 reveals that both patients had multiple measurements that were OORR high. Patient (b) (6) has a TEAE entry of "hyperuricemia". Patient (b) (6) has a baseline urate value OORR

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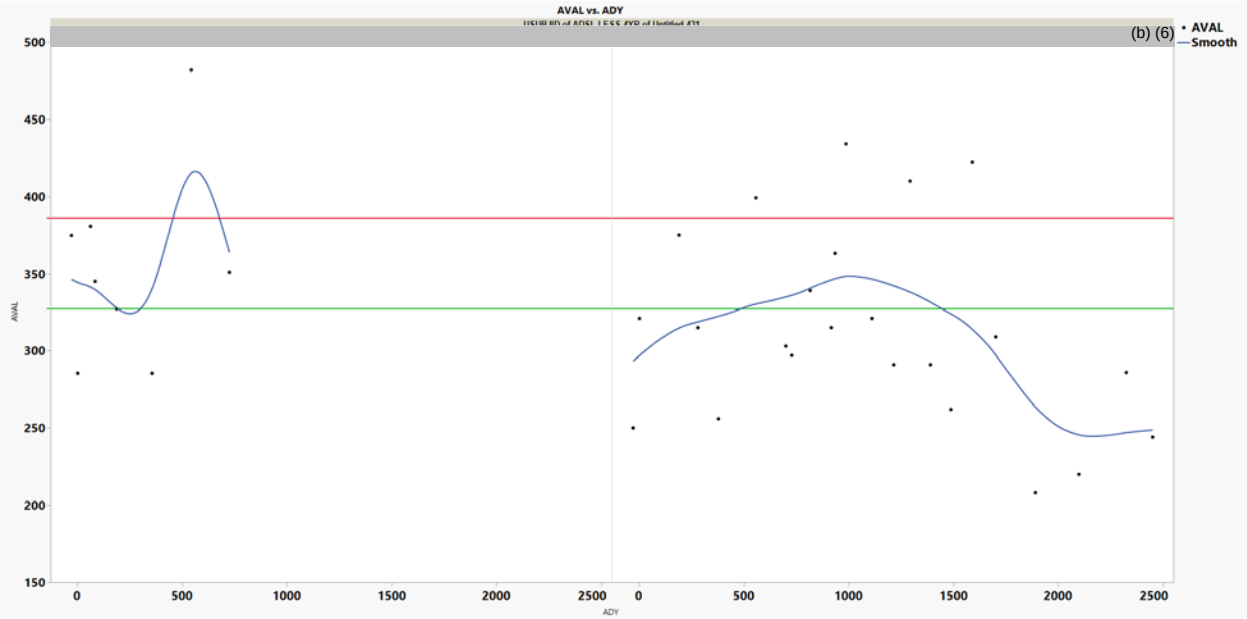
high at 374 umol/L. This patient's urate elevation may be due an underlying medical condition, given the elevated baseline. The elevations observed for patient (b) (6) are of uncertain significance. The overall trend of urate values of all pooled study participants is examined. The trendline is nearly flat with a slope of -0.0033 (39 patients, maximum duration 2712 days). This does not forecast a systematic effect of brivaracetam on urate over time, see Figure 7.

Figure 7 Study N01266, Critical Value Urate Measurements, Timeline of All Values During Study Participation (Patients (b) (6))



Alanine Aminotransferase (U/L) (RR= 5 to 30 U/L, critical value= > 3 x ULN): there were two patients, (b) (6) with elevations of ALT greater than 3 x ULN found to be 158 and 168 U/L respectively. The critical ALT elevations for both patients are sporadic and not sustained. As the study timeline progresses the iterative values enter the reference range. Patient (b) (6) has a single AST elevation that corresponds to the ALT elevation. The bilirubin remains within reference range for both patients and well below ULN, see Figure 8.

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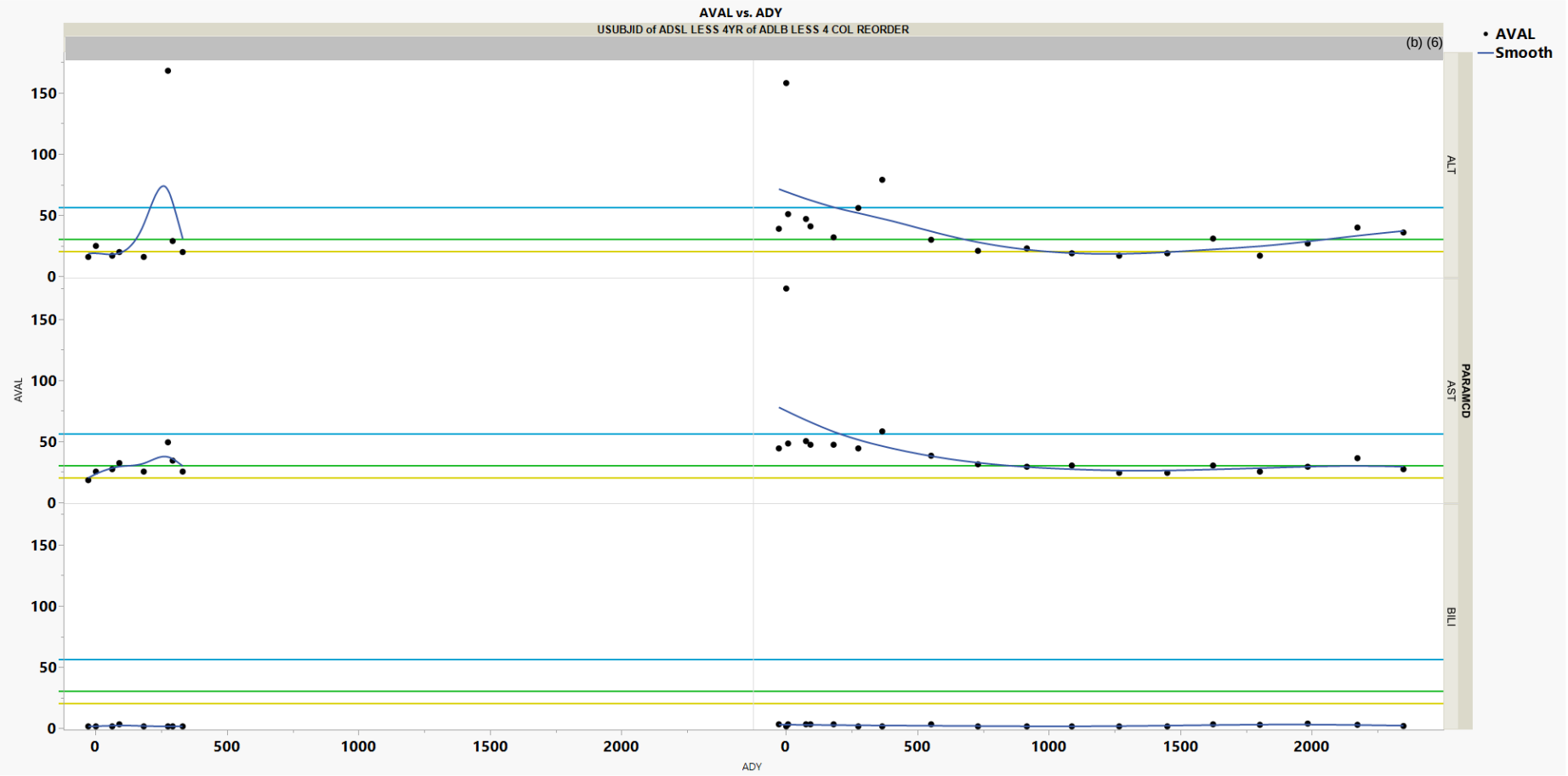
Figure 8 Study N01266, ALT, AST, Bilirubin Over the Course of Study for Patients (b) (6).
(Upper Limit of Normal: Blue= AST, Green = ALT, Yellow= Bilirubin)



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Glucose (RR = 59.4 to 100.8 mg/dl) One patient (b) (6) has a single elevation of serum glucose to 143 mg/dl on study day 181. The event is closely bracketed by adverse events of "pyrexia". Examination of all glucose values for patient (b) (6) entered during the study reveal there are 14 subsequent measurements obtained, all but one are within reference range. The only subsequent OORR high value is 113 mg/dl that occurs on study day 412. This glucose value is a sporadic occurrence likely related to stress or underlying infection and does not represent a systematic physiologic influence of brivaracetam.

Hemoglobin: One patient has a critical value entry of 16.3g/dl on study day 1. No baseline is provided. This lone event does not likely represent a physiologically threatening trend introduced by study drug. It may represent hemoconcentration. Examination of the adverse event dataset reveals "dysphagia" on day 1 and "dehydration" on day 62.

Platelets (RR = 140 to 450 x 10^3 cells/ul): One patient, (b) (6), had thrombocytosis of 608 x 10^3 cells/ul on study day 62. Examination of the platelet values over this patient's course of 2415 days in Study N01266 reveals that all other values were within reference range. The event of platelet elevation was a sporadic event not associated with a persistent or systematic trend of thrombocytosis.

Reviewer Comment: Analysis of the Critical Value laboratory outliers reveal that most events are sporadic during ongoing brivaracetam treatment or a plausibly associated with emergent medical illness that are the driver of the observed laboratory abnormality. The analysis does not identify evidence that these events are causally related to brivaracetam treatment.

Study EP0065

Hematology and Clinical chemistry studies are obtained at screening and follow up visit down titration visit 13 for patients who are not entering a long term follow up study. Only a single patient (b) (6), 4yo female) had a visit number 13 with entries for clinical chemistry. One post baseline abnormality of a decrease in follicle stimulation hormone from 2.37 U/L to 0.4 U/L in a 4-year-old female was identified.

6.4.7. Vital Signs

Study N01263

Sponsor summary: "There were no clinically meaningful differences in baseline vital sign parameters or in the mean changes from Baseline to the Last Value in the Post-Baseline Period for all age groups."

