31 May 2018
EMA/472006/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Briviact

International non-proprietary name: brivaracetam

Procedure No. EMEA/H/C/003898/II/0010/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADHD attention deficit hyperactivity disorder

ADR adverse drug reaction

AE adverse event

AED antiepileptic drug(s)

BRIEF Behaviour Rating Inventory of Executive Function®

BRIEF-P Behaviour Rating Inventory of Executive Function®-Preschool Version

BRV brivaracetam, BRIVIACT®

CBCL Child Behaviour Checklist

CBZ carbamazepine

CI confidence interval

CL clearance

CSR clinical study report

CYP cytochrome-P

EMA European Medicines Agency

FDA Food and Drug Administration

HSS/DRESS hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms

ILAE International League Against Epilepsy

IQ intelligence quotient

IR incidence rate

ISS Integrated Summary of Safety

iv intravenous

LEV levetiracetam

LTFU long-term follow-up

PB phenobarbital

PD pharmacodynamics(s)

PIP Paediatric Investigational Plan

PK pharmacokinetic(s)

POS partial-onset seizures

PT Preferred term

RR relative risk

SAE serious adverse event

SD standard deviation

SmPC Summary of Product Characteristics

SOC System Organ Class

SUDEP sudden unexplained death in epilepsy

SV2A synaptic vesicle protein 2A

TEAE treatment-emergent adverse event

ULD Unverricht-Lundborg disease

VPC Visual predictive check

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, UCB Pharma S.A. submitted to the European Medicines Agency on 26 June 2017 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type IB	I
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB
B.IV.1.a.1	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	Type IAin	IIIA

Extension of Indication to include adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy of 4 years of age and older for Briviact. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated.
In addition, the Marketing authorisation holder (MAH) proposed to add a 5ml oral syringe and adaptor in the oral solution (10mg/mL) presentation for the paediatric population.

The Package Leaflet and Labelling are updated in accordance.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0048/2017 on the agreement of a paediatric investigation plan (PIP) and the granting of a partial waiver.

At the time of submission of the application, the PIP P/0048/2017 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC)

No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Daniela Melchiorri

Timetable	Actual dates
Submission date	26 June 2017
Start of procedure:	15 July 2017
CHMP Co-Rapporteur Assessment Report	14 September 2017
CHMP Rapporteur Assessment Report	12 September 2017
PRAC Rapporteur Assessment Report	13 September 2017
PRAC members comments	20 September 2017
Updated PRAC Rapporteur Assessment Report	21 September 2017
PRAC Outcome	28 September 2017
CHMP members comments	2 October 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	6 October 2017
Request for supplementary information (RSI)	12 October 2017
CHMP Rapporteur Assessment Report	26 February 2018
PRAC Rapporteur Assessment Report	8 February 2018
PRAC members comments	28 February 2018
Updated PRAC Rapporteur Assessment Report	1 March 2018
PRAC Outcome	8 March 2018
Updated CHMP Rapporteur Assessment Report	16 March 2018
Request for supplementary information (RSI)	22 March 2018
PRAC Rapporteur Assessment Report	5 May 2018
PRAC members comments	7 May 2018
PRAC Outcome	17 May 2018
Updated CHMP Rapporteur Assessment Report	21 May 2018
Opinion	31 May 2018

2. Scientific discussion

2.1. Introduction

Brivaracetam displays a high and selective affinity for synaptic vesicle protein 2A (SV2A) in the brain. Binding to SV2A is believed to be the primary mechanism for BRV anticonvulsant activity.

Brivaracetam was first approved in January 2016 by the EMA as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adult and adolescent patients from 16 years of age with epilepsy.

Three pharmaceutical formulations are available:

- Film coated immediate-release tablets (strengths: 10mg, 25mg, 50mg, 75mg and 100mg)
- Solution for injection/infusion (10mg/mL)
- Oral solution (10mg/mL)

Brivaracetam is approved for use at doses between 50 and 200 mg/day. In adults, initial dose titration to an effective dose is not required for tolerability.

The scope of this variation is extension of the indication for brivaracetam (BRV) as adjunctive therapy for the treatment of partial-onset seizures (POS) down to 4 years of age in paediatric patients. Doses of 1mg/kg/day to 4mg/kg/day are proposed for the treatment of children and adolescents <50kg, the adult dose range is proposed for adolescents 50kg or greater. In addition, the Marketing authorisation holder (MAH) proposed to add a 5ml oral syringe and adaptor in the oral solution (10mg/mL) presentation for the paediatric population.

No clinical study data supporting the efficacy of BRV in children ≥4 to <16 years of age are included in this application. Previously submitted adult efficacy data of BRV as therapy for the treatment of POS in adults is referred. Pharmacokinetic (PK) modelling and the bridging of clinical evidence support the dosing recommendations to children with POS.

Efficacy extrapolation of adult data to the paediatric population was discussed with the Scientific Advice Working Party (SAWP) during the 2011 EMA Scientific Advice procedure (EMEA/H/SA/1570/3/2011/PED/II) for Vimpat.

The BRV Paediatric Investigational Plan (PIP) (EMEA-000332-PIP01-08) included a systematic review of the literature of all published trials focusing on the possibility of extrapolating efficacy from adults to paediatric patients with POS .

2.2. Quality aspects

Quality variation of this Grouped variation application: Type 1Ain B.IV.1a.1: Addition of a 5 ml oral syringe dosing device to accommodate smaller volumes

Introduction

The available approved formulations of Briviact are film-coated tablets of the 10 mg, 25 mg, 50 mg, 75 mg and 100 mg strengths; Oral solution 10 mg/ml; Solution for injection/infusion 10 mg/ml.

In connection with the Type II variation application for extension of the indication from adults and

adolescents from 16 years old, to include children from 4 years of age, the Applicant wishes to introduce an additional oral dosage syringe of 5 ml. This is to provide for the accurate administration of the oral solution in the target age group. A CE-marked 10 ml oral syringe is already approved for use with the oral solution. A syringe adaptor for the product bottle is also utilised, the same adaptor is used for the 5 ml syringe as for the approved 10 ml syringe.

To support the introduction of the 5 ml oral syringe, updated Module 3 sections have been provided.

The addition of the oral dosing syringe affects Section 6.5 of the SmPC of the Briviact oral solution and revision has been made to the product information.

No justifications as to the appropriateness of the available formulations for the paediatric population in line with the Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012 Rev.2 were provided in the original submission and this was requested. During the procedure adequate and acceptable justifications have been provided by the applicant.

2.2.1. Discussion on quality aspects

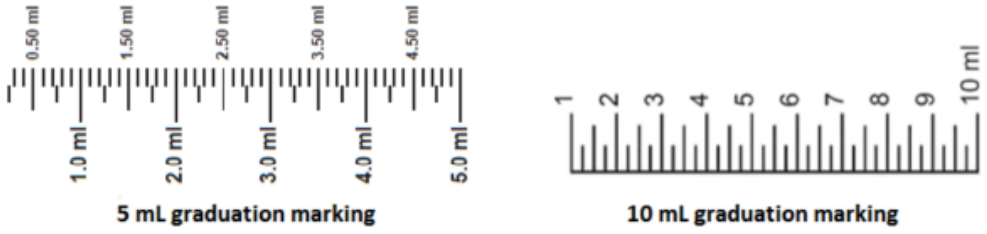
Oral dosing syringe

The 5 ml (and 10 ml) oral dosing syringes are classified by the manufacturer as Class I, non-sterile with measuring function, medical devices, according to Annex IX, rule number 5 of the Council Directive 93/42/EEC concerning medical devices as amended by Directive 2007/47/EC and have been CE marked according to Annex V of the European Directive 93/42/EEC concerning medical devices as amended by Directive 2007/47/EC.

The materials of the 5 ml syringe are the same as for the already approved 10 ml dose syringe (polypropylene barrel and high density polyethylene plunger). The syringe complies with Ph. Eur. 3.2.2 Plastic containers and closures for pharmaceutical use and EC regulations as laid down in the EEC Commission directive 2002/72 EEC (relating to plastic materials and articles intended to come into contact with foodstuffs) and amendments for plastic materials as well as regulatory requirements for food-contact materials. The identity of the plastic materials is verified by IR spectrometry. Drawings of the syringe components have been provided.

The 5 mL dosing syringe has graduations from 0.3 mL to 5.0 mL (3 mg to 50 mg) in 0.1 mL (1 mg) intervals and from 0.25 mL to 5.0 mL (2.5 mg to 50 mg) in 0.25 mL (2.5 mg) intervals and the 10 ml syringe has graduations from 1 mL to 10 mL (10 mg to 100 mg) in 0.25 mL (2.5 mg) intervals

Figure 1–1: Graduation Markings of the 5 mL and 10 mL Syringes



During the procedure the applicant was requested to provide a sample of the 5 ml syringe for the assessment of the graduation markings. Two separate scales are marked on the device (one side with 0.1 ml increments and the other side with 0.25 ml increments) and it was not evident that

these are sufficiently clear to interpret for the user. The Applicant has in his response provided a sample of the 5 ml syringe. The markings were considered by the CHMP sufficiently clear and acceptable.

Dose accuracy

The CHMP considers that the dosing accuracy of the 5 ml oral syringe has been acceptably demonstrated and the syringe complies with the requirements of Ph Eur 2.9.27 Uniformity of mass of delivered doses from multi-dose containers. The following volumes were tested: 0.25 ml, 2.5 ml and 5 ml. Also the 10 ml oral syringe has shown compliance for dose accuracy at 1.0 ml, 5.0 ml and 10.0 ml.

Doses of the oral solution

In children, the dose is defined based on the patient's weight. The 10 mL dosing syringe is however not considered a sufficiently accurate dosing device for administration of Briviact 10mg/mL oral solution in children aged between 4 and 16 years of age weighing less than 20 kg. Therefore, UCB would like to introduce a 5mL plastic syringe dosing device to allow accurate dosing of Briviact 10mg/mL oral solution in the youngest paediatric population proposed in this application.

The 5 mL plastic syringe dosing device will be presented as an additional dosing device and will not replace the currently approved 10 mL dosing syringe. Initially, the intention was to provide the 5 ml oral syringe and the 10 ml oral syringe in different package presentations, The 5 mL plastic syringe would have been the dosing device for the Briviact 10 mg/mL oral solution package for treatment of children weighing less than 20 kg and the 10 mL dosing syringe would remain the dosing device for the 10 mg/mL oral solution package for treatment of adults and adolescents and children weighing 20 kg or more.

The CHMP considered that two different presentations of the oral solution – one with a 5 ml oral syringe and another with a 10 ml syringe – are not appropriate and therefore both syringes should be available in all packages with the bottle of 300 ml product. This would, for example avoid the risk of dispensing the wrong presentation (not containing the age appropriate syringe) at the pharmacy. Also, the placement of both the oral dosing syringes within the same pack would result useful especially for borderline weighed children, thus warranting to reduce the risk of dosing errors while providing the patients with the opportunity to adequately choose the correct device, according to the clinician's prescription. Therefore, the CHMP concluded that only one 300mL pack of oral solution containing both dosing devices (5mL and 10mL syringes) should be marketed.

In addition, section 6.5 of the SmPC for the oral solution was revised: "or" should be replaced with "and" in order to indicate that both syringes should be packaged into each carton.

Suitability of formulations for the paediatric population 4-16 years of age

The Applicant has justified the levels of the various excipients. The amount of preservative was minimised whilst still maintaining adequate preservation. The amounts of other excipients are below the levels recommended in relevant EU guidance. The palatability of the oral solution in paediatric patients has been adequately addressed.

2.2.2. Conclusion on the quality aspects

The CHMP considers that the dosing accuracy of the 5 ml oral syringe has been acceptably demonstrated. The palatability of the oral solution in paediatric patients has been adequately addressed therefore the formulation is considered suitable for the paediatric population 4-16 years of age.