Reviewer Comment: the reviewer performed an analysis of the change in systolic pressure between baseline and visit number 5 that was available for 33 patients. The mean change in

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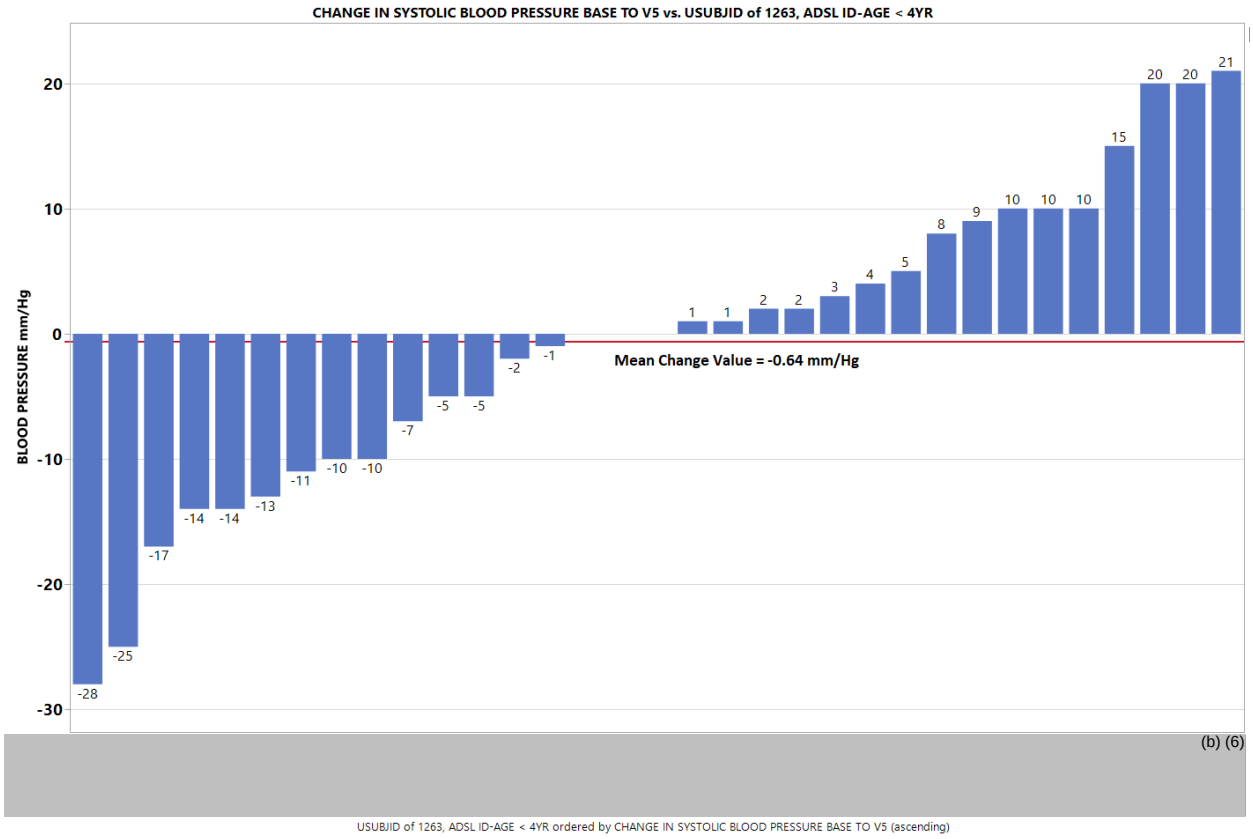
systolic pressure was -0.64 mm/Hg with a median change of zero. The change from baseline is seen in the plot of Figure 9, where the frequency and magnitude of SPB change in patients with an increase in systolic blood pressure is similar in frequency and magnitude to those with a decrease in systolic blood pressure. This finding is in alignment with the sponsor's summary conclusion.

Figure 9 Study N01263 Change in Systolic Blood Pressure, Baseline to Visit 5 (day 22), n=33



Study N01266

Systolic Blood Pressure

As a measure of hemodynamic impact of study drug an analysis of SBP is performed. The mean SBP of all study visits is examined as well as the variability of the measures shown by the standard deviation, interquartile range, and full minimum to maximum range. The mean change from baseline is also examined for each patient, see Table 24.

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When the patients with fewer than 6 study visits are excluded from analysis the standard deviation and interquartile range of the mean SBP across the timeline of study visits for each patient are 9.6mmHg and 13.5mmHg respectively. This indicates variability among measurements during the course of the study are not extreme. There are large mean SBP mean range values seen for some patients (column 8). Ten patients have a mean SBP range value greater than 45 mmHg. These large magnitude values indicate there are high or low outliers present. Examination of the mean change from baseline for each patient reveals the larger declines or increases in SBP are associated with corresponding higher or lower range baseline blood pressures. This trend tends to offset the starting (baseline) SBP toward a resulting value near 100 mmHg, see Figure 10.

Table 24 Study N01266 Systolic Blood Pressure Analysis: Baseline, Mean SBP by Patient, SD, Mean Change from Baseline, Interquartile Range, Min-Max Range (note: top row is column number for reference)

1	2	3	4	5	6	7	8
patient ID	# Study Visits	BASELINE	Mean SBP mmHg	Standard Deviation Mean SBP	Mean Change from Baseline SBP	Mean SBP Interquartile Range	Mean SBP Range- MIN-MAX MEASURE
(b) (6)	2	76	79	4	5	5	5
	10	90	85	6	-6	10	15
	30	90	87	13	-3	15	50
	13	95	87	13	-9	18	45
	11	88	88	9	0	18	24
	14	86	88	8	3	9	30
	13	90	88	7	-2	8	24
	8	90	89	6	-1	4	20
	35	70	90	8	21	5	35
	34	70	91	14	22	16	68
	7	95	91	4	-4	5	10
	6	92	92	9	0	20	21
	9		93	5		8	16
	4	101	94	8	-9	14	14
	34	72	95	13	24	14	62
	6	99	95	3	-5	5	7
	8	87	97	11	12	24	27
	30	82	97	11	16	16	49
	34		97	10		14	50
	18	99	97	9	-2	11	35
	32	88	98	13	11	26	41
	29	98	99	12	1	14	55

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1	2	3	4	5	6	7	8
patient ID	# Study Visits	BASELINE	Mean SBP mmHg	Standard Deviation Mean SBP	Mean Change from Baseline SBP	Mean SBP Interquartile Range	Mean SBP Range- MIN-MAX MEASURE
(b) (6)	4	99	99	0	0	0	0
	5	98	100	4	2	6	10
	14	122	102	14	-22	23	47
	30	94	103	17	10	20	68
	9	90	103	7	15	9	23
	30	99	104	10	5	13	40
	31	105	104	9	-1	10	35
	10	100	104	5	4	10	10
	28	100	105	9	5	14	34
	34	110	105	7	-5	10	30
	30	101	106	13	6	20	44
	2	127	107	28	-40	40	40
	8	101	109	16	9	32	41
	10	100	109	3	10	0	10
	14	96	113	15	18	20	48
	31	109	115	8	6	10	36
	4	148	129	13	-25	21	27

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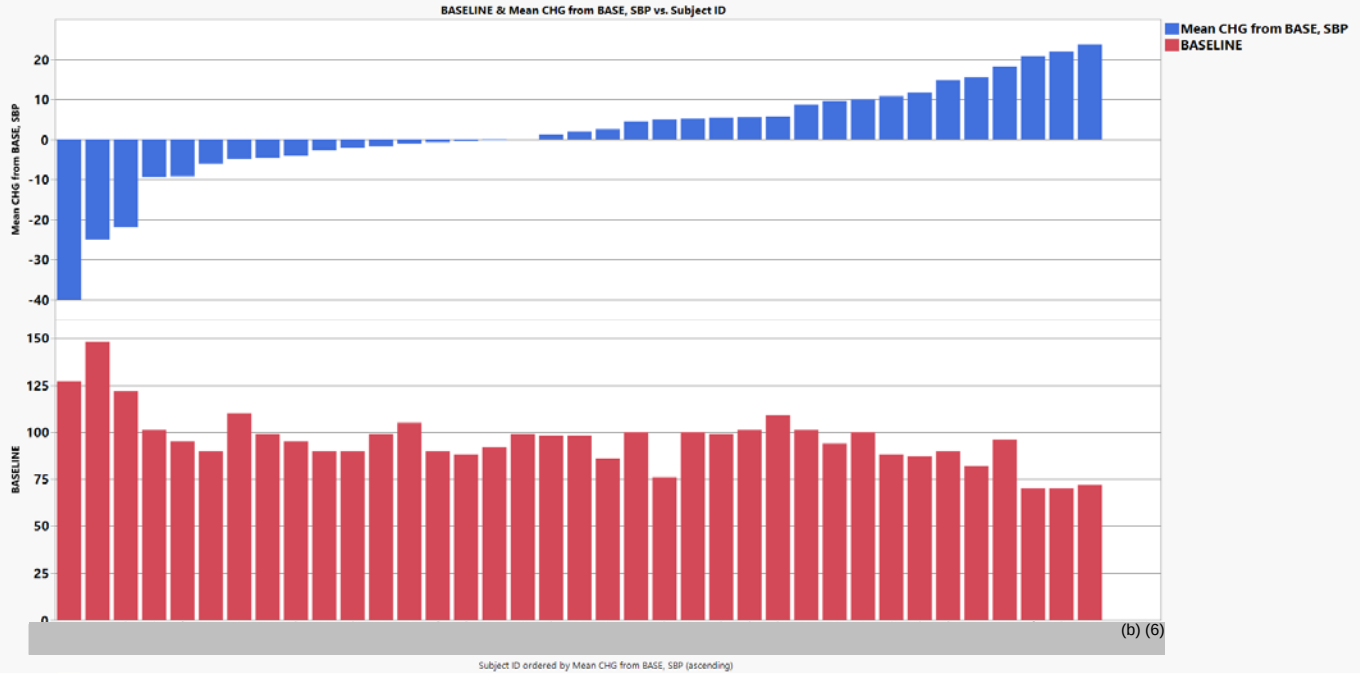
Figure 10 Study N01266, Systolic Blood Pressure Analysis, Baseline BP Compared to Mean Change from Baseline by Patient ID



Systolic Blood Pressure at Visit 5, Change from Baseline (6 months)
An examination of systolic blood pressure at six months is performed. Change from baseline value is available for 29 patients. The proportion of patients with an increase in systolic blood pressure over baseline is similar to the proportion with a decline from baseline. The magnitude of these changes across the spectrum of increase or decrease is also similar. This analysis reveals there is no systematic shift in blood pressure associated with brivaracetam treatment.

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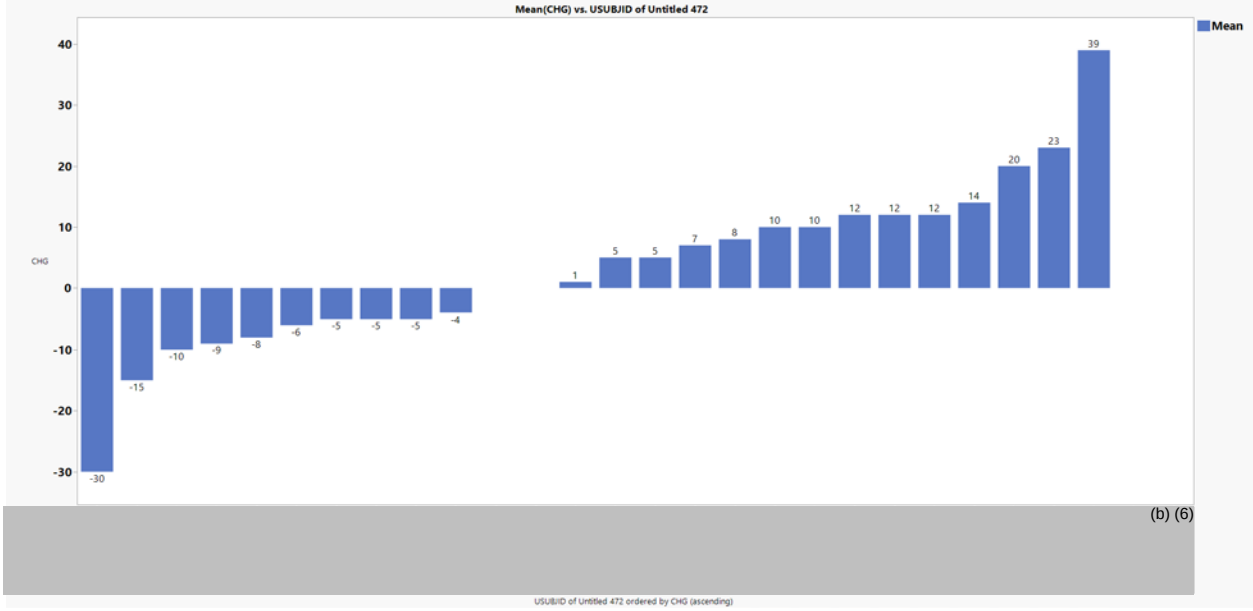
Figure 11 Study N01266, Systolic Blood Pressure, Change from Baseline at 6 Months by Patient ID (n=28)



Sponsor's Report on Vitals Signs of Blood Pressure and Pulse

"In general, the overall incidence of PCST SBP, DBP, and pulse rate values remained low through Month 75 of the study (SBP: ≤4.1%, DBP: ≤8.5%, and pulse rate: ≤4.0%)." **Note**- this sponsor statement is in reference to the overall population of Study N01266 of 247 patients of age range 3 months to 16.9 years old.

Pulse:

Low Outliers: Three were 4 patients, (b) (6) with any post baseline recording of pulse less than 65 beats per minute (BPM). Three patients (b) (6) had a single entry of pulse less than 65 BPM out of a minimum of 28 measurements over a minimum of 2444 days. Patient (b) (6) had 3 entries of pulse less than 65 BPM out of 31 post baseline measurements with a mean pulse of 94 BPM spanning 2759 days.

High Outliers: There were 3 patients (b) (6) with any post baseline recording of pulse greater than 150 Beats per minute (BPM). Patients (b) (6) had a single post baseline pulse greater than 150 BPM. Patient (b) (6) had 3 of 27 pulse measurements that were greeter than 150 BPM where the overall mean pulse of 27 post baseline visits was 125 BPM (note:

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baseline pulse = 123, age = 1.38 yrs. old).

Reviewer Comment: Analysis of pulse reveals few high or low post baseline outlier values from among the 622 post baseline measurements obtained from the cohort less than 4 years of age in Study N01266. The analyses of SBP reveal variability in values that are generally consistent across patients and the study timeline with scattered outlier values present that do not represent a systematic trend of increasing or declining blood pressure. The examination of mean change from baseline SBP at study visit number 5 reveals a similar distribution of patients with mean decline from baseline SPB compared to those with a mean increase from baseline SBP. The magnitude of the changes in the increasing and declining direction are also similar. Overall, there is no signal of an adverse effect of brivaracetam on Pulse or SBP in the study population.

Study EP0065

Sponsor Analysis: "Overall, SBP and DBP Baseline values were of no clinical concern for this population. Mean BP at each time point fluctuated; however, there was no obvious trend. In some participants, there were somewhat large decreases from Baseline in both SBP and/or DBP at the time points shortly after infusion at Visit 3; however, these decreases were generally short lived. Mean changes from Baseline for SBP and DBP in the 15-minute infusion and bolus infusion groups were generally consistent across age cohorts. The mean change from Baseline in SBP and DBP was similar across age cohorts, infusion durations, and study participant groups (RxB and IOB [non-naïve] and IIB [naïve]).

Reviewer Analysis

Systolic BP

The systolic blood pressure was selected for reviewer examination as an index of potential hemodynamic influence of intravenous delivery of brivaracetam. The blood pressure entries from the ADVS dataset were examined. All analyses examine the Visit 3 (IV PK Period) post treatment measurements. The review strategy includes analysis of outlier excursions of blood pressure from baseline value in the cohort 1 (≥12 to <16 years) bolus infusion compared to the 15-minute infusion rate and again in cohort 4 (≥1 month to <2 years) bolus infusion compared to the 15-minute infusion. The divergent age cohorts 1 and 4 are compared because they are the oldest and youngest of the pediatric age spectrum cohorts in the study. This difference in age may allow emergence of notable difference in hemodynamic effect and tolerability of the intravenous formulation with the bolus and 15-minute infusion rates. A direct comparison is also performed on the change from baseline at the 6 post treatment measurement intervals, prescribed by Study EP0065, between cohorts 1 and 4 with bolus infusion administration and

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again with the 15-minute infusion administration. An analysis of the overall variability and excursions from baseline value (change from baseline) compared to the baseline SBP as well as the resulting SBP at the specified time interval are performed for the condition of bolus administration and again for 15-minute infusion administration. The measures of central tendency and distribution variability are also examined for the pool of all for age cohorts by infusion administration method, bolus or 15-minute infusion.

Analysis of the cohort 1 change from baseline comparing bolus to 15-minute infusion administration reveals more instances of notable decline from baseline in the bolus subset. There were no declines greater than 5mmHg in the 15-minute infusion group while there were single instances of SBP decline of -26mmHg at the 2 minute and 60-minute measurements and a decline of -25mmHg at 5 minutes. All changes from baseline to <-25 were seen in measurements from patient (b) (6), a 14-year-old female, see Figure 14. There were no TEAE entries for this patient who is reported as a study completer.

Analysis of the cohort 4 changes from baseline where the bolus and 15-minute infusion administrations are compared reveals more instances of notable decline from baseline in the 15-minute infusion subset. There are 6 instances of change from baseline of greater magnitude than -25mmHg. The largest declines are seen in the measurements from patient (b) (6) (8-month-old female) at 30 minutes, 60 minutes, and 120 minutes with values of -39mmHg, -40mmHg, and -45mmHg respectively. An additional instance in a measurement from patient (b) (6) (2-year-old male) occurs at 60 minutes post start of IV treatment where a value of -39mmHg is observed, see Figure 15. Both of these patients completed the study. Patient (b) (6) had no TEAE entries while patient (b) (6) had two TEAEs entered as the preferred terms “conjunctivitis” and “rash”. The declines in SBP were more prominent in the longer infusion interval but there is no indication from the adverse event dataset or by withdrawal from the study that a hemodynamically significant event intruded into the treatment of these two patients.

Analysis of the cohort 1 and 4 change from baseline profiles for both the bolus and 15-minute infusion subsets reveals a trend of more frequent SBP declines larger than -20 mmHg in cohort 1 of the bolus subset than in the cohort 4 group. This higher frequency in cohort 1 was due to one patient (b) (6) with 4 instances of large changes from baseline at 5 minutes, 30 minutes, 60 minutes, and 120 minutes where the changes were -25mmHg, -23mmHg, -26mmHg, and -26mmHg respectively. This patient was a 14-year-old female with no TEAE entries who completed the study, see Figure 16. Examination of the change in SBP seen in cohorts 1 and 4 who were in the 15-minute infusion subset reveals 3 instances of change from baseline near -40mmHg in magnitude at 30, 60 and 120 minutes contributed by a cohort 4 patient (b) (6) identified above in the comparison of the cohort 4 responses to bolus and 15-minute IV infusion. If the entries from this patient were excluded, there are no instances of decline from baseline in either cohort in the 15-minute infusion subset with a

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magnitude greater than -5mmHg. Overall, in the Cohort 1 and 4 comparison during the 15-minute infusion there are small magnitude positive changes from baseline that are generally near +10mmHg. There is one instance of +35mmHg at 15 minutes post start of IV infusion, see Figure 16 and Figure 17. The remaining changes from baseline seen for this patient (Subject ID (b) (6)) were +11mmHg or less.

An analysis of central tendency and variability comparing the 15-minute infusion to the bolus cohort reveals a trend of larger decline in mean change from baseline and larger standard deviation in the 15-minute infusion subset.

To further inform the assessment of change from baseline blood pressures an analysis of the overall variability and excursions from baseline value (change from baseline) compared to the baseline SBP, sample time SBP resulting SBP at the specified time interval are performed for the condition of bolus administration and again for 15-minute infusion administration. This analysis reveals a tendency for the larger declines in SBP from baseline to align with baseline SBP that are at the higher observed values of the corresponding group (same group, Baseline to post-baseline). A similar trend is seen for positive change from baseline values. This trend mitigates the impact on the resulting SBP, see Figure 12 and Figure 13.

To provide a frame of reference for the pediatric SBP analyses an examination of the change from baseline at visit 3 for the bolus and 15-minute infusion are examined compared to the corresponding baseline and specified time interval SBP value for adults < 35 years of age at visit 3 (1st day IV administration) of Study N01258. This analysis reveals overall smaller changes from baseline in either the positive or declining direction for both the bolus and 15-minute infusion subsets, see Figure 18 and Figure 19. This is reflected in smaller mean positive or negative changes from baseline and smaller standard deviations in the examination of central tendency and variability, see Table 29.

Reviewer comment: Analysis of SBP changes from baseline in the oldest and youngest pediatric cohorts does not reveal a consistent age-related trend for post baseline elevation or decline in SBP values. Where there were large excursions these were driven by a single patient, one each in cohort 4 and cohort 1. Comparison with changes from baseline observed in the adult cohort less than age 35 from study N01258 reveal a greater stability of post baseline SBP values. Among the pediatric patients with higher magnitude changes from baseline, there were no entries of adverse effects and none had study interrupted or discontinued. The magnitude of change in the pediatric cohorts, although greater than in adults, does not show evidence of a destabilization of blood pressure that would be considered a safety signal.