2.3. Non-clinical aspects

No new non-clinical pharmacology, pharmacokinetics or toxicology data have been submitted to support the extension of indication to include adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy 4 years of age and older for Briviact. This was considered acceptable by the CHMP.

2.3.1. Introduction

In the initial MAA (EMEA/H/C/003898, 2016), Briviact was approved in the same indication in patients from 16 years of age.

Juvenile toxicity studies were included in the initial MAA of Briviact and are briefly summarized in section 2.3.2.

An updated ERA has also been submitted. The updated ERA includes a new water sediment degradation study as requested by the CHMP and accounts for the extension of indication to include paediatric populations.

2.3.2. Toxicology

No new non-clinical toxicology data was submitted by the MAH. A summary of juvenile toxicity data included in the initial MAA of Briviact (EMEA/H/C/003898) originating from the EPAR is presented below:

Juvenile toxicity studies

Juvenile rats and dogs were evaluated from postnatal day 4 to 70 and 4 to 276, respectively, corresponding to neonatal to early (0 to 12 years) and adolescent (12 to 18 years) stages of development in humans.

Juvenile rats were dosed by oral gavage at 150, 300 and 600 mg/kg between postnatal day 4 to 70, followed by a 30-day recovery period. The main findings were lower absolute brain weights, -5.2% to -11.4% at 600 mg/kg in males and females on postnatal days 22, 71 and 100, corresponding with shorter brain length and width. At 150 mg/kg and 300 mg/kg, the lower absolute brain weights were of lesser amplitude (-0.1% to -6.5%). There were no relevant differences in relative brain weights between control and treated groups and there was no histopathology observed at any dose. In addition, there were no adverse effects in any of the behavioral tests performed, apart from a slightly increased startle response on postnatal day 78 in males and females in the high-dose group. An additional study in rats at postnatal days 22, 71 and 100 showed that mean absolute and relative (to final body weight) brain weights were similar within sexes in untreated animals on the three days studied. The percentage of variation between maximum and minimum absolute brain weight values within the three evaluation ages ranged from -12% to -26% for males and from -14% to -19% for females. Thus, the differences seen in the brivaracetam treated juvenile rats were within the range of differences seen inter-individually at the same developmental ages in untreated rats.

Reversible centrilobular hepatocellular hypertrophy, accompanied with higher liver weights, was observed in both sexes. The size and number of hyaline droplets in the kidneys of males given 300 mg/kg or 600 mg/kg increased on postnatal day 71, a finding that was no longer present on postnatal day 100. The hyaline droplets were considered a male rat-specific change. Lower prostate weight in males given 600 mg/kg, only on postnatal day 71, was without concurrent histological findings. All the findings in the liver and kidney were also seen in repeat-dose toxicity studies in adult rats. The NOAEL for rat pup growth and development, including CNS development,

was set at 150 mg/kg in females and 300mg/kg in males, giving exposure margin to maximum human exposure of 4. The NOAEL for reproductive toxicity was 600 mg/kg, giving an exposure to maximum human exposure of 10. Exposure margins in adult rats, based on NOAEL and AUC values derived from the main repeat-dose toxicity study, generate a margin to clinically relevant exposure of approximately 5 to 8.

In addition to studies in rats, juvenile dogs were dosed by oral gavage at 15, 30 and 100 mg/kg between postnatal day 4 to 276 (9 months duration), followed by a 56-day recovery period. The main findings concerned a partially to fully reversible decrease in thyroid hormone T4 level, seen mainly in females given 100 mg/kg. At the same dose, changes in the liver parameters were noted, as well as brown pigment accumulation (most likely porphyrin), centrilobular and periportal fibrosis, bile duct hyperplasia, hepatocellular hypertrophy and degeneration, associated with higher liver weights and concretion in the gall bladder. The effects on the liver were partially or fully reversible, apart from the brown pigment accumulation and concretion in the gall bladder. A reversible decrease in thymus weight in females was also seen and was accompanied by a slight increase in severity of thymic atrophy. All the findings in the liver, thyroid and thymus were also seen in repeat-dose toxicity studies in adult dogs. In another study in juvenile dogs, the pups were dosed at 15, 50 and 100 mg/kg between postnatal days 4 to 31. In males only, a lower bone mineral content, bone area and bone mineral density in femur was seen, as well as a shorter femoral length, lower bone mineral content and density in L3-L5 lumbar vertebral column. However, these effects were not seen in the longer duration, main 9-month study in juvenile dogs using the same dosage regimen. The NOAEL for dog pup growth and development, including CNS development, was set at 30 mg/kg, giving no margin to maximum human exposure. Similarly, in adult dogs, based on NOAEL and AUC values derived from the pivotal repeat-dose toxicity study, no margin was observed to clinically relevant exposure.

2.3.3. Ecotoxicity / environmental risk assessment

An Environmental Risk Assessment (ERA) was submitted in the initial MAA of Briviact (EMEA/H/C/003898). As summarized in the EPAR, brivaracetam is not readily biodegradable and is not expected to bioaccumulate in aquatic systems. Furthermore, brivaracetam does not persist in water-sediment systems, and is degraded to one extractable metabolite and several polar metabolites. Overall, the CHMP concluded that brivaracetam is unlikely to represent a risk to the environment under the proposed conditions of use. However, the CHMP recommended that the water sediment degradation study be repeated and additional information on the identity of metabolites appearing at a concentration higher than 10% in the total water-sediment system at one or more sampling points be submitted post-authorization. As part of this procedure, a new water sediment degradation study (OECD 308, GLP) has been submitted and the ERA has been updated to account for the extension of indication to include paediatric populations.

Phase 1

PREDICTED ENVIRONMENTAL CONCENTRATIONS (PEC)

Surface water

In the original ERA, a predicted environmental concentration (PEC) for surface water of 1 µg/L was determined using the following equation, and based on the maximum daily dose of 200 mg and default values for F_{PEN}, $WASTEW_{INH}$ and Dilution.

$$PEC_{SURFACE\ WATER} = \frac{Dose_{A.I.} * F_{PEN}}{WASTEW_{INH} * Dilution}$$

In the new indication for the use of brivaracetam in paediatric indications, the maximum daily dosage has not changed (200 mg for adults and children).

The share of brivaracetam in the total paediatric population is estimated to be in the range of 0.02 to 0.03% across various European Union Member States in the peak use year of 2025 (UCB internal information). Assuming that brivaracetam is the only drug used for paediatric epilepsy treatment, a refined F_{PEN} can be estimated as follows:

$$F_{PEN} = P_{REGION} \times \frac{T_{TREATMENT} \times n_{TREATMENT,P}}{N_D}$$

Where:

F_{PEN}: Market penetration factor,
P_{REGION}: Prevalence in the region (average),
$T_{TREATMENT}$: Duration of one treatment period (assumed to be 365 days/year for a conservative estimate),
$n_{TREATMENT,P}$: Number of treatment periods per year (since the treatment is assumed to continue throughout the year, this is considered to be 1),
ND: Number of days per year

Hence, F_{PEN} = 0.03 x 365 x 1/365 = 0.03% considering only the paediatric population. The value is lower if total population is taken into account, knowing that on average children of 0 to 14 years old represent 13 to 22% of the total population in the EU-28 (Eurostat: http://ec.europa.eu/eurostat/ statistics-explained/index.php/Population_structure_and_ageing). Given the above estimations, the additional indication is therefore not expected to impact the default F_{PEN} value of 0.01 previously used for the $PEC_{Surface\ water}$ calculation. F_{PEN} can therefore be kept at 0.01.As a consequence, the existing $PEC_{Surface\ Water}$ of 1 µg/L remains valid.

Environmental fate – follow-up water-sediment study

A second water sediment study was performed in 2016-2017 in accordance with OECD Guideline 308. The environmental fate and transformation of (^{14}C)-labelled brivaracetam was studied in two natural water-sediment systems maintained under aerobic conditions at 20 ± 2°C, in the dark, over a period of 100 days. The substance was applied at 10 µg/vessel (0.07 µg/L), a rate chosen to provide adequate analytical sensitivity. The characteristics of the two systems were as follows:

Sediment	pH ($CaCl_2$)	OC %	Sand[1] %	Silt[1] %	Clay[1] %	Classification[1]	Biomass (µg C/g sediment)
Calwich Abbey (CA)	7.2	5.1	34	57	9	Silt loam	1581
Swiss Lake (SL)	5.3	3.0	75	13	12	Sandy Loam	556

[1] USDA Particle Size Distribution and Classification; OC = organic carbon

Water	pH (at sampling)	TOC (mg/L)	Suspended solids (mg/L)
Calwich Abbey	8.2	6.5	9
Swiss Lake	6.8	11.2	5

TOC = total organic carbon

The degradation rates of (^{14}C)-brivaracetam from the total system (water and sediment) and the dissipation rates of (^{14}C)-brivaracetam from the water and sediment phases were determined using single first-order (SFO) and best fit kinetics. A water sample and a sediment extract from each system were analysed by LC-MS to confirm the presence of brivaracetam, UCB1148379 and 4-propylpyrrolidine-2-one.

For the present study, an extensive range of state of the art techniques was therefore employed during method development and in the main test to improve recovery. However, despite all reasonable efforts, it was not possible to improve the mass balance of some samples. This suggests that the losses were an inevitable result linked to the chemical characteristics of the parent compound and its degradation pathway.

A significant amount of applied radioactivity (AR) remained unextracted in the sediment (up to 61.5% of AR at 100 days, Swiss Lake system). Several additional extraction procedures were performed on the 100 day samples to analyze the type of bound residues. Only with bound residue fractionation it was possible to extract an unknown component with 4.9% (Calwich Abbey, CA) and 45.5% (Swiss Lake, SL) of applied radioactivity in the Fulvic acid fraction. This fraction was analyzed by HPLC and LC-MS, comparing the results to the reference substance. The results of the study are summarized below:

Distribution of AR: The biomass values were > 800 µg C/g sediment at the end of the incubation period, therefore the systems were considered viable throughout the incubation phase. The recovery and distribution of radioactivity in the systems are shown in Table 1. . For both systems, radioactivity decreased from the water layers from 97 to <80% within 7 days, with further decreases to 4.5 (CA) and 3.6% (SL) after 100 days. At the same time, the amount of radioactivity trapped as $^{14}CO_2$ in the NaOH traps increases to 54 (CA) and 56% (SL) after 100 and 61 days. The recovery of radioactivity in the sodium hydroxide traps for Swiss Lake sediment at 100 DAT was lower than at 61 days. Although this is unusual, examination of the chromatography results confirm that this had no effect on the calculation of degradation and dissipation rates.