Figure 12 Study EP0065, Bolus Subset SBP, Visit 3- All Cohorts (1 to 4), Change from Baseline – Resulting SBP- Baseline SBP, by Post Infusion Time (2, 5, 15, 30, 60 and 120 minutes), n=24

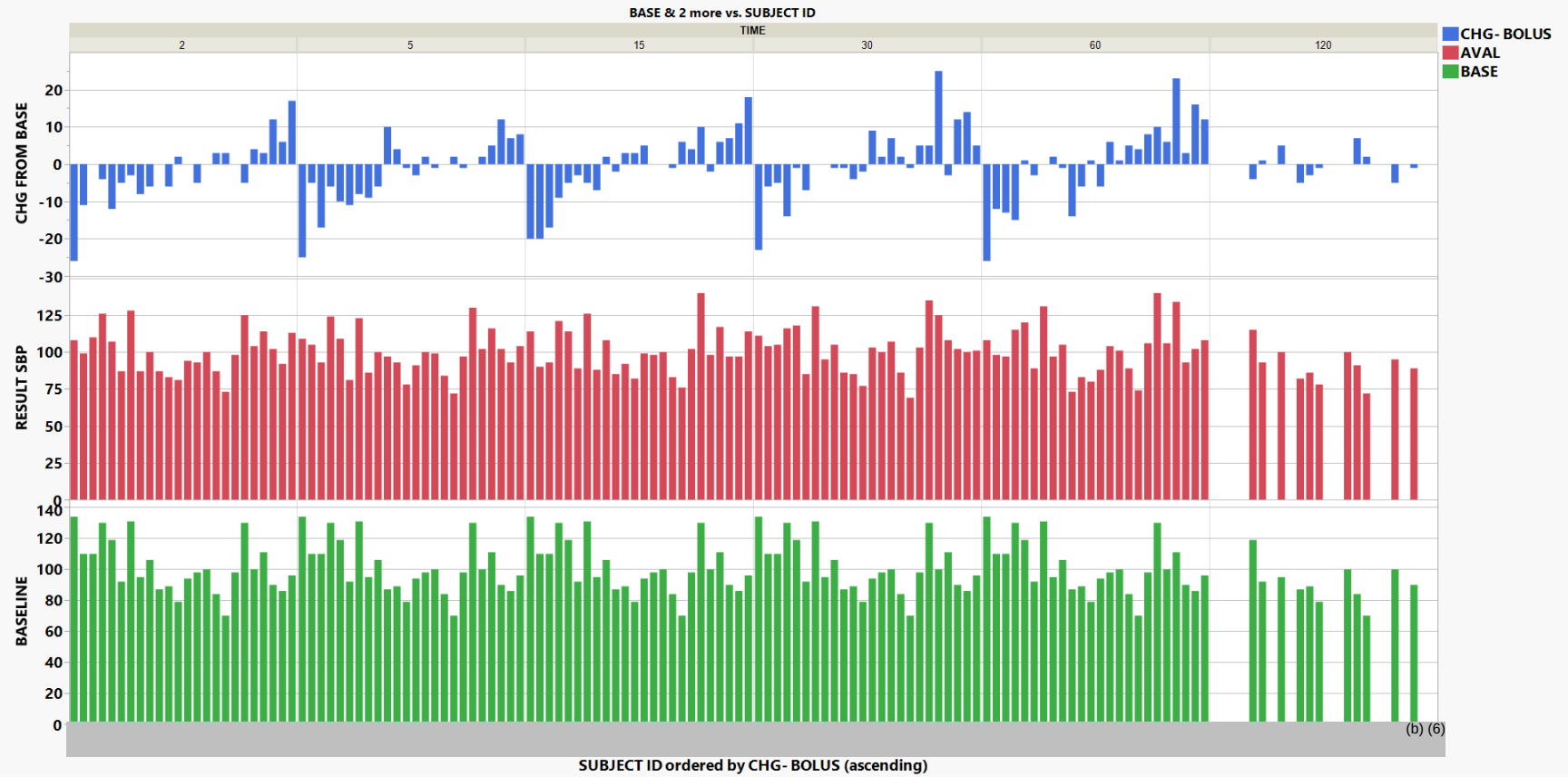

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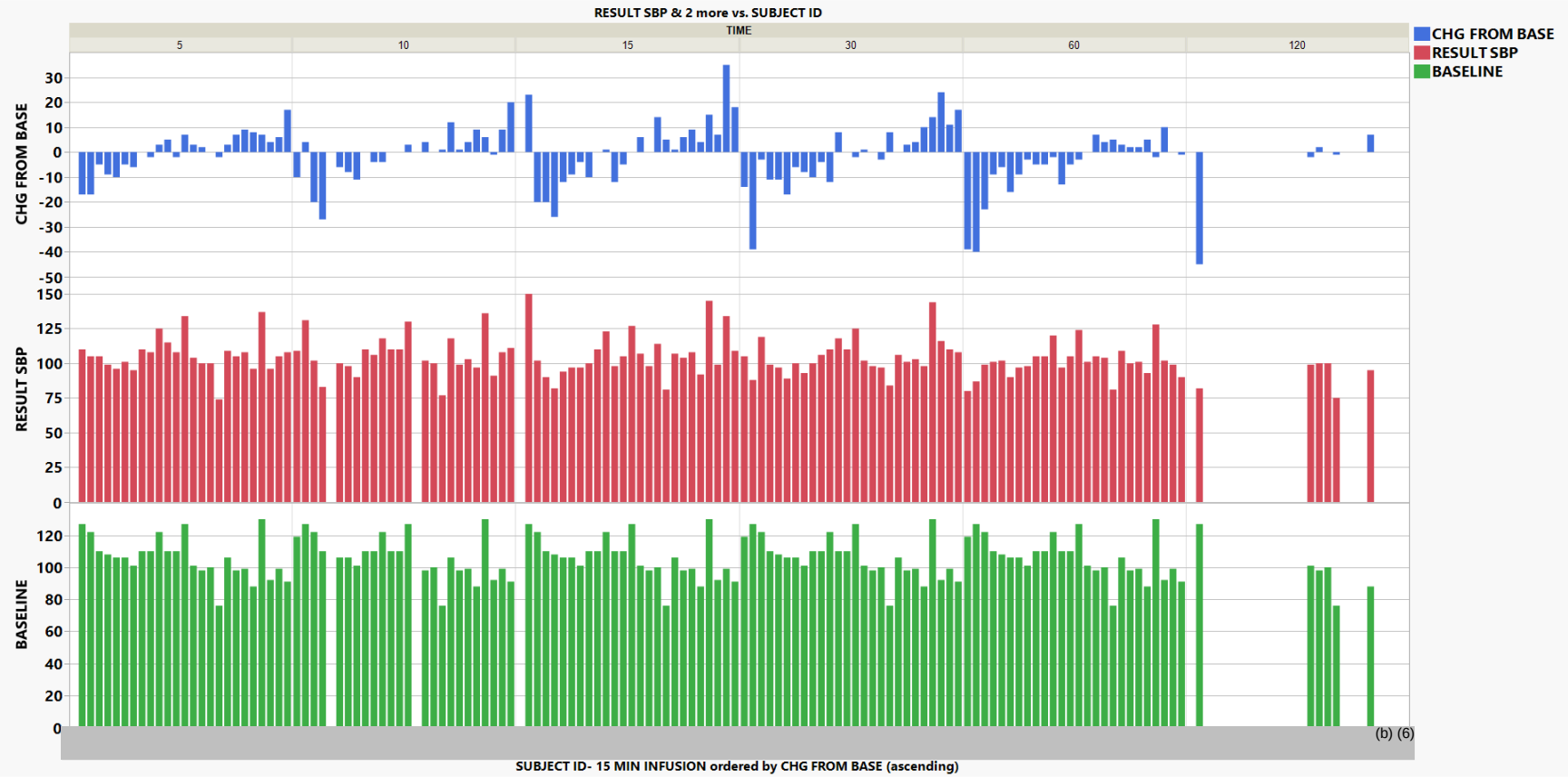
Figure 13 Study EP0065, 15 Minute Infusion Subset SBP, Visit 3- All Cohorts (1 to 4), Change from Baseline – Resulting SBP- Baseline SBP, by Post Infusion Time (2, 5, 15, 30, 60 and 120 minutes), n=26



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6.4.8. Electrocardiograms (ECGs)

Study N01263

Reviewer examination of the ECG dataset ADEG at Visit 5 (day 22) reveals that no patient with a normal ECG interpretation at baseline had a change to abnormal at visit 5. There was one patient with an interpretation of "abnormal" at baseline that remained "abnormal" at Visit 5.

Study N01266

Sponsor Assessment (from CSR, ECG Findings, page 141). (note: *study report discussion is relevant to the entire Study N01266 study population, n=247, age 3 months to 16.9 yrs. old*):

"ECG findings over time"

"During the Evaluation Period, the majority of study participants had normal ECG findings (145 study participants [59.2%]). A total of 91 study participants (37.1%) had abnormal but not clinically significant ECG findings and 9 study participants (3.7%) had clinically significant ECG findings. The proportion of study participants with normal and abnormal but not clinically significant ECG findings during the Evaluation Period was consistent across age groups. One study participant (3.7%) with clinically significant ECG findings was in the ≥1 month to <2 years age group, 4 study participants (2.6%) were in the ≥2 to <12 year age group, and 4 study participants (6.1%) were in the 12 to <17 years age group (Table 16.1.1)."

"For DE study participants during the Up-Titration Period, 74 study participants (62.7%) and 44 study participants (37.3%), respectively, had normal or abnormal but not clinically significant ECG findings, and no DE study participants had clinically significant ECG findings (Table 16.1.2)."

"Treatment-emergent abnormal ECG findings"

"Reported TEAEs associated with ECG findings were in the SOC of Cardiac disorders and Investigations. Of those study participants with abnormal clinically significant ECG findings at any visit, 6 study participants had TEAEs associated with the ECG finding. Sinus tachycardia was reported by 2 study participants, bradycardia was reported by 2 study participants, cardiac failure was reported by 1 study participant, and ST elevation and early repolarization were reported in 1 study participant. All of the events were nonserious, mild or moderate in intensity, considered not related to IMP by the Investigator, and did not require a dose change or discontinuation of IMP."

Reviewer Comment: the subset of ECG data on patient less than 4 years of age was examined in the ADEG dataset. All data is present. A separate analysis was not performed. The sponsor

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analysis did not report a significant safety signal for any population subset.

Study EP0065

Sponsor analysis: ECG recordings were obtained at pre-initiation of intravenous brivaracetam infusion then at 5, 10, 15, 30, 60, and 120 minute post infusion. "No clinically relevant changes from Baseline were observed for vital signs or 12-lead ECGs."

6.5. Analysis of Submission-Specific Safety Issues

6.5.1. Decreased Appetite

The frequency of the adverse event preferred term "decreased appetite" was seen to increase with decreasing age. In the adult LTFU study ISS ADAE dataset at the time on initial NDA submission there were 2079 patients age 16 or older in studies N01125, N01199, N01372 and N01379. From among these patients there were 107 (5.1%) entries in the safety dataset for "decreased appetite". In study N01266 there were 205 patients from age equal to or greater than 4 years to less than 16 years. From among these patients there were 21 (10.2%) patients with an entry of "decreased appetite", one was an SAE. In Study N01266 there were 39 patients between age 1 month and less than 4 years of age. From among these patients there were 6 with and entry of "decreased appetite", see Table 25.