Table 1. Recovery and distribution of radioactivity in the test systems

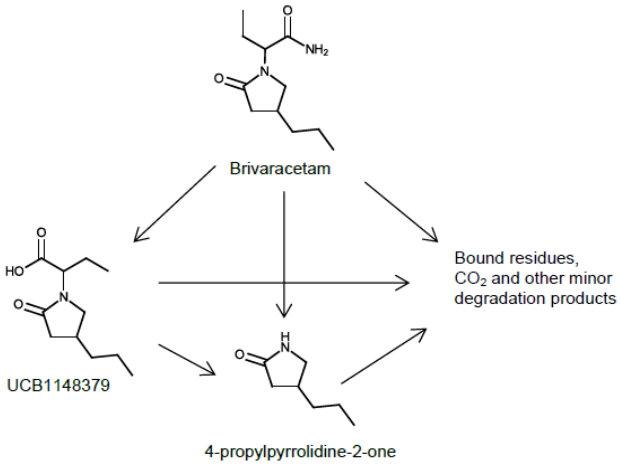
System	Sampling Time (DAT)	% Applied Radioactivity (AR) in						
		Surface Water	Sediment Extract	Unextracted from Sediment	Total in Sediment	NaOH Traps	Activated Charcoal	Mass Balance
Calwich Abbey, CA	0	96.8	2.2	ND	2.2	NA	NA	99.0
	7	78.0	16.0	2.5	18.4	0.3	ND	96.6
	14	64.5	21.2	5.8	26.9	1.8	0.1	93.2
	30	46.4	25.1	11.0	36.1	9.5	0.1	92.0
	61	16.8	17.4	18.4	35.7	36.9	ND	89.4
	100	4.5	8.2	19.6	27.8	54.3	ND	86.6
Swiss Lake, SL	0	96.9	1.5	ND	1.5	NA	NA	98.4
	7	70.9	12.8	7.4	20.2	2.4	ND	93.5
	14	45.9	11.0	15.7	26.7	10.0	0.2	82.7
	30	16.4	7.3	21.6	28.9	41.0	ND	86.2
	61	5.4	3.1	26.3	29.4	55.7	ND	90.5
	100	3.6	3.2	61.5	64.7	27.7	ND	95.9

NA = Not applicable; ND = Not detectable

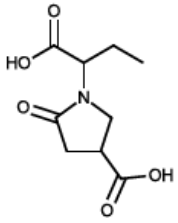
Radioactivity partially partitioned to the sediment up to 36.1% on 30 days (CA) and 64.7% on 100 days (SL), with bound residues of 19.6 (CA) and 61.5% (SL) on 100 days. The amount of volatile substances trapped in activated charcoal was negligible. On 61 and 100 days for Calwich Abbey and 14 and 30 days for Swiss Lake, the mass balances were below 90%.

Identification and quantification of brivaracetam and transformation products: Two metabolites with >10% of AR were detected by HPLC in surface water and sediment extract and were identified by LC-MS/MS in comparison to reference substances provided by the applicant. The metabolites were identified to be 4-propylpyrrolidin-2-one and UCB1148379, the butanoic acid degradant of brivaracetam. It was considered, based on chemical structures, that brivaracetam degrades to 4-propylpyrrolidine-2-one via UCB1148379, although direct transformation is possible. All these may

be slowly incorporated into unextracted sediment residues and/or mineralised to carbon dioxide. With CO_2 production of 54.3% AR (CA, DAT 100) and 55.7% AR (SL, DAT 61), mineralisation is the main transformation route.



Sediment samples of the Calwich Abbey and Swiss Lake systems at 100 days were further analyzed by bound residue fractionation to identify main components of the bound residue if possible. An additional metabolite was recognized by HPLC with radioactive amounts of 4.9% (CA) and 45.5% (SL). The unknown component present in the Swiss Lake Fulvic acid extract was analysed by LC-MS/MS. The accurate mass measurement of the ion gave the empirical formula $C_9H_{14}O_5N$ ($[M+H]^+$), with an error of 0.5 ppm. Based on the product ion spectrum for this component, it was postulated that this was the result of partial cleavage of the propyl side chain of UCB1148379 and subsequent formation of the carboxylic acid to give a dicarboxylic acid degradant. An authentic standard of this compound (UCB1147043) was provided by the Sponsor and analysed. The standard eluted at along with the minor peak in the radiochromatogram for the fulvic acid extract which also shows the same mass as the major peak. The product ion spectra of the authentic standard and component in the fulvic acid extract were consistent with major ions at m/z 170, 152, 113, 96, 85, 70 and 56 Da. Subsequent analysis of UCB1147043, the fulvic acid extract and UCB1147043 spiked into the fulvic acid extract did not show a shift of the [M-H]-ion to match the retention time of the major peak on the radio trace. It is likely, therefore, that the major component is an isomer of UCB1147043. As the unknown was only observed in the fulvic acid fraction, created by destruction of the soil matrix, it cannot be considered to be bioavailable.



UCB1147043

The detailed recoveries of brivaracetam, UCB1148379 and 4-propylpyrrolidine-2-one in the various test systems are shown in Tables 2 and 3. The results show that brivaracetam gradually dissipated from the systems down to 0.6 (CA) and 2.0% (SL). It partially shifted into the sediment with a maximum of 6.4 (CA) and 9.2% (SL) on 7 days. UCB1148379 was formed with maxima of 21.6% (CA) on 14 days and 6.0% (SL) on 7 days. It dissipated from the system to 0.2% (CA) and was not detectable (SL) on 100 days. The amount of 4-propylpyrrolidine-2-one increased with maxima of 55.7% (CA) at day 30 and 8.3% (SL) at 14 days and decreased to 7.5% in the CA system and was not detectable in the SL system at 100 days.

Table 2. Recoveries of brivaracetam, UCB1148379 and 4-propylpyrrolidine-2-one in the Calwich Abbey (CA) system (% of AR; mean values)

Time (DAT)	Brivaracetam			UCB1148379			4-propylpyrrolidine-2-one		
	Water	Sediment	Total	Water	Sediment	Total	Water	Sediment	Total
0	95.8	NA	95.8	ND	NA	ND	ND	NA	ND
7	52.7	6.4	59.1	13.6	6.8	20.3	11.4	2.6	13.9
14	10.9	2.4	13.3	13.3	8.3	21.6	33.7	10.3	44.0
30	1.2	0.1	1.3	5.3	4.8	10.1	35.6	20.0	55.7
61	1.2	0.5	1.8	ND	0.6	0.6	12.8	14.8	27.6
100	ND	0.6	0.6	ND	0.2	0.2	ND	7.5	7.5

NA = Not Applicable; ND = Not Detected (or <0.1% AR)

Table 3. Recoveries of brivaracetam, UCB1148379 and 4-propylpyrrolidine-2-one in the Swiss Lake (SL) system (% of AR; mean values)

Time (DAT)	Brivaracetam			UCB1148379			4-propylpyrrolidine-2-one		
	Water	Sediment	Total	Water	Sediment	Total	Water	Sediment	Total
0	96.0	NA	96.0	ND	NA	ND	ND	NA	ND
7	65.7	9.2	74.9	2.7	3.3	6.0	ND	ND	ND
14	34.0	5.5	39.5	1.4	3.7	5.0	6.6	1.7	8.3
30	14.7	0.9	15.6	1.6	3.7	5.3	ND	2.7	2.7
61	2.5	NA	2.5	0.8	NA	0.8	ND	NA	ND
100	2.0	NA	2.0	ND	NA	ND	ND	NA	ND

NA = Not Applicable; ND = Not Detected (or 0.1% AR)

Calculation of half-lives: The percent of applied radioactivity present as brivaracetam, UCB1148379 and 4-propylpyrrolidine-2-one were plotted against the time after treatment in days. Curves were constructed through appropriate data points using non-linear regression analysis to give lines of best fit. The degradation rates of the test substance, the parameters used to calculate them and parameter statistics were determined using CAKE version 2 software. In all cases, the values used for fitting were the experimentally derived, individual values from the two replicates per sampling interval. Degradation rates for brivaracetam, UCB1148379 and 4-propylpyrrolidine-2-one are shown in Tables 4 and 5. The half-life values of brivaracetam in water were 7.49 (CA) and 10.8 days (SL) and in sediment 4.8 (CA) and 8.11 days (SL). For the total systems, the half-life values were calculated to be 8.06 (CA) and 12.7 days (SL). Taking into account the differences of water sediment systems, this correlates well with the results of the first water sediment study with $DT_{50,system}$ = 18.8/16.5 days.

According to ECHA recommendations, a surface water temperature of 12° C is considered representative for European surface waters. The Applicant was therefore asked to correct the OECD TG308-derived DT50-values from 20° C to 12° C using the Arrhenius equation, and evaluate the substance persistence to degradation in the ERA based on those values. The corrected OECD TG308-derived DT50-values taking into account a surface water temperature of 12°C, using the Arrhenius equation, are given in Table 4. and Table 5.

Table 4. Degradation rates at 20°C for brivaracetam, UCB1148379 and 4-propylpyrrolidine-2-one in the Calwich Abbey (CA) system (results with correlation coefficients r2 <0.6 are not included). **Values in parenthesis are calculated conversions to 12°C (Arrhenius equation)**

Phase	Parameter	Model	DT_{50}/days	DT_{90}/days	χ^2	r^2
Water	Brivaracetam	HS	7.49 (15.91)	14.8	2.60	0.9992
	UCB1148379		4.78 (10.16)	15.9	17.6	0.9076
	4-propylpyrrolidine-2-one		21.90 (46.53)	72.8	4.91	0.9524
Sediment*	Brivaracetam	SFO	4.80 (10.20)	15.9	14	0.9664
	UCB1148379		16.60 (35.27)	55.2	8.61	0.9136
	4-propylpyrrolidine-2-one		53.60 (113.88)	178	5.11	0.9703
Total system	Brivaracetam	HS	8.06 (17.12)	16.3	3.75	0.9984
	UCB1148379		5.86 (12.45)	19.5	19.2	0.9134
	4-propylpyrrolidine-2-one		25.90 (55.03)	86.1	4.50	0.9731

HS - hockey stick; SFO - Single First Order

Table 5. Degradation rates at 20°C for brivaracetam, UCB1148379 and 4-propylpyrrolidine-2-one in the Swiss Lake (SL) system (results with correlation coefficients r2 <0.6 are not included). **Values in parenthesis are calculated conversions to 12°C (Arrhenius equation)**

Phase	Parameter	Model	DT_{50}/days	DT_{90}/days	χ^2	r^2
Water	Brivaracetam	HS	10.80 (22.95)	31.8	6.67	0.9937
	UCB1148379		5.94 (12.62)	19.7	90	0.4188
	4-propylpyrrolidine-2-one		0.699 (1.49)	2.32	42.9	0.5077
Sediment	Brivaracetam	SFO	8.11 (17.23)	26.9	4.74	0.9671
Total system	Brivaracetam	HS	12.70 (26.98)	33.1	F5.6	0.9941
	UCB1148379		2.75 (5.84)	9.13	39.3	0.7118
	4-propylpyrrolidine-2-one		3.26 (6.93)	10.8	57.3	0.807

HS - hockey stick; SFO - Single First Order

Summary of main study results

Substance (INN/Invented Name): Brivaracetam (ucb 34714, (2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1H-pyrrol-1-yl] butanamide)			
CAS-number (if available): NA			
PBT screening		**Result**	**Conclusion**
Bioaccumulation potential log K_{ow}	OECD117	1.5 at pH=7	Potential PBT - No
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	logK_{ow}	N/A	not B
	BCF	N/A	not B

Persistence	DT_{50} or ready biodegradability	See OECD 301B and OECD 308	P
Toxicity	NOEC or CMR	See Phase II below	not T
PBT-statement :	The compound is not considered a PBT nor vPvB. However, a ready biodegradability test (see Phase II assessment) showed that it is not biodegradable, and hence should be considered persistent. In addition, the transformation product 4-propylpyrrolidine-2-one is persistent in the Calwich Abbey system.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	1	µg/L	>0.01 threshold -Yes
Other concerns (e.g. chemical class)	N/A	N/A	N/A
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 121	Koc = 20.9 mL/g	Max value: 10000
Ready Biodegradability Test	OECD 301B	<60% degradation over 10 days	Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = 14.1-15.1 days $DT_{50,\ sediment}$ = 14.3-21.2 days $DT_{50,\ whole\ system}$ = 16.5-18.8 days % shifting to sediment >10% after 14 days	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems, new study	OECD 308, new study	Brivaracetam: $DT_{50\ water,\ 12°C}$=15.91-22.95 days $DT_{50\ sediment,\ 12°C}$=10.20-17.23 days $DT_{50\ whole\ system,\ 12°C}$=17.12-26.98 days UCB1148379: $DT_{50\ water,\ 12°C}$=10.16-12.62 days $DT_{50\ sediment,\ 12°C}$=35.27 days $DT_{50\ whole\ system,\ 12°C}$=5.84-12.45 days 4-propylpyrrolidine-2-one: $DT_{50\ water,\ 12°C}$=1.49-46.53 days $DT_{50\ sediment,12°C}$=113.88 days $DT_{50\ whole\ system,\ 12°C}$=6.93-55.03 days % shifting to sediment >10% after 14 days	The transformation product 4-propylpyrrolidine-2-one is persistent in the Calwich Abbey system.

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	100	mg/L	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	100	mg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	10	mg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	100	mg/L	
Phase IIb Studies					
Sediment dwelling organism	OECD219	NOEC	100	mg/kg	*Chironomus riparius*

2.3.4. Discussion on non-clinical aspects

Assessment of paediatric data on non-clinical aspects

No new non-clinical pharmacology, pharmacokinetics or toxicology data have been submitted to support the extension of indication to include adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy 4 years of age and older for Briviact. In the initial MAA (EMEA/H/C/003898, 2016), Briviact was approved in the same indication in patients from 16 years of age.

The pharmacology, pharmacokinetics and toxicology of brivaracetam were investigated during the initial MAA of Briviact (EMEA/H/C/003898) and juvenile toxicity studies in rats and dogs were included. The absence of new data is therefore acceptable.

In the previously conducted studies, juvenile rats and dogs were evaluated from postnatal day 4 to 70 and 4 to 276, respectively, corresponding to neonatal to early (0 to 12 years) and adolescent (12 to 18 years) stages of development in humans.

The data from the non-clinical juvenile toxicity studies have not identified any new or unique risks with regard to the safety of brivaracetam in a juvenile population.

The findings are adequately reflected in the SmPC, and no further updates are considered necessary.

Environmental risk assessment

An updated ERA has also been submitted that includes a new water sediment degradation study as requested by the CHMP and accounts for the extension of indication to include paediatric populations.

Based on the assumptions and estimations presented, the Applicant´s conclusion that the additional indication is not expected to impact the default FPEN value of 0.01 previously used for the PECSurface Water calculation is agreed. FPEN can therefore be kept at 0.01, and consequently the existing PECSurface Water 1 µg/L remains valid. A Phase II of the ERA with environmental fate and effects analysis was performed in the initial MAA of Briviact. As outlined in the EPAR, Tier A analysis showed that brivaracetam was not readily biodegradable. It is not expected to bioaccumulate in aquatic systems. Brivaracetam is degraded in water-sediment system to one extractable metabolite and several polar metabolites. Predicted no effect concentrations (PNEC) were calculated including ground and surface water, microorganisms and sediment. The resulting PEC:PNEC ratios indicated that brivaracetam was unlikely to be a concern for the aquatic environment or for the sediment compartment. The PEC:PNEC ratio for microorganisms indicates that brivaracetam is unlikely to be a concern in sewage treatment works.

In the repeated OECD 308 study, the mean recovery of applied radioactivity was between 83 and 99% for all replicates. The first OECD 308 study also showed several results with low mass balances below the validity criterion of 90% AR. As an extensive range of techniques were employed to improve or prevent suboptimal recovery of radioactivity, this suggests that the losses were an inevitable result of the nature of the compound.

Low recoveries for the Swiss Lake system at 14 and 30 days were considered to be due a transient volatile compound lost during extraction procedures. Low recoveries for the Calwich Abbey system at the end of the test could have been due to loss of the same volatile component.

Brivaracetam degraded rapidly in the two water-sediment systems used with DT50 values of 8 and 13 days by biphasic kinetics (HS) at 20 ± 2°C. Brivaracetam also disappeared rapidly from the water phase and the DT50 values were 7 and 11 days, by HS kinetics.

Degradation occurred to UCB1148379 (maximum of 22% AR), 4-propylpyrrolidine-2-one (maximum of 56% AR), unextracted sediment residues (maximum 62% AR) and CO2 (maximum 56% AR), depending on the sediment system.

[14C]-Brivaracetam and its major transformation products are unlikely to persist or accumulate in natural water-sediment systems as they either degraded rapidly in or were lost from the test systems during the course of the study.

At the CHMP request, the applicant was asked to correct the OECD 308-derived DT50 values from 20°C to 12°C in agreement with ECHA recommendations and to evaluate the substance persistence to degradation in the ERA based on those values.

The requested corrections were provided. The data show that a transformation product of brivaracetam, 4-propylpyrrolidine-2-one, is persistent in one out of two water/sediment systems tested (i.e. Calwich Abbey system) and at the CHMP's request this was appropriately reflected in the updated ERA.

The CHMP agrees that based on the presented data the extension of indication does not significantly affect the environmental exposure to brivaracetam.

2.3.5. Conclusion on the non-clinical aspects

No new clinical data have been submitted to support the extension of indication to add a new indication as monotherapy in the treatment of partial-onset seizures with or without secondary generalisation in adult and adolescent (16-18 years) patients with epilepsy. The non-clinical data submitted and assessed in the original MAA (EMEA/H/C/000863) are considered adequate to support also the new indication. No updates in SmPC section 5.3 are needed.

Environmental risk assessment

Based on the updated data submitted in this application, the new/extended indication does not lead to a significant increase in environmental exposure further to the use of brivaracetam.

- Considering the above data, brivaracetam is not expected to pose a risk to the environment.

A transformation product of brivaracetam, 4-propylpyrrolidine-2-one, is persistent in one out of two water/sediment systems tested (i.e. Calwich Abbey system). The applicant updated the ERA to include this information.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

The BRV paediatric development program supporting the application for an indication in children ⩾4 years to <16 years of age, consists of 1 completed study (N01263) and 1 ongoing long-term safety study (N01266) (Pool Paediatric Studies), is summarized in Table 6. .

Table 6. Table 6. Phase 2/3 studies of BRV in paediatric subjects with epilepsy

Study number	Study description	Number of subjects receiving BRV		Maximum duration of treatment	Status
		Total	By age group: M/F		
N01263	Phase 2a, open-label, single-arm, multicenter, pharmacokinetic, safety, and efficacy study of adjunctive administration of BRV in subjects from ≥1mo to <16y old with epilepsy	99	≥1mo to <2y: 15/15 ≥2y to <12y: 26/25 ≥12y to <16y: 7/11	5 weeks	Complete
N01266	Phase 3, open-label, single-arm, multicenter, long-term, study to evaluate safety and efficacy of BRV used as adjunctive treatment in pediatric subjects with epilepsy	206	≥1mo to <2y: 12/13[a] ≥2y to <12y: 76/55[a] ≥12y to <17y: 27/23[a]	NA[b]	Ongoing

BRV=brivaracetam; CSR=clinical study report; F=female; M=male; mo=months; NA=not applicable; y=years
Note: N01266 was initially designed as a LTFU to N01263 (enrolled subjects with either partial-onset or generalized seizures), but was amended to allow direct enrollment of subjects with POS from ≥4 to <17 years of age with epilepsy.

No Phase III BRV controlled studies have been conducted in paediatric subjects with POS given that efficacy, as adjunctive treatment can be extrapolated from adult subjects with POS.

The following clinical pharmacology studies are included in this application in support of extrapolation:

- CL0187: A population PK study in paediatric subjects with POS
- CL0258: An exposure-response modeling study of BRV as adjunctive therapy in paediatric subjects with POS

The following modeling study was performed to support proposed BRV doses when used as iv injection/infusion:

- N01331: Population PK study to predict iv PK of BRV in the paediatric population (0 to <17 years of age)

Further support of the proposed paediatric indication is provided by updated safety data from 3 adult safety pools included in the original application Pool S4, Pool Monotherapy, and Pool Unverricht-Lundborg disease (ULD). No new subjects were added to these pools since the original application was reviewed; however, the clinical cutoff date for the current application provides data for approximately 2 years of additional exposure to BRV.

Phase 2/3 studies of adjunctive BRV (and LTFU) in subjects ⩾16 years of age with epilepsy

- LTFU studies of adjunctive BRV in subjects ⩾16 years of age with epilepsy

The studies of adjunctive BRV in subjects ⩾16 years of age with epilepsy included subjects from core studies N01114, N01193, N01252, N01253, N01254, N01358, and N01395; and LTFU studies N01125, N01199, N01372, and N01379. Of the 4 adult LTFU studies included in the original application, 3 remain ongoing (N01125, N01199, and N01379) and 1 (N01372) has been completed. Updated safety data (data cutoff date: 31 Aug 2016) from these 4 studies are included

in Pool S4.

- Studies of conversion to monotherapy in subjects ⩾16 years of age with epilepsy

Two conversion to monotherapy studies (N01276 and N01306) in 150 subjects ⩾16 years of age had been completed. One LTFU study (N01315) that enrolled 108 subjects was ongoing at the time of the original application. After the original application, 6 subjects originally enrolled in N01315 were transferred to LTFU study N01125 due to site closure. N01315 and N01125 both remain ongoing with no additional subjects enrolled since the original application.

- Studies in other indications: ULD

Studies in subjects with ULD included subjects from core studies N01187 and N01236, and LTFU study N01125. Updated safety data from the 94 subjects with ULD enrolled in the LTFU study N01125 were included in Pool ULD.

Lastly, postmarketing data from both adult and paediatric patients (data cutoff date: 14 Oct 2016), and literature as well as reference to previously submitted adult data are included in the application.

2.4.2. Pharmacokinetics in paediatric population

The PK of BRV has been investigated in paediatric subjects with epilepsy in one study (N01263). Brivaracetam plasma concentration data from this study were included in a population PK analysis (CL0187) to simulate BRV exposure after oral BRV using a weight-based dosing scheme. A summary of the PK and PK/PD modelling and simulation studies to support an indication for BRV as adjunctive therapy in the treatment of POS in paediatric patients ≥4 years of age with epilepsy is presented in Table 7. below.

Table 7. Summary of BRV PK and PK/PD modelling and simulation studies supporting paediatric adjunctive therapy

Study number	High-level objectives[a]	BRV study data included	Total number of subjects[b]
CL0187 (Amended report)	1) To develop a population PK model for BRV in pediatric patients 2) To perform simulations to provide pediatric dosing adaptations	N01263 (pediatric Phase 2a)	96
CL0258	1) To develop a combined population PK/PD model for LEV in pediatric and adult subjects, to assess the potential change in PK/PD relationship between adult and pediatric subjects 2) To use the obtained scaling in LEV PK/PD relationship from adult to pediatric subjects to predict the BRV efficacious dose in pediatric subjects based on the existing PK/PD model for BRV in adult subjects	N01252 (adult Phase 3) N01253 (adult Phase 3) N01358 (adult Phase 3) N01263 (pediatric Phase 2a)	1549 (adult) 96 (pediatric)
N01331	1) To develop a population PK model for BRV following iv administration 2) Combine the model/model parameters with CL0187 to predict the PK of BRV following iv administration in the pediatric population 3) To propose dose adaptation rules, if necessary, for iv administration in children 1m to <17 years of age	N01256 (adult Phase 1) N01263 (pediatric Phase 2a)	48 (adult) 95 (pediatric)

BRV=brivaracetam; iv=intravenous; LEV=levetiracetam; PK=pharmacokinetic; PK/PD=pharmacokinetic/pharmacodynamics
[a] Some objectives have been summarized to provide a high level overview; full objectives are provided in the study-specific descriptions below. For CL0187 and N01331, objectives specific to neonatal subjects are not included.
[b] The total number of subjects is the number of subjects with data included in the PK or PK/PD modeling and simulation study referenced.

The BRV dosing recommendations in adults and children, according to the Applicant, are summarised in Table 8. below.