Table 25 Preferred Term "decreased appetite". Summary of Frequency by Age Group in LTFU Studies

LTFU Study / Study Group	# patients in group	# patients with AE entry of "decreased appetite"	% of patients
Adult LTFU, initial NDA submission, study pool = N01125, N01199, N01372 and N01379	2079	107	5.1
N01266 16 years> age ≥4 years	205	21	10.2
N01266 age < 4 years	39	6	15.4

Reviewer Comment: The sponsor has proposed language in labeling, Section 6.1 under the "Pediatric Patients" subheading to address this observation. The proposed language is entered as "Decreased appetite was also observed in these pediatric trials.". The reviewer agrees this proposed language is supported by the findings in the ADAE safety datasets identified in the discussion above.

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6.6. Safety Analyses by Demographic Subgroups

6.7. Additional Safety Explorations

6.7.1. Pediatrics and Assessment of Effects on Growth

No analysis on performed

6.8. Integrated Assessment of Safety

Study N01263

All SAEs were related to infection associated preferred terms with no fatal outcomes. Analysis of Hematology and Clinical laboratory mean change from baseline and outlier values did not reveal systematic changes to support a new safety signal or causally related outlier values. ECG did not show abnormalities at Visit 5. Vital sign analysis did not reveal systematic change in systolic blood pressure, there were 16 patients with an increase in systolic blood pressure, 14 patients with a decrease in systolic blood pressure and 3 patients with no change where the group mean change was -0.64 mm/Hg.

Study N01266

SAE: the profile of serious adverse events in the patient cohort less than age four years is similar to those in the age ≥ 4 years of age. There is a higher frequency of fatal outcome in the younger population, however, none of these events had a TTO that was consistent with a causal temporal relationship. From among these four fatal outcome events two patients had underlying predisposing medical vulnerability and in the remaining two patients there was no plausible mechanism.

There was also a higher relative proportion of SAE in the < 4-year-old population of Study N01266 compared to patients ≥ 4 years of age. All SAE except convulsion were likely related to infection, these include 3 events that are not in the “infection and infestations” SOC, “pyrexia”, “dehydration” and “Diarrhoea”. This age-related shift of SAE proportionality may be related to the increased vulnerability to infection of the younger pediatric patient. The overall TTO of the SAE events in the younger age group was not consistent with a causal relationship to brivaracetam treatment in 82% of the SAE occurrences.

An analysis of Hematology and Clinical Chemistry studies that had a Critical Value flag was performed. This analysis of the Critical Value laboratory outliers did not identify evidence that these events are causally related to brivaracetam treatment.

A trend of increasing TEAE entries of “decreased appetite” was observed in an inverse

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relationship to the age cohort examined. These cohorts include the pediatric cohort > 4 years of age, pediatric patients ≥ 4 years of age, and the adult population. Finally, the preferred term "decreased appetite" was examined in LTFU studies that were submitted with the initial NDA submission. This latter group had the lowest frequency of this adverse event across the age spectrum.

Study EP0065

There were no SAEs in study EP0065 and only one patient with post baseline laboratory study values available. In that 4-year-old female patient there was one OORR change from baseline, a decrease in follicle stimulation hormone from 2.37 U/L to 0.4 U/L.

In the assessment of Study EP0065 there was a focus on blood pressure evaluation due to the short overall exposure and potentially acute effects of a short rise to Tmax of an intravenous delivery. Systolic blood pressure was examined as an index of potential hemodynamic effect. This analysis did identify larger excursion of values from baseline, of both increase and decline, in the pediatric cohorts. There was also a higher proportion of declines seen in the pediatric cohorts compared to those seen in the change from baseline analysis of adult patients (Study N01258), see Figure 12 and Figure 13- Study EP0065 as well as Figure 18 and Figure 19 from derived from Study N01258. In the analyses within the pediatric cohorts of Study EP0065 there was no consistent difference between age cohorts or between bolus or 15-minute delivery of IV brivaracetam in the frequency of low shifts in SBP from baseline. Among the pediatric patients with higher magnitude changes from baseline there were no associated entries of adverse effects and none had study interrupted. The magnitude of change in the pediatric cohorts, although greater than in adults, does not show evidence of a destabilization of blood pressure that would be considered a safety signal.

The sponsor did not report notable abnormalities in ECG values obtained during Study EP0065.

Conclusion: Review of the pediatric cohorts of Studies N01263 and N01266 as well as Study EP00565 did not reveal a new safety signal or worsening of a known safety issue associated with brivaracetam treatment in the older age cohorts. There was on observation of increased frequency of "decreased appetite" in the younger age group that will be included in labeling,

7. Labeling Recommendations

7.1. Prescription Drug Labeling

The review findings are in agreement with proposed language in Section 6.1 to address the

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observation of decreased appetite in the pediatric age group, see discussion in Section 6.5.1, Decreased Appetite.

8. Appendices

8.1. References

See footnotes

8.2. Laboratory Data

8.2.1. Hematology Change from Baseline Mean Analysis

Table 26 Study N01266 Hematology, Baseline Mean and Mean Change from Baseline at visit 5 (6 months), visit 7 (12 months), Visit 9 (18 months) and Visit 15 (36 months).

Laboratory Parameter	Visit #, Month	# Patients	Baseline Mean	SD Baseline Mean	Mean Change from Baseline	SD Mean Change from Baseline
Basophils (10^9/L)	V5, M6	26	0.036	0.023	0.002	0.034
	V7, M12	18	0.032	0.017	-0.004	0.017
	V9, M18	18	0.032	0.017	0.002	0.028
	V15, M36	12	0.033	0.018	0.001	0.021
Eosinophils (10^9/L)	V5, M6	26	0.3	0.2	0	0.2
	V7, M12	18	0.3	0.2	0.1	0.4
	V9, M18	18	0.3	0.2	-0.1	0.2
	V15, M36	12	0.3	0.1	-0.1	0.2
Mean Corpuscular HGB Concentration (g/L)	V5, M6	26	330.8	10.4	0	11.2
	V7, M12	19	328.9	10.5	0	10.5
	V9, M18	18	330.6	10.6	1.1	8.3
	V15, M36	13	327.7	11.7	-4.6	11.7
Hematocrit (%)	V5, M6	26	36.8	2.1	0.7	1.6
	V7, M12	19	36.6	1.6	1.5	3
	V9, M18	18	36.9	1.9	0.5	2.2
	V15, M36	13	37.5	1.8	1.5	3.6
Hemoglobin (g/L)	V5, M6	26	121.5	8.3	2.1	6.9
	V7, M12	20	121.5	7.6	4.3	8.5
	V9, M18	19	122	7.4	2.3	8
	V15, M36	13	122.8	7.7	3.5	13.6
Leukocytes (10^9/L)	V5, M6	26	10.1	3.4	-0.9	3.4
	V7, M12	20	10.6	3.5	-0.7	3.6

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Laboratory Parameter	Visit #, Month	# Patients	Baseline Mean	SD Baseline Mean	Mean Change from Baseline	SD Mean Change from Baseline
	V9, M18	19	10.4	3.5	-2	3
	V15, M36	13	10.3	3.7	-1.8	3.3
Lymphocytes (10^9/L)	V5, M6	26	5.1	2.1	-0.7	1.7
	V7, M12	18	5.2	2.4	-0.8	1.6
	V9, M18	18	5.4	2.4	-1.7	2.1
	V15, M36	12	5.1	2.5	-1.8	1.6
Monocytes (10^9/L)	V5, M6	26	0.6	0.3	0	0.4
	V7, M12	18	0.7	0.3	0	0.3
	V9, M18	18	0.7	0.3	-0.1	0.3
	V15, M36	12	0.7	0.3	0	0.5
Neutrophils (10^9/L)	V5, M6	26	4.1	1.9	-0.3	2.4
	V7, M12	18	4.3	1.9	0.4	3
	V9, M18	18	4.2	1.8	-0.4	2.3
	V15, M36	12	4.5	1.9	-0.2	2.4
Platelets (10^9/L)	V5, M6	24	344.7	117.2	-40.2	123.3
	V7, M12	19	342.4	113.5	8.3	94.8
	V9, M18	16	336.3	102.2	-68.1	90.5
	V15, M36	13	334.8	120.1	-55.2	139.7

8.2.2. Clinical Chemistry Change from Baseline Mean Analysis

Table 27 Study N01266 Clinical Chemistry, Baseline Mean and Mean Change from Baseline at visit 5 (6 months), visit 7 (12 months), Visit 9 (18 months) and Visit 15 (36 months).

Clinical Chemistry						
Laboratory Parameter	**Visit #, Month**	**# Patients**	**Baseline Mean**	**SD Baseline Mean**	**Mean Change**	**SD Mean of Change**
Alanine Aminotransferase (U/L)	V5, M6	27	18.6	13.3	4.2	11.8
	V7, M12	19	18.1	14.8	2.2	12.3
	V9, M18	18	19.8	15.5	3.4	9.9
	V15, M36	15	19.1	17	-0.9	12.4
Albumin (g/L)	V5, M6	28	44.7	3.8	-0.3	2.8
	V7, M12	20	43.7	3.8	0.8	2.9
	V9, M18	20	43.8	3.8	0.2	3.9
	V15, M36	15	43.4	4.1	0.3	3.8
Alkaline Phosphatase (U/L)	V5, M6	28	269.4	110.1	-14.1	61.3