Table 8. Summary of adult and paediatric BRV dosing adaptations

	Adults	Children ≥50kg	Children <50kg
Maximum recommended dose	200mg/day	200mg/day	4mg/kg/day
Therapeutic dose range	50 to 200mg/day	50 to 200mg/day	1 to 4mg/kg/day

Population PK modelling

Trial N01263 was an open-label, single-arm, multicenter, fixed 3-step up-titration study evaluating the PK, safety, and efficacy of BRV in children aged ≥ 1 month to <16 years. Brivaracetam oral solution was administered at weekly increasing doses of approximately 0.4mg/kg bid, 0.8mg/kg bid, and 1.6mg/kg bid for subjects ≥ 8 years of age and 0.5mg/kg bid, 1.0mg/kg bid, and 2.0mg/kg bid for subjects <8 years of age. The doses were to be capped at the adult doses of 25mg bid, 50mg bid and 100mg bid, respectively, for body weight (WT) ≥ 50kg.

A population PK model was developed for BRV in sparsely sampled paediatric patients (two to three samples per visit, with one visit for each of three dosing levels) using non-linear mixed-effects modelling. 600 BRV plasma concentration-time records were available in 96 paediatric patients with a balanced distribution of patient numbers aged 1 month to <2 years, 2 to <6 years, 6 to <12 years and 12 to <16 years age groups of 29, 26, 24 and 17 patients respectively.

Estimated body surface area-normalized glomerular filtration rate (eGFR) was calculated for paediatric patients using the Schwartz bedside equation:

eGFR (mL/min/1.73m2) = (36.2 × Height in cm) / Creatinine in µmol/L

Lean body weight (LBW) was calculated according to James formula:

LBW [kg] in males = 1.10 × weight[kg] – 0.0128 × BMI[kg/m2] × weight[kg]

LBW [kg] in females = 1.07 × weight[kg] – 0.0148 × BMI[kg/m2] × weight[kg]

Post-conceptional age (PCA) was only considered relevant for patients below 3 years; for all other patients, and for patients where PCA was missing, PCA was calculated as age (years) + 0.75.

A summary of the categorical and continuous covariates in the paediatric dataset available for testing in the analysis is provided in Table 9. , Table 10. and Table 11. , respectively.

Table 9. Co-medication intake (number of patients and percentage of total number of patients)

Co-medication	*N*	*%*
Carbamazepine	9	9.4
Phenytoin (PHT)	1	1.0
Phenobarbital or primidone	16	16.7
Inducer (CBZ, PHT and/or PB/PRM)	25	26.0
Valproate	49	51.0
CYP3A inhibitor*	2	2.1
CYP2C19 inhibitor*	7	7.3
AEDs:		
Absent or neutral*	19	19.8
Inducer*	14	14.6
Inhibitor*	37	38.5
Mixed*	26	27.1

* Specification on file. Appendix A.1 Report CL0187

Table 10. Race, ethnicity, sex and age distribution (number of patients and percentage of total number of patients)

Category	*N*	*%*
Caucasians	77	80.2
Blacks	4	4.2
Others	15	15.6
Hispanic or latino	18	18.8
Boys	47	49.0
Girls	49	51.0
1 month - <2 yrs.	29	30.2
2 yrs. - <6 yrs.	26	27.1
6 yrs. - <12 yrs.	24	25.0
12 yrs. - <16 yrs.	17	17.7
Preterm (<3 yrs.)	4	4.2
Total	96	100.0

Table 11. Overall summary of demographics

Variable	*Mean*	*SD*	*Median*	*Min*	*Max*	*N*
WT (kg)	24.2	16.17	18.9	3.9	75.0	96
LBW (kg)	20.0	12.42	16.8	3.6	53.8	96
eGFR (mL/min/1.73m^2)	114.4	33.05	112.6	49.0	218.1	96
Age (yrs.)	6.2	4.74	5.5	0.2	15.6	96

The final paediatric population PK model consisted of first order absorption, single compartment distribution and first order elimination components with allometric scaling of clearance and volume parameters using fixed theoretical allometric exponents. Residual error was modelled using a proportional error term. A step-wise covariate modelling procedure was used to determine factors influencing BRV clearance. The final model parameters are summarised in Table 12. including the adult PK parameter estimates, for comparison. In the paediatric model inter-individual variability were estimated on clearance (22.8 %CV), volume of distribution (16.7 %CV) and absorption (31.9 %CV), with shrinkage 6.1%, 45.6% and 73.4%, respectively. Model evaluations, presented as visual predictive checks are presented in Figure 1. , Figure 2. and Figure 3. .

Table 12. BRV population PK estimates: adult vs paediatric subjects

Parameter	Adults CL0028 Estimate (95% CI)	Children CL0187 Estimate (95% CI)
CL (L/h)	3.58 (3.50, 3.66)	3.63 (3.42, 3.85)
V (L)	48.1 (45.8, 50.4)	47.8 (43.1, 52.5)
Ka (1/h)	1.42 (1.26, 1.57)	1.84 (0.906, 2.78)
Exponent for weight on Cl	0.565 (0.499, 0.631)	0.750 Fixed
Exponent for weight on V	0.639 (0.483, 0.795)	1.000 Fixed
Effects on CL		
CBZ	34.8% (30.5, 39.2)	47.9% (27.8, 71.2)
PB	23.9% (15.0, 33.4)	40.8% (19.9, 65.2)
PHT	26.8% (20.0, 33.9)	No data
VPA	Not significant	-10.1% (-18.5, -0.81)
Residual error		
Residual error (CV, %)	20.7 (19.7, 21.7)	23.4 (19.6 ,27.1)

BRV=briveracetam; CBZ=carbamazepine; CI=confidence interval; CV=coefficient of variation; PB=phenobarbital; PHT=phenytoin; PK=pharmacokinetic; VPA=valproic acid

Figure 1. VPCs for BRV time profiles (run411). Left: linear y-axis, right: logarithmic y-axis. Red lines are the 5th, 50th (median) and 95th percentiles of the observed data and the light blue areas contain 95% of the simulated quantiles.

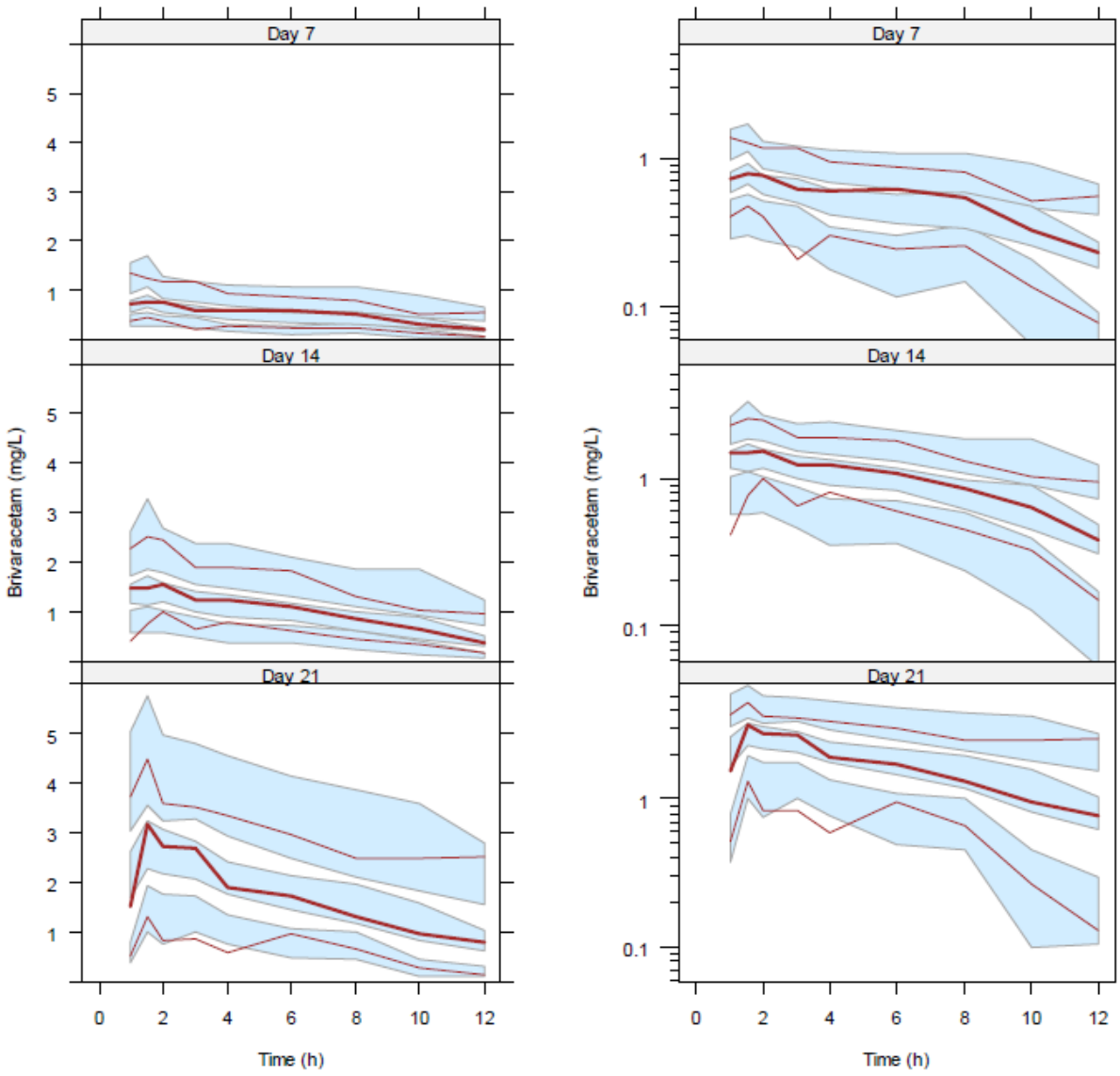


Figure 2. VPCs for BRV time profiles (run411) by age category and visit. Red lines are the 5th, 50th (median) and 95th percentiles of the observed data and the light blue areas contain 95% of the simulated quantiles.

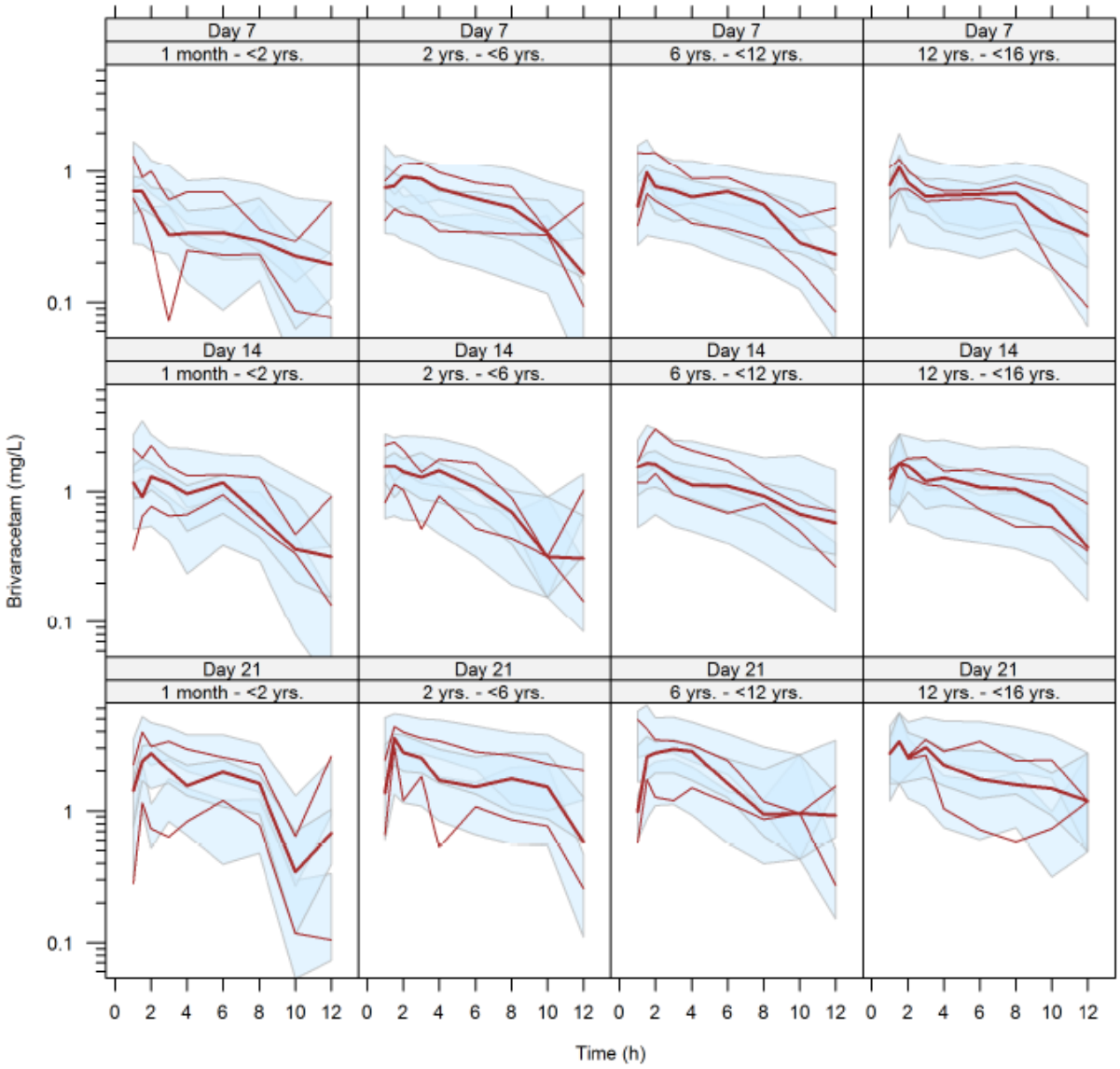
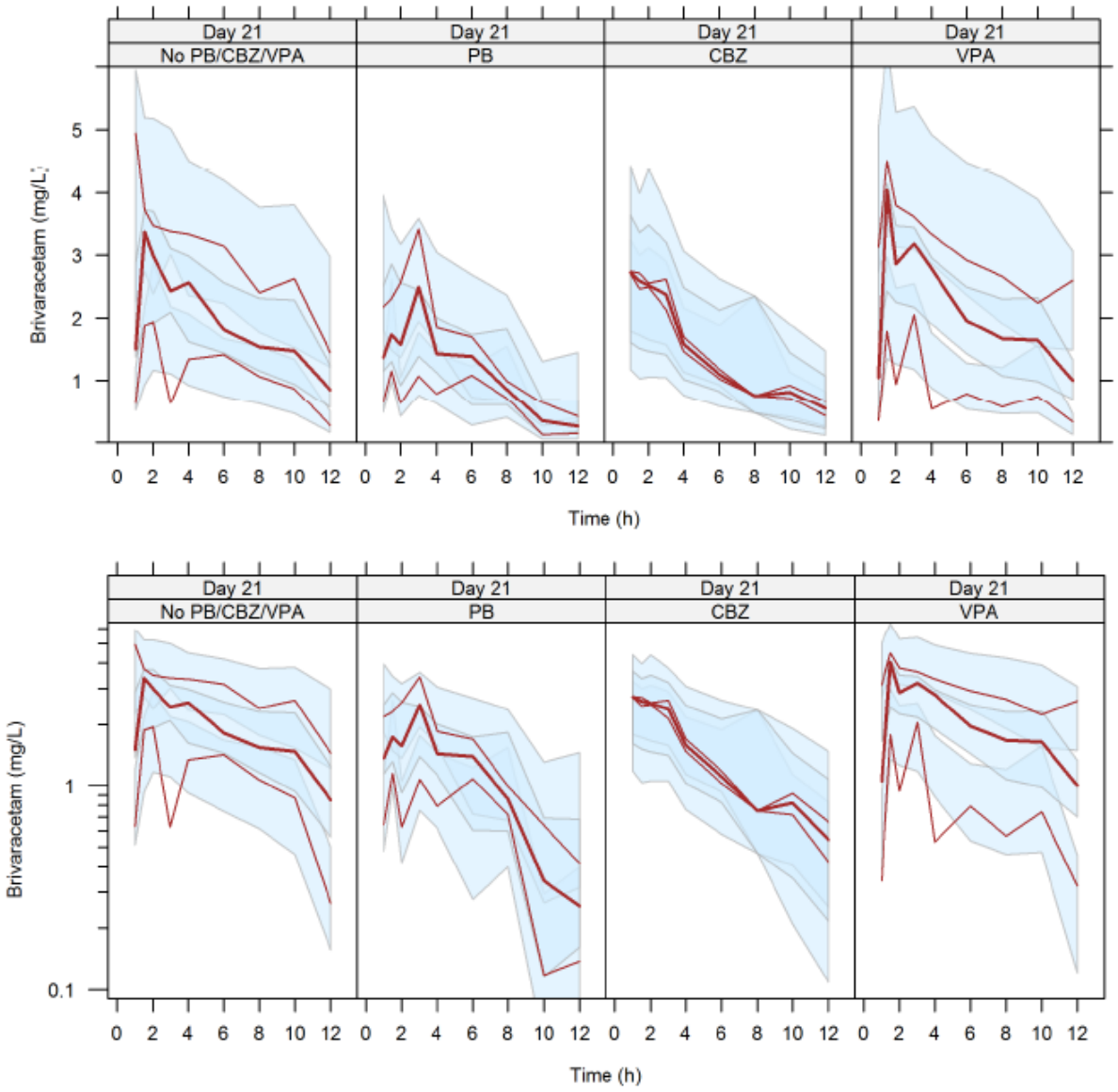

Day 7
1 month - <2 yrs.
Day 7
2 yrs. - <6 yrs.
Day 7
6 yrs. - <12 yrs.
Day 7
12 yrs. - <16 yrs.
Day 14
1 month - <2 yrs.
Day 14
2 yrs. - <6 yrs.
Day 14
6 yrs. - <12 yrs.
Day 14
12 yrs. - <16 yrs.
Day 21
1 month - <2 yrs.
Day 21
2 yrs. - <6 yrs.
Day 21
6 yrs. - <12 yrs.
Day 21
12 yrs. - <16 yrs.
Brivaracetam (mg/L)
1
0.1
0 2 4 6 8 10 12
Time (h)

Figure 3. VPCs for BRV time profiles (run411) by PB, CBZ and VPA co-administration for Day 21. Top panels: linear y-axis, lower panels: logarithmic y-axis. Red lines are the 5th, 50th (median) and 95th percentiles of the observed data and the light blue areas contain 95% of the simulated quantiles.



Covariate analysis indicated that co-administration of phenobarbital or primidone (PB), carbamazepine (CBZ), or valproate (VPA) was associated with a clearance modification: PB was estimated to induce a 40.8% increase in clearance (95%CI: 19.9%/ 65.2%), CBZ a 47.9% increase (27.8%/ 71.2%) and VPA a 10.1% (0.8%/18.5%) decrease. No effects on clearance could be attributed to race, ethnicity, sex, co-administration of CYP3A or CYP2C19 inhibitors, age, postconceptional age (PCA) or body surface area-normalized glomerular filtration rate (eGFR). Age-related maturation of metabolism could not be detected. According to the Applicant, the increased clearance in young children could be associated with the more frequent coadministration of PB as compared to older children.

The available data in young children were limited in absolute numbers but nevertheless represented about a third of the total (n=96) as there were 37 children aged <4 years (including 29 aged <2 years): The presence of a relevant age effect on clearance could have been detected. The absence of any detectable maturation effect is consistent with the known disposition pathways of BRV: As BRV is extensively biotransformed with <10% excreted unchanged by the kidneys, renal maturation in younger children cannot influence its clearance significantly.

In order to assess further the presence or absence of clearance maturation effects, a maturation function has been incorporated in the expression of BRV clearance using either fixed or estimated parameters, as requested by the CHMP. The results are summarized in Table 13. .

Table 13. record for inclusion of maturation factor on BRV clearance

2: Model	MS	OFV	ΔOFV	comments	$MATCL_{50}$	HillCL
411	Yes	-1031.866		Final full model	-	-
413	No	-	-	Numerical issues	0.63month	6.96
414	Yes	-730.104	+307	Fixed MAT50 and Hill	Fix 47month	Fix 3.5
415	Yes	-1031.866	0	Fixed Hill	0.47month	Fix 3.5
416	Yes	-1031.866	0	Fixed Hill	0.489month	Fix 6.2

MS minimization successful; OFV objective function value; ΔOFV change in OFV from #411; $MATCL_{50}$ time to reach 50% of full maturation; HillCL sigmoidicity term of the Hill function.

Estimating the values of MATCL50 and HillCL (run413) led to numerical issues (model termination with rounding errors) and MATCL50 and HillCL values of 0.63 months and 6.96, respectively. Fixing the Hill coefficient to a value of 3.5 and MATCL50 to 47 months (run414) as observed for glomerular filtration rate and paracetamol clearance (Holford TN et al., 2009) led to successful minimization, and an increase in delta objective function value of 307 points, compared to the model without maturation (-730.104 vs. -1031.866), demonstrating a highly significant deterioration of goodness of fit. Fixing the Hill coefficient to a value of 3.5 (run415) as observed for glomerular filtration rate, paracetamol clearance and morphine clearance (Holford N et al., 2009) led to successful minimization, an objective function value identical to the model without maturation (-1031.866), and an estimate of MATCL50 of 0.47 months. Fixing the Hill coefficient to a value of 6.2 (run416) as observed for acyclovir clearance (Holford TN et al., 2009; Tod M et al., 2001) led to successful minimization, an objective function value identical to the model without maturation (- 1031.866), and an estimate of MATCL50 of 0.489 months. Based on the available results the applicant considered that the data provide no support for a maturation function with PMA to describe BRV clearance.

Absorption

No specific studies have been performed to evaluate the absorption of BRV in paediatric subjects. In adults, BRV is completely and rapidly absorbed throughout the gastrointestinal tract after oral administration. There is no pre-systemic metabolism or active (efflux) transport. The high oral bioavailability of approximately 100% is not affected by food. As BRV is a Biopharmaceutics Classification System class-I drug, it is expected that the BRV absorption profile in paediatric patients after administration of a tablet or oral solution is similar to that in adults.

Distribution

Brivaracetam is weakly bound to plasma proteins in adults (≤ 20%); no change in the low plasma protein binding is expected to occur in paediatric patients. The volume of distribution of BRV is 0.5L/kg in adults, a value close to that of the total body water. Based on the paediatric population PK model, the typical distribution volume of BRV in the paediatric population was estimated to be 47.8L for a lean body weight of 50kg (95% CI: 43.1, 52.5) or 55.7L for a total body weight of 70kg (95% CI: 51.0, 60.5), ie, 0.8L/kg. The mean volume of distribution was slightly higher than that reported in adult patients with epilepsy (Vz/F=48.1L; 95% CI: 45.8, 50.4).