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Clinical Chemistry						
Laboratory Parameter	**Visit #, Month**	**# Patients**	**Baseline Mean**	**SD Baseline Mean**	**Mean Change**	**SD Mean of Change**
	V7, M12	20	267.7	119.2	-8.8	77.2
	V9, M18	20	268.4	120.3	17.2	297.5
	V15, M36	15	258.9	134.6	-39	93
Aspartate Aminotransferase (U/L)	V5, M6	27	33.8	10.6	-0.5	11.1
	V7, M12	19	35.9	11.6	-5.1	9.5
	V9, M18	18	35.4	11.5	-4.4	10.2
	V15, M36	15	33.6	9.5	-4.2	7.7
Bicarbonate (mmol/L)	V5, M6	28	17.4	2.6	0.7	3.2
	V7, M12	19	18.1	2.4	-0.7	2.3
	V9, M18	18	17.9	2.5	1.5	2.9
	V15, M36	15	17.6	2.5	0.1	2.6
Bilirubin (umol/L)	V5, M6	27	2.5	0.8	0.6	1.1
	V7, M12	20	2.5	0.9	0.3	1.3
	V9, M18	19	2.4	0.7	0.7	1.6
	V15, M36	15	2.5	0.7	0.9	2.6
Calcium (mmol/L)	V5, M6	28	2.5	0.2	0	0.1
	V7, M12	20	2.5	0.2	0	0.1
	V9, M18	20	2.5	0.2	0	0.2
	V15, M36	15	2.4	0.2	0	0.2
Chloride (mmol/L)	V5, M6	28	105.6	3.3	-1	3.7
	V7, M12	20	104.6	3.1	-0.2	4.9
	V9, M18	19	105	3.7	-1.2	4.8
	V15, M36	15	105.8	3.4	-4.1	4.1
Cholesterol (mmol/L)	V5, M6	28	4.1	0.7	-0.3	0.8
	V7, M12	20	4.1	0.8	0	0.7
	V9, M18	20	4.2	0.7	0	0.8
	V15, M36	15	4.1	0.7	-0.1	0.7
Creatinine (umol/L)	V5, M6	28	27	7.2	-1	5.8
	V7, M12	20	26.2	7.2	-0.6	7.5
	V9, M18	20	27	7.4	1.7	8.4
	V15, M36	15	26.8	8.3	1.6	8.9
Gamma Glutamyl Transferase (U/L)	V5, M6	28	44.5	46.5	3.1	25.9
	V7, M12	20	47.1	52.4	-0.6	42.1
	V9, M18	19	46.6	52.8	8.5	72.8
	V15, M36	15	52.1	58.1	-17.6	34
Glucose (mmol/L)	V5, M6	28	5	0.5	0	1.8
	V7, M12	20	5	0.6	-0.6	0.8
	V9, M18	19	5	0.6	-0.4	0.8
	V15, M36	15	5.1	0.6	-0.3	0.9

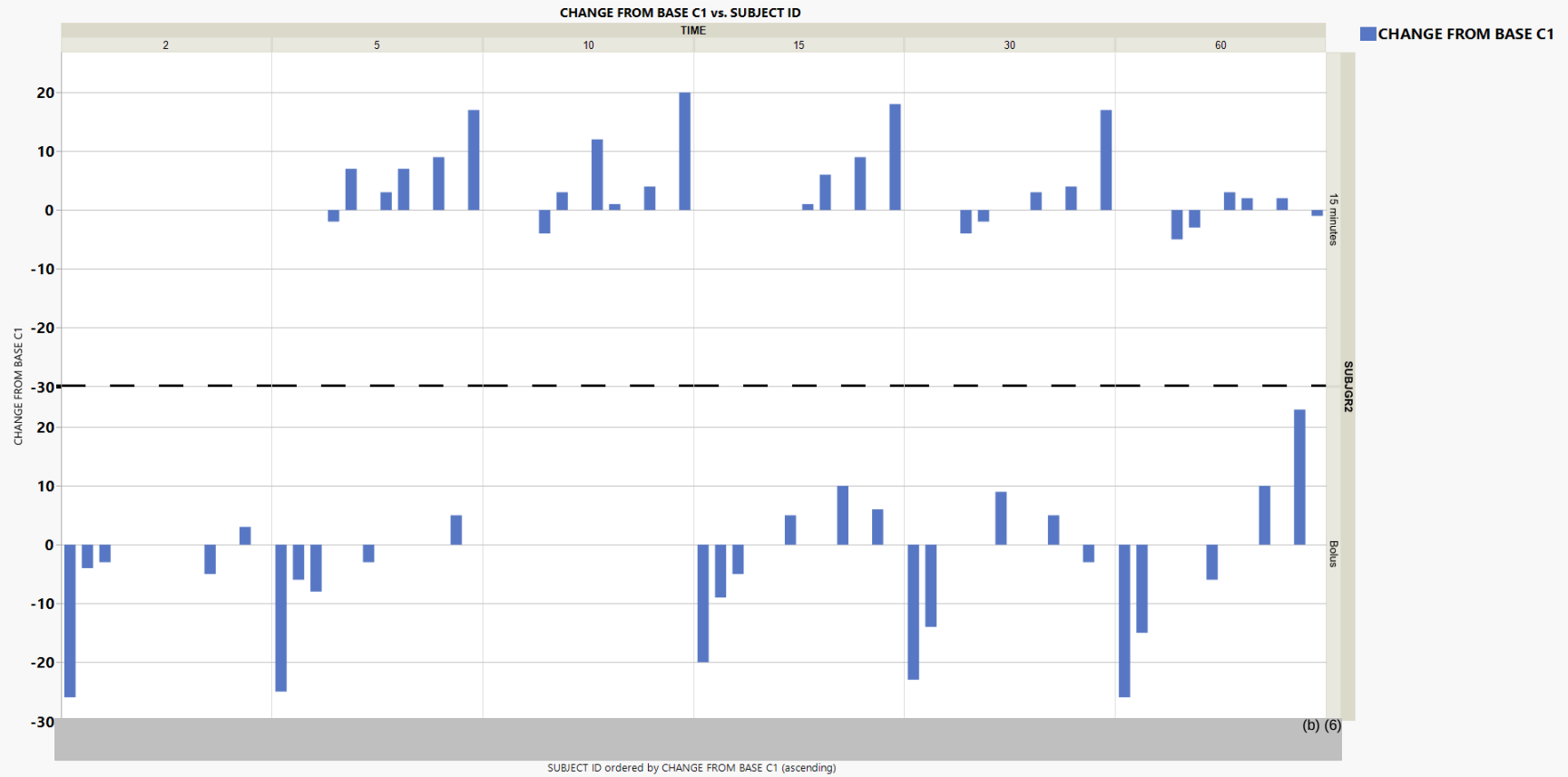
Clinical Chemistry						
Laboratory Parameter	**Visit #, Month**	**# Patients**	**Baseline Mean**	**SD Baseline Mean**	**Mean Change**	**SD Mean of Change**
Phosphate (mmol/L)	V5, M6	28	1.8	0.3	-0.1	0.3
	V7, M12	20	1.8	0.3	-0.1	0.3
	V9, M18	20	1.8	0.3	-0.1	0.3
	V15, M36	15	1.8	0.3	-0.2	0.4
Potassium (mmol/L)	V5, M6	28	4.7	0.5	-0.3	0.6
	V7, M12	20	4.8	0.5	-0.3	0.5
	V9, M18	19	4.8	0.6	-0.4	0.5
	V15, M36	15	4.7	0.6	-0.3	0.5
Protein (g/L)	V5, M6	28	65.9	6.3	0.4	4.4
	V7, M12	20	64.4	5.7	4.3	5
	V9, M18	20	64.3	5.7	3.1	5.9
	V15, M36	15	63.2	5.3	6.2	5.7
Sodium (mmol/L)	V5, M6	28	142.7	2.8	-1.3	3.6
	V7, M12	20	142.4	2.6	0.9	4.3
	V9, M18	19	142.8	2.9	-1.5	5
	V15, M36	15	142.9	2.4	-2.4	2.6
Thyrotropin (mU/L)	V7, M12	21	2.5	1.8	0.2	1.5
	V15, M36	14	2.4	2	-0.1	1
Thyroxine, Free (pmol/L)	V7, M12	21	13.9	2.4	1	2.6
	V15, M36	14	13.7	2.2	0.9	3.2
Triglycerides (mmol/L)	V5, M6	28	1.3	0.5	0	0.7
	V7, M12	20	1.3	0.5	0	0.7
	V9, M18	20	1.3	0.5	-0.1	0.5
	V15, M36	15	1.3	0.5	-0.4	0.5
Triiodothyronine, Free (pmol/L)	V7, M12	21	5.7	1	0.3	1.1
	V15, M36	14	6	0.6	0	0.9

8.3. Study EP0065 Blood Pressure Analysis

Study EP0065 Systolic Blood Pressure 15-minute Infusion to Bolus Comparison

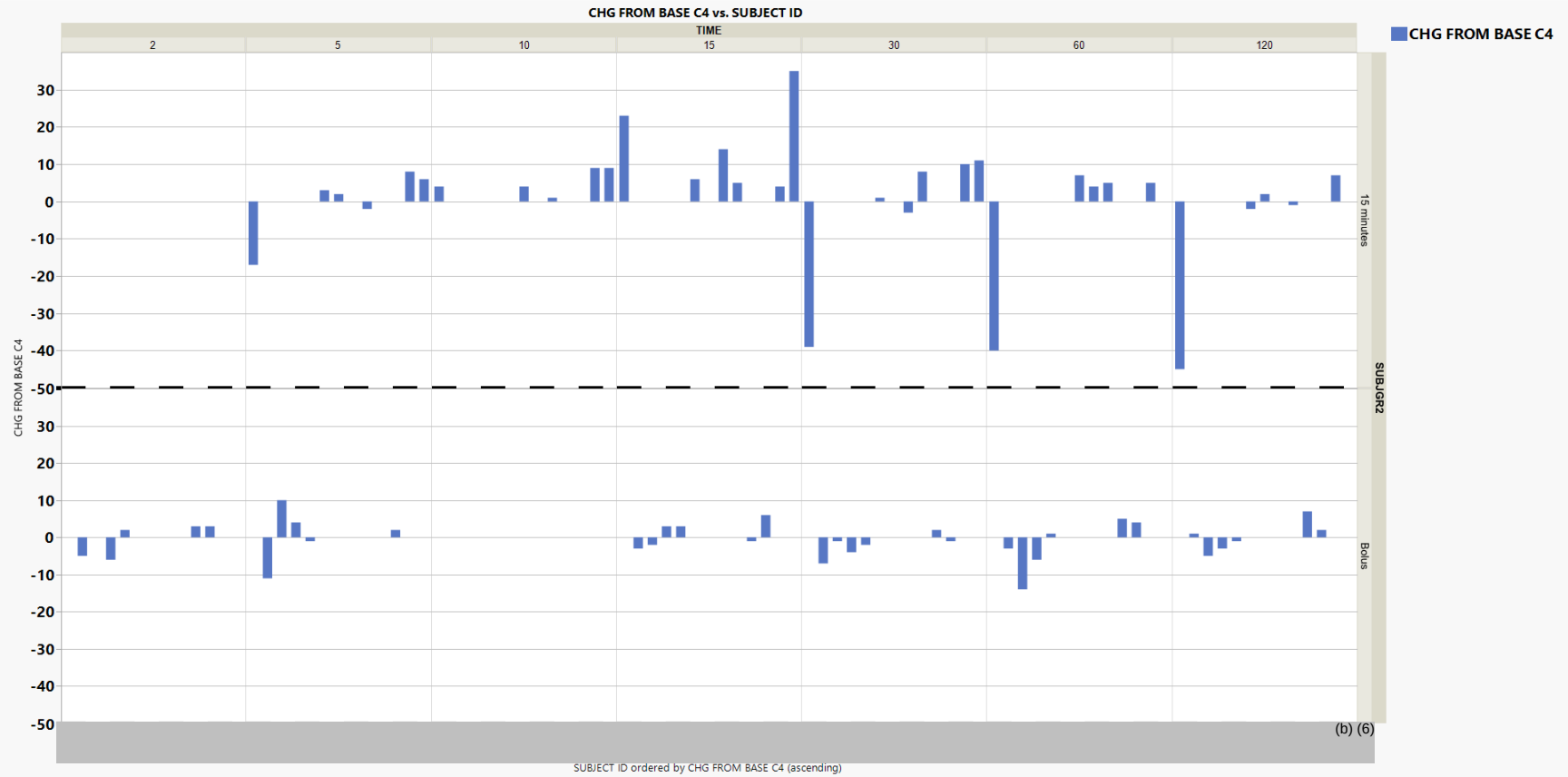
Reference ID: 4845026

Figure 14 Study EP0065 Cohort 1 *(≥12 to <16 years)*, **Bolus Compared to 15 Minute Infusion, SBP Change from Baseline by Post Treatment Time (15 min Infusion= upper panel, Bolus = Lower Panel)**