Metabolism

Expression of the amidase enzyme, which represents the main disposition pathway of BRV, is not known to be age dependent and it is assumed to be widely expressed at birth. The secondary hydroxylation pathway on the other hand, is supported by cytochrome-P (CYP)2C19 which has been reported to have a fractional expression of 0.23 at birth relative to adults, a time to half adult expression of 0.99 year, and a fractional expression of 0.92 or 92% of adults at the age of 4 years (Johnson et al, 2006). Therefore, the ontogeny of this secondary disposition pathway could have an effect of BRV metabolism and contribute to a lower clearance (CL) in young children; however, such an effect was not evidenced in the small dataset of paediatric subjects. Irrespective of the minor contribution of the hydroxylation pathway to the disposition of BRV, over 90% of the CYP2C19 adult expression is reached by the age of 4 years; therefore, no age dependency is expected in paediatric patients ≥ 4 years of age.

Excretion

No specific studies have been performed to evaluate the excretion of BRV in paediatric subjects. In adults, BRV is primarily eliminated from the systemic circulation by renal excretion following extensive biotransformation. The terminal half-life ($t_{½}$) of BRV in adults is approximately 9 hours. As BRV is extensively biotransformed with <10% excreted unchanged by the kidneys, renal maturation in younger children is not expected to influence its clearance significantly.

The mean (standard deviation [SD]) plasma half-life of BRV in children, estimated by simulation in CL0187, ranged from 6.9 hours (2.3 hours) in the group from 4 to <5 years of age to 9.0 hours (3.1 hours) in the group from 15 to <16 years of age. Overall, plasma half-life in paediatric populations was in the same range as adult subjects with epilepsy.

Special populations

Age and gender

The population PK analysis did not detect a significant effect of gender or age on BRV CL in paediatric subjects. Clinical studies in adult subjects with epilepsy showed that gender does not have a clinically significant influence on the plasma concentrations of BRV.

Race

The population PK analysis did not detect a significant effect of race on BRV CL in paediatric subjects. Based on these data, it is expected that BRV PK profile in paediatric subjects would be consistent with the known PK profile of BRV derived from adult studies where there were no clinically relevant differences in the PK of BRV among Asian, Black, and Caucasian subjects.

Body weight

The results from the population PK analysis show that BRV steady-state plasma concentrations resulting from the proposed BRV weight-based dosing scheme for paediatric subjects (2mg/kg/day for subjects with body weights <50kg) approximate those observed in adults with POS taking the therapeutic dose BRV 100mg/day as adjunctive therapy.

Genetic polymorphism

The effect of genetic polymorphisms was not evaluated in the paediatric studies.

Results from a PK study in healthy Japanese adults demonstrated that BRV AUCt underwent small increases as shown by values of 16.6, 20.0, and 23.1µg.h/mL (normalized to a dose of 1mg/kg) in homozygous extensive metabolizer (EM), heterozygous EM, and poor metabolizer (PM) subjects,

respectively; whereas, the hydroxy metabolite decreased to less than 1/10th, from 2.55 (homozygous EM subjects) to 0.968 (heterozygous EM subjects) to 0.191 (PM subjects) µg.h/mL (normalized to a dose of 1mg/kg). The carboxylic acid metabolite and hydroxyacid metabolite AUCs were not consistently modified among the 3 genotypes. These observations indicate that CYP2C19 is the isoenzyme responsible for the hydroxylation of BRV into hydroxyl metabolite, and that this pathway is secondary compared to hydrolysis. As such, the potential for CYP2C19-mediated interactions with BRV is expected to be low. Thus, no dose adjustment is expected to be needed in paediatric patients with CYP2C19 polymorphisms or paediatric patients who received CYP2C19-inhibiting drugs concomitantly with BRV.

Renal impairment

The effect of renal impairment was not evaluated in the paediatric studies.

Based on renal impairment from adults, no dose adjustment is recommended for paediatric patients with renal impairment. Brivaracetam is not recommended in paediatric patients with end stage renal disease undergoing dialysis due to lack of data.

Hepatic impairment

The effect of hepatic impairment was not evaluated in the paediatric studies.

Based on hepatic impairment data from adults, a starting dose of BRV 1mg/kg/day (for body weights <50kg) or 50mg/day (for body weights ≥ 50kg) is recommended for paediatric patients at any stage of hepatic impairment. Based on the maximum dose recommended for adults, similar BRV maximums (3mg/kg/day for patients with body weights <50kg and 150mg/day for patients with body weights ≥ 50kg) are recommended for paediatric patients with hepatic impairment.

Drug – drug interactions

Potential interactions between BRV (50mg/day to 200mg/day) and other AEDs were investigated in a pooled analysis of plasma drug concentrations from all adult Phase 2 and Phase 3 studies and in a population exposure-response analysis of PBO-controlled Phase 3 studies in adjunctive therapy in the treatment of POS.

In adults, co-administration of rifampicin with BRV resulted in a 45% decrease in BRV plasma concentration. Prescribers should consider increasing the BRV dose in patients starting treatment with rifampicin and decreasing when stopping rifampicin therapy.

As in adults, for paediatric subjects prescribers should consider increasing the BRV dose in patients starting treatment with rifampicin and decreasing when stopping rifampicin therapy. For paediatric subjects, co-administration of PB and of CBZ increased BRV clearance, and co-administration of valproic acid decreased BRV clearance.

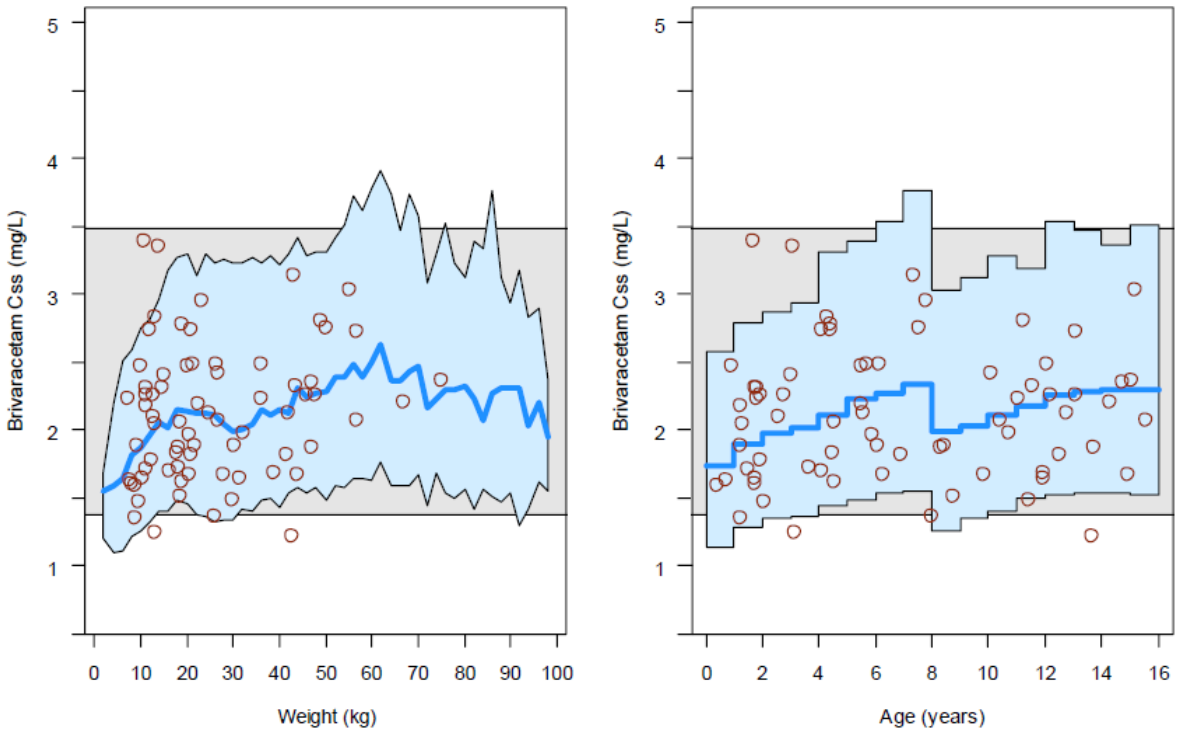
2.4.3. Simulations to establish dosing recommendations for oral administration

Paediatric simulations using the population estimates from the final paediatric model were performed with the study administration schedule (2.0 mg/kg bid for patients <8 years and 1.6 mg/kg bid with a maximum of 100 mg bid for patients ≥ 8 years). Additional schedules of 2.0 and 2.5 mg/kg bid were investigated with a maximum of 100 mg bid, independent of age. The population estimates from the adult patient population PK model were used to derive the median and 90% of the predicted steady state concentration (Css) levels for adults receiving 100 mg BRV bid. In these predictions, effects of inducer coadministration (carbamazepine,

phenobarbital/primidone, and phenytoin) were excluded from both adult and paediatric populations to allow an unbiased comparison.

The Nhanes DXA database [Nhanes 2013] was used to provide demographic variables (age, weight, and calculated lean body weight using the James formula) to drive the simulations. Valproate coadministration for children was sampled from the paediatric dataset because the paediatric PK model contained a valproate effect. In the graphs, the gray shaded area depicts 90% of the adult Css values receiving 100 mg bid, the blue shaded area and line depict the median and 90% of the paediatric Css values for the different simulations, and the red circles indicate the predicted Css values for the individual clearance values in study N01263 using the final model, where only paediatric patients not taking inducer AEDs are selected. The trial dosing scheme (Figure 4.) put most of the model-predicted concentrations (blue area) in the adult range (gray area) and individual predictions for paediatric patients (red circles) were mostly contained within the model-predicted range.

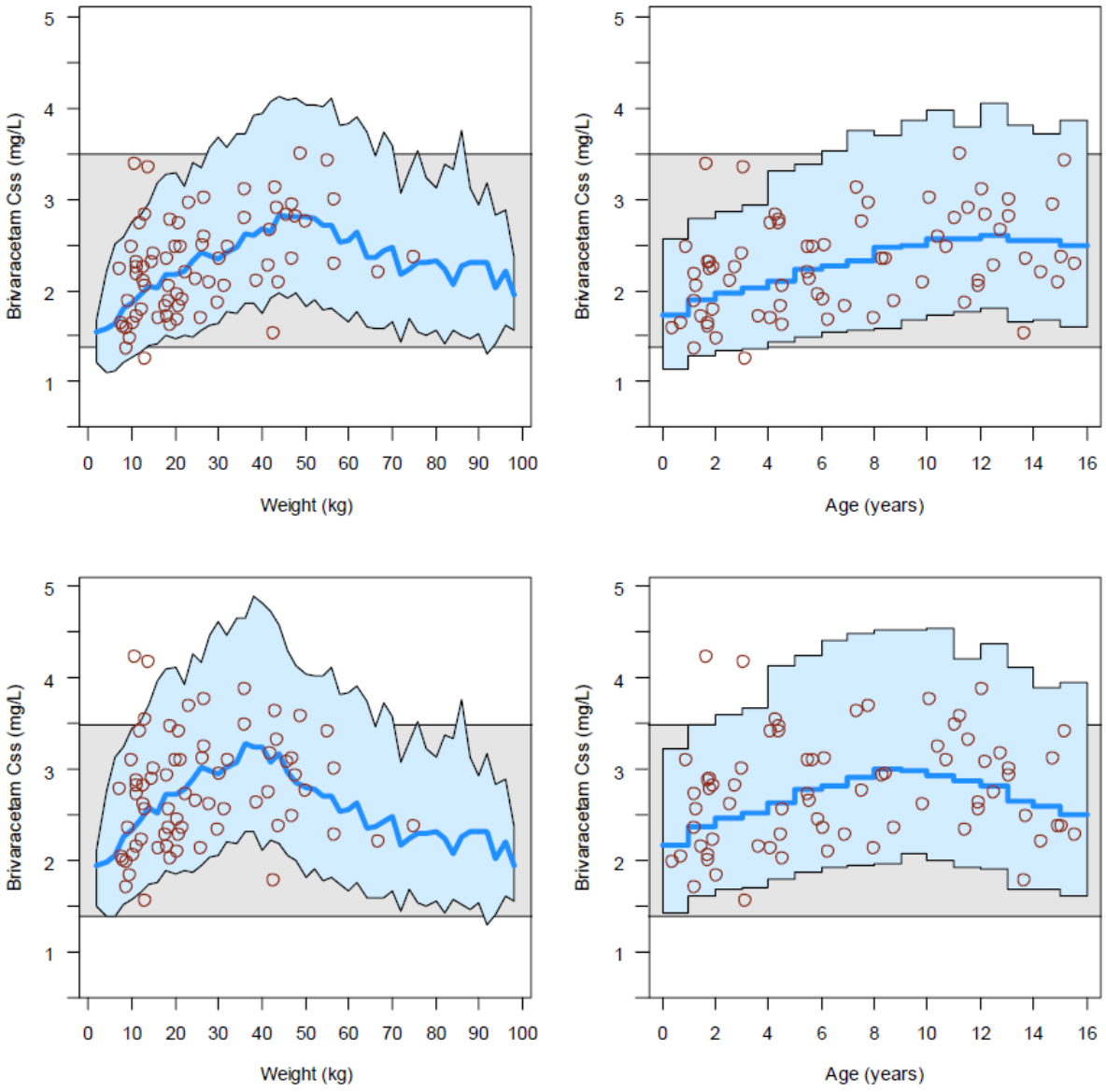
Figure 4. Predicted Css for patients without inducer AEDs by weight (left) and age (right) using the final paediatric population PK model (red circles: individual predictions for patients without inducer AED coadministration) and predicted ranges for children from the Nhanes database <16 years and ⩽100 kg using 2 mg/kg bid for patients <8 years, and 1.6 mg/kg bid for patients ⩾8 years with 100 mg bid maximum dose. The blue shaded area encompasses 90% of the simulated paediatric patients, the blue line is the median simulated paediatric Css. The horizontal gray bar is the predicted 90% CI Css of the adults receiving 100 mg bid, and not coadministered with inducer AEDs.