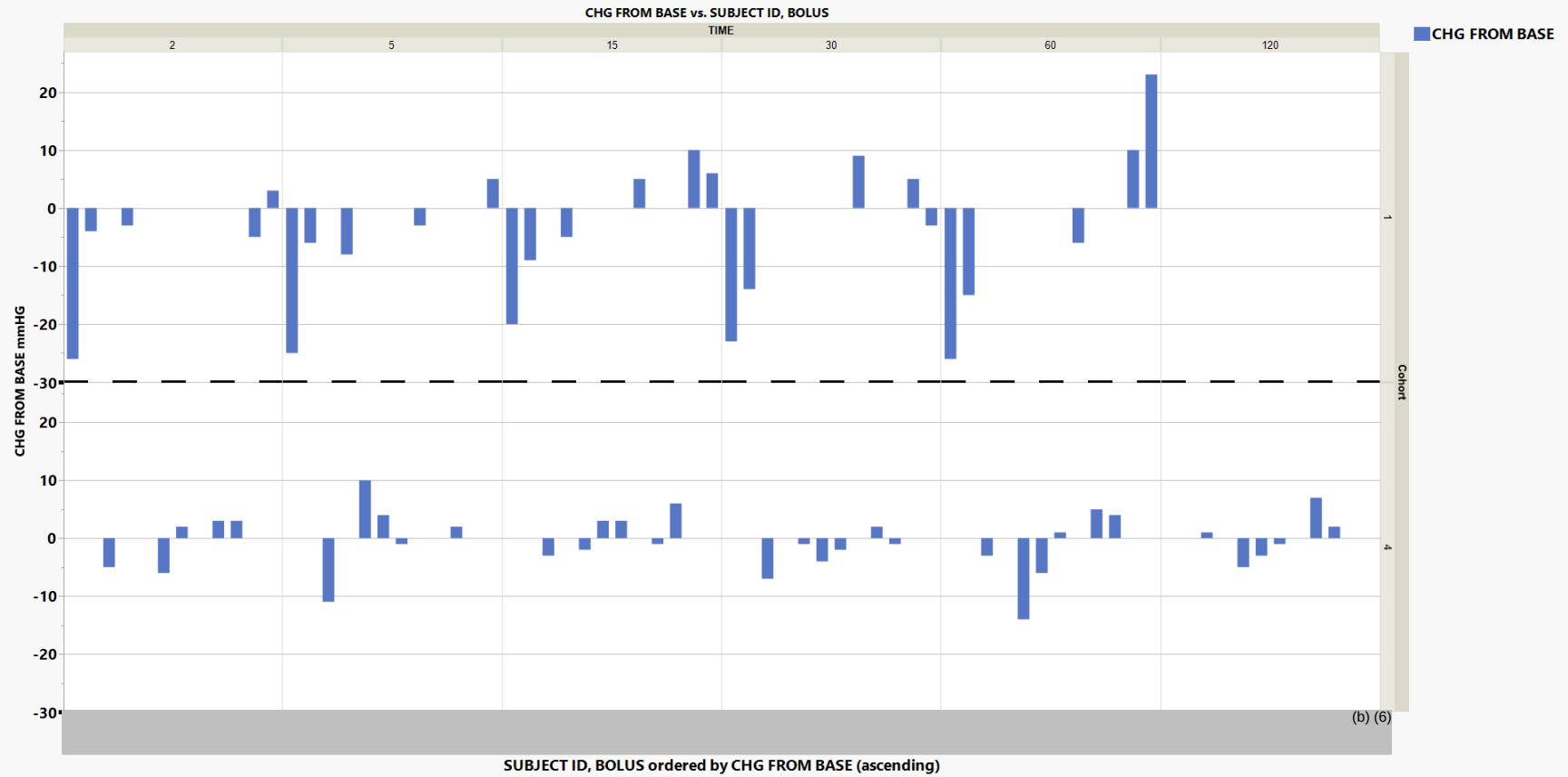
Reference ID: 4845026

Figure 15 Study EP0065 Cohort 4 *(1 month to <2 years)*, **Bolus Compared to 15 Minute Infusion, SBP Change from Baseline by Post Treatment Time (15 min Infusion= upper panel, Bolus = Lower Panel)**



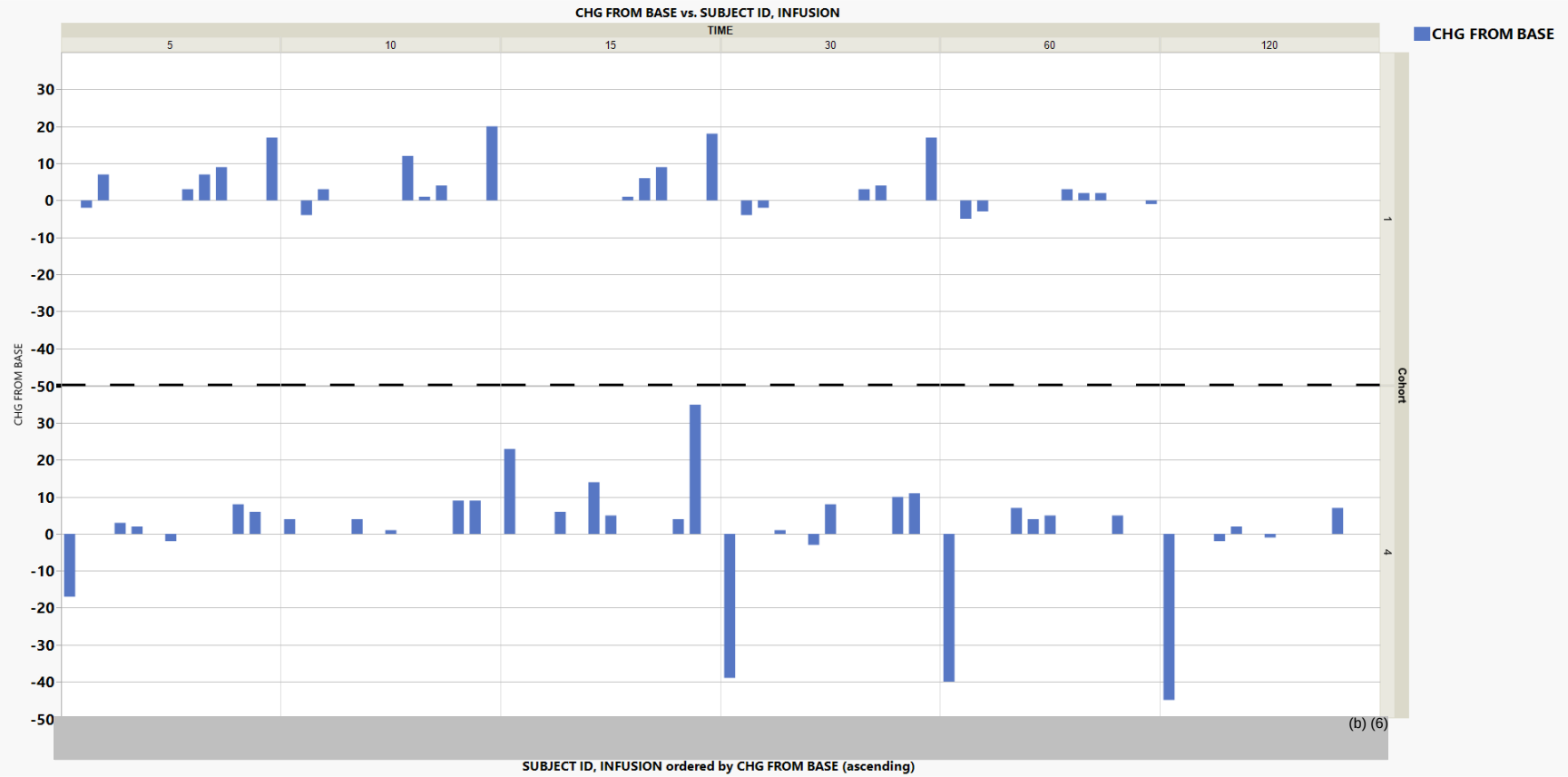
Reference ID: 4845026

Figure 16 Study EP0065 Cohort 1 (*≥12 to <16 years*) & 4 (*1 month to <2 years*), Bolus, SBP Change from Baseline by Post Treatment Time (Cohort 1= upper panel, Cohort 4 = Lower Panel)



Reference ID: 4845026

Figure 17 Study EP0065 Cohort 1 (*≥12 to <16 years*) & 4 (*1 month to <2 years*), 15-minute Infusion, SBP Change from Baseline by Post Treatment Time (Cohort 1= upper panel, Cohort 4 = Lower Panel)



Reference ID: 4845026

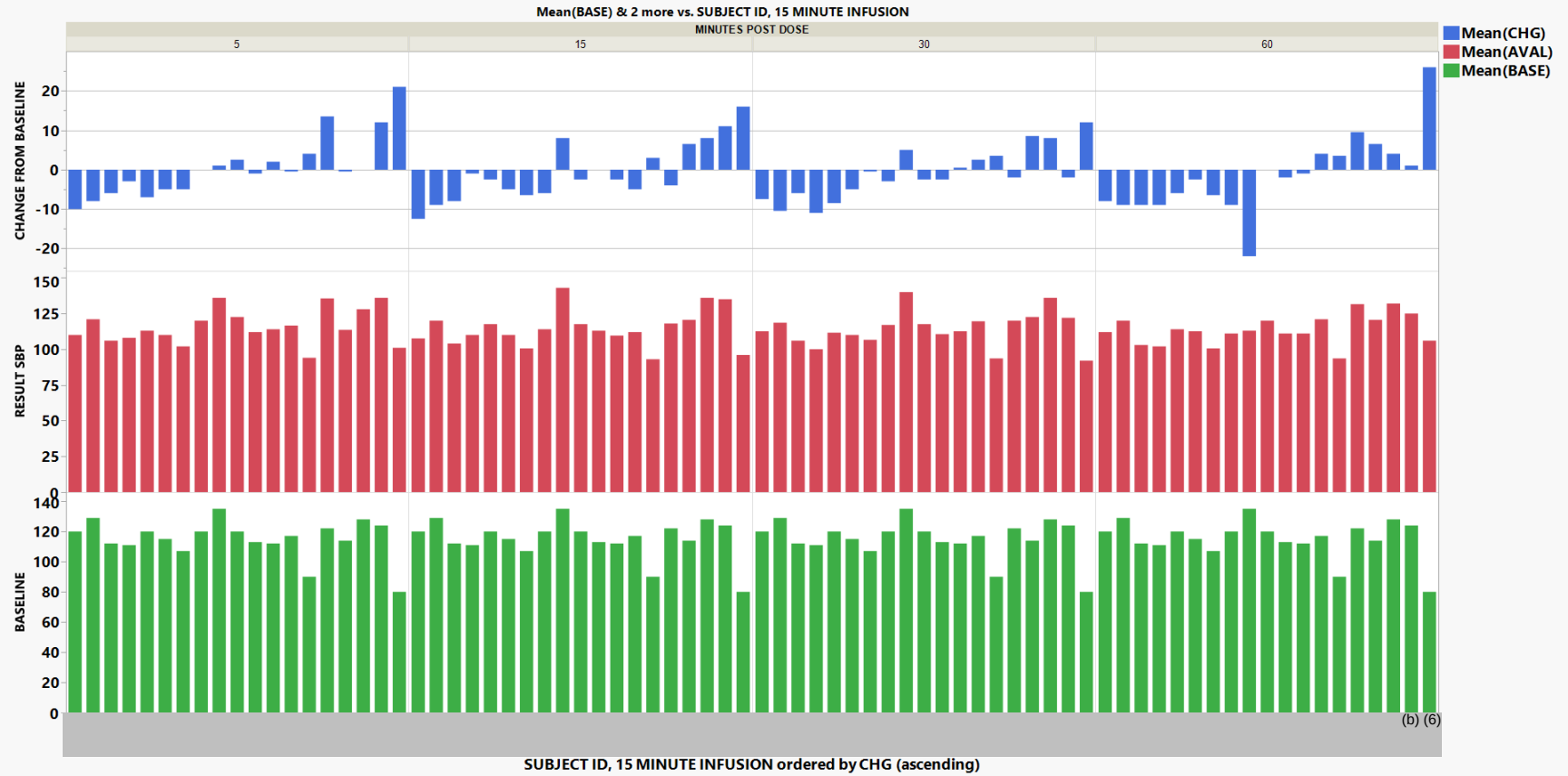
Table 28 Study EP0065 IV Brivaracetam in Pediatric Patients 2mo to < 16 years, SBP, Mean, SD, Median Change from Baseline by Time Post Infusion Start

Study EP0065	Time	N Rows	Mean (CHG- 15 MIIN INF)	Std Dev (CHG- 15 MIIN INF)	Median (CHG- 15 MIIN INF)
Infusion	5	25	0	8	2
	10	24	-1	10	0
	15	25	1	14	1
	30	26	-2	13	-1
	60	26	-6	12	-2.5
	120	6	-7	19	-0.5
Bolus	2	24	-2	9	0
	5	24	-2	9	-1
	15	24	-1	9	0
	30	24	1	9	-0.5
	60	24	0	11	1
	120	11	0	4	-1

Reference ID: 4845026

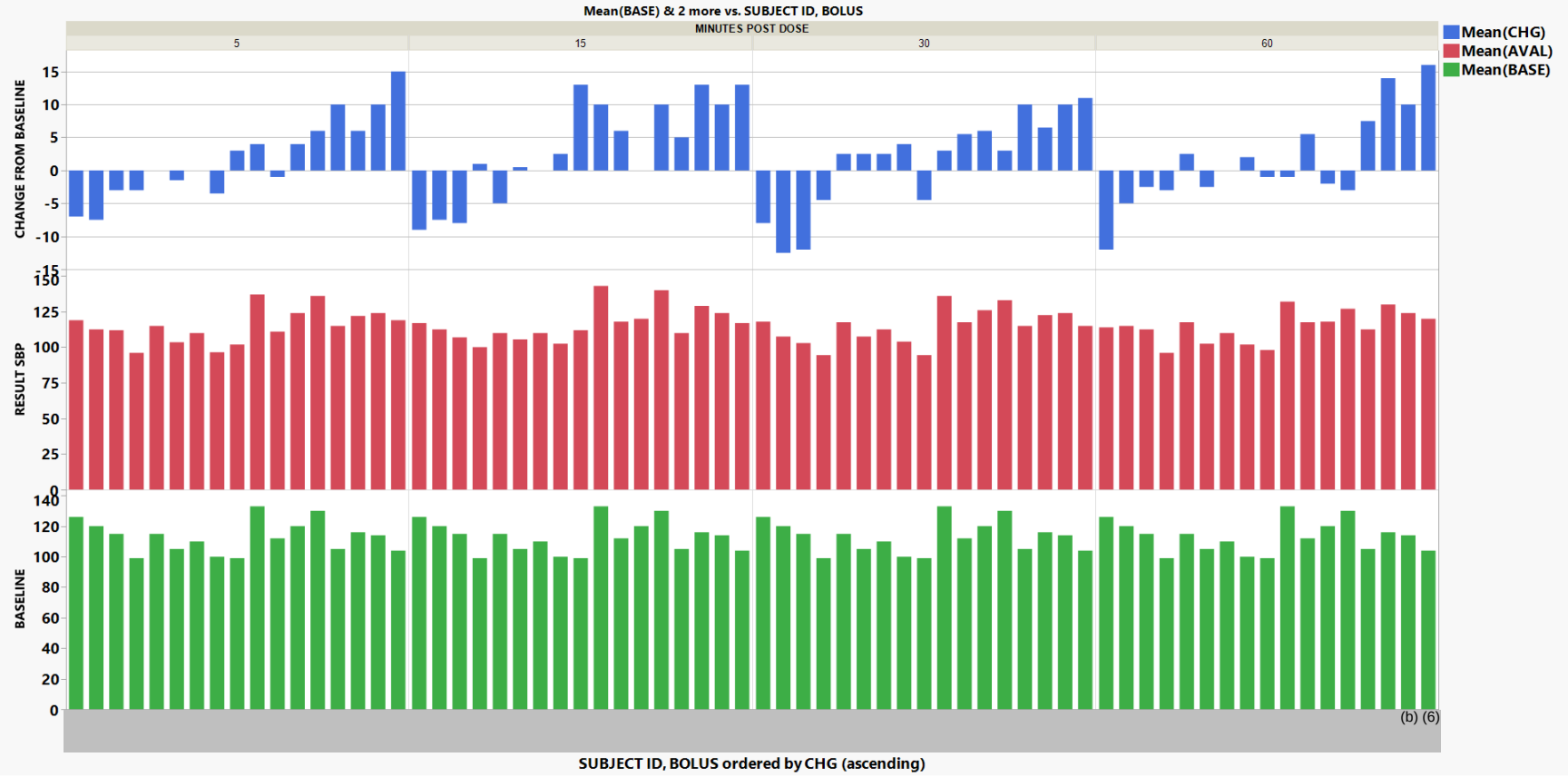
Study N01258 Analysis of Change from Baseline Compared to Baseline and Resulting SBP

Figure 18 Study N01258 (Adult <35 Years) SBP – Visit 3, 15 Minute Infusion Subset (n=19) with Baseline SBP, Resulting SBP and Change from Baseline at Time from IV Infusion Start (5, 15, 30, 60 minutes)



Reference ID: 4845026

Figure 19 Study N01258 (Adult, < 35 Years) SBP – Visit 3, Bolus Subset (n=17) with Baseline SBP, Resulting SBP and Change from Baseline at Time from IV Infusion Start (5, 15, 30, 60 minutes)



Reference ID: 4845026

Table 29 Study N01258 IV Brivaracetam in Adult Patients < 35 Years, SBP, Mean, SD, Median Change from Baseline by Time Post Infusion Start

Study N01258	infusion				
Infusion	MINUTES POST DOSE	N Rows	Mean (CHG)	Std Dev (CHG)	Median (CHG)
	5	37	0.5	8.8	0
	15	37	-0.9	8.8	-1
	30	37	-1.3	8.0	-2
	60	37	-1.0	9.9	0
Bolus	5	34	1.9	8.2	0
	15	34	3.2	9.7	3.5
	30	34	1.5	8.0	1.5
	60	34	1.5	9.1	1

Reference ID: 4845026

8.4. Financial Disclosure

Review of Financial Disclosure forms 3454 and 3455 reveals there was a single investigator (b) (4) in Study N01263 with disclosable financial interests. Examination of the patient subset less than 4 years old (the population of interest for this submission) does not identify any patient enrollment by this investigator. Examination of Study N1266 reveals 4 investigators with disclosable financial interests. From among these investigators there was a single patient ((b) (6)) with 21 TEAE entries over a span of 2028 days in 11 preferred terms enrolled by site (b) (4) who was in the study subpopulation < 4 years of age. A sub investigator (b) (4) at site (b) (4) had disclosable financial interests. This study was not an efficacy study but a long-term safety study. The TEAE frequency and composition does not suggest a bias toward altered AE reporting. The single patient would not significantly influence assessment of safety. There were no investigators in Study EP0065 with disclosable financial interests.

Reviewer Comment: The single site where a subinvestigator that had disclosable financial interests contributed one patient to the safety dataset. There is no evidence of altered AE reporting identified for this patient. There is no evidence that this single patient associated with site (b) (4) where a subinvestigator had disclosable financial interest had an influence on the overall safety analysis of Study N01266.

Covered Clinical Study (Name and/or Number): N01263

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 (no patient enrollment in the subpopulation of interest)		
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: _____		

Reference ID: 4845026

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

Covered Clinical Study (Name and/or Number): N01266

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 318		
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): 4		
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: - no potential impact, see associated discussion in Section 8.4 narrative & Reviewer Comment	Yes ☐	No ☒ (Request information from Applicant)

Reference ID: 4845026

Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): EP0065

Was a list of clinical investigators provided:	Yes ☐	No ☒ (Request list from Applicant)
Total number of investigators identified: 0		
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): 0		
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: N/A	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: N/A	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

Reference ID: 4845026

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/s/

STEVEN T DINSMORE
08/20/2021 01:52:33 PM

PHILIP H SHERIDAN
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