By removing the age classification in the dosing recommendation and simply dosing all patients with 2.0 mg/kg bid with a maximum of 100 mg bid, the predicted concentration profile across the paediatric population was comparable to the age-based trial dosing regimen (Figure 5. , top panels, compared to Figure 4.). Increasing the dose to 2.5 mg/kg bid across the entire population may bring the smaller/younger children closer to the desired concentration range, but increases the likelihood of over-dosing in older children (Figure 5. , lower panels)

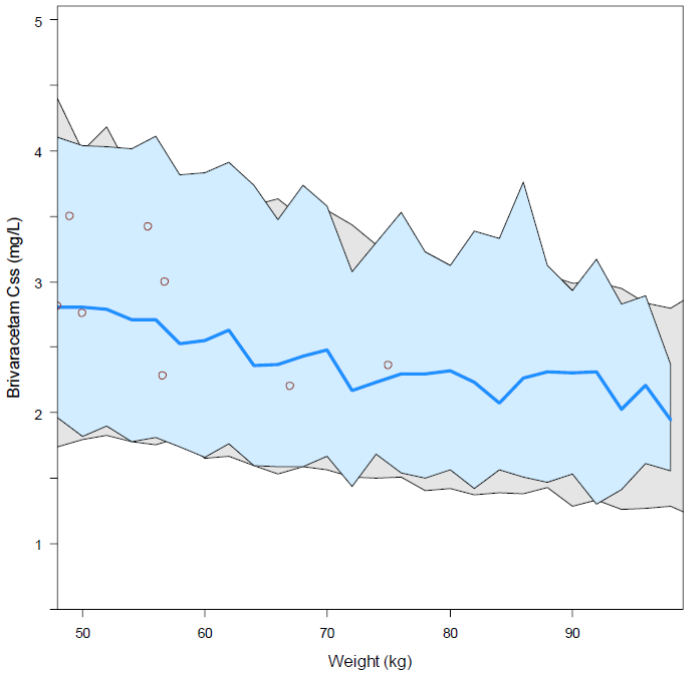
Figure 5. Predicted Css for patients without inducer AEDs by WT (left) and age (right) using the final paediatric population PK model (red circles: individual predictions for patients without

inducer AED coadministration) and predicted ranges for children from the Nhanes database <16 years and ⩽100 kg using 2 mg/kg bid with 100 mg bid maximum dose for all patients (top) or 2.5 mg/kg bid with 100 mg bid maximum dose for all patients (bottom). The blue shaded area encompasses 90% of the simulated paediatric patients, the blue line is the median simulated paediatric Css. The horizontal gray bar is the predicted 90% CI Css of the adults receiving 100 mg bid, and not coadministered with inducer AEDs.



Paediatric and adult PK models were estimated separately, and adult models were scaled by weight while paediatric models were scaled by lean body weight. In addition, allometric scaling factors were estimated freely for the adult PK model, while the factors were fixed to the theoretical values of ¾ and 1 for scaling clearance and volume respectively in the paediatric model. The graphs with age independent dosing seem to suggest a deviation between adult predictions and paediatric predictions for the ranges of weights where these predictions should correspond (≥ 50kg for 2 mg/kg bid and ≥ 40kg for 2.5 mg/kg bid), for children receiving a dose of 100 mg (see Figure 5.). However, the adult reference range was calculated across the entire adult population and was not represented as a function of weight. A new graph was generated with predicted adult Css values but this time as a function of weight (Figure 6.). This graph shows that the apparent discrepancy disappears when weight is taken into account and also demonstrates that for this weight range, the models, even though parameterized and scaled differently, provide similar predictions.

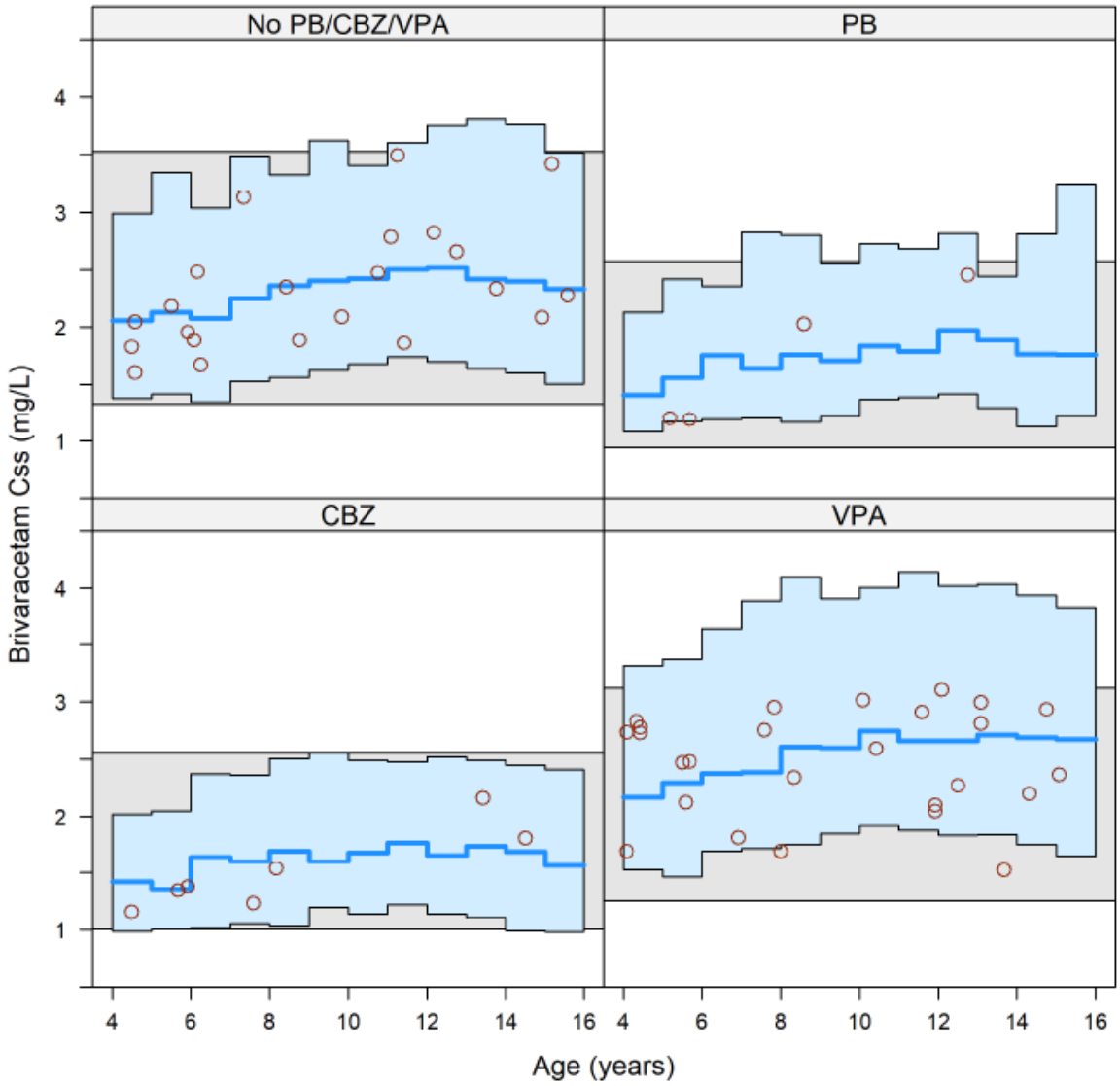
Figure 6. Predicted Css for patients without inducer AEDs by weight using the final paediatric population PK model (red circles: individual predictions for patients without inducer AED coadministration) and predicted ranges for children from the Nhanes database <16 years, ⩽100 kg and ⩾50 kg, with the 100 mg bid maximum dose. The blue shaded area encompasses 90% of the simulated paediatric patients, the blue line is the median simulated paediatric Css. The underlying gray area is the predicted 90% CI Css of the adults receiving 100 mg bid, summarized by WT, and not coadministered with inducer AEDs.



At the CHMP's request additional analyses were conducted to further elucidate the predicted BRV concentrations in children compared to adult reference ranges with background antiepileptic drugs (AEDs) corresponding to the pediatric population.

An additional adult population PK model was executed including the effect of valproate (VPA) co-administration, as the original adult reference model only contained effects of carbamazepine (CBZ), phenytoin (PHT) and phenobarbital (PB) while VPA was not significant. 0 below provides the predictions for BRV Css in children as a function of age, with the horizontal scale being restricted to patients aged ≥ 4 years, but using the originally submitted final pediaric population PK model including all children from 1 month to <16 years (run411). Of note, only 4 individuals are visible in the PB group (red circles) as the large majority of patients co-medicated with PB were aged <4 years. The updated graph now contains adult reference ranges for adults taking the same class of co-medication as the pediatric patients and shows a near perfect match between children and adults except for the upper limit of the VPA confidence interval (but not for individual patients):

Figure 7. Predicted Css by age split by co-administration with PB, CBZ and VPA or absence of PB/CBZ/VPA using the final paediatric population PK model but limiting the x-axis of graph to children of >=4 years (red circles: individual predictions) and predicted ranges for children from the NHANES database using 2 mg/kg bid with 100 mg bid maximum dose. The blue shaded area encompasses 90% of the simulated paediatric patients, the blue line is the median simulated paediatric Css. The horizontal grey bar is the predicted 90% CI Css of the adults receiving 100 mg bid with the same AED background therapy as the pediatric groups.



The next graphs (Figure 8. by age and Figure 9. by weight) were created by rerunning the paediatric model after excluding patients aged <4 years in the analysis:

Figure 8. Predicted Css by age split by co-administration with PB, CBZ and VPA or absence of PB/CBZ/VPA using the final paediatric population PK model but excluding patients <4 years (red circles: individual predictions) and predicted ranges for children from the NHANES database using 2 mg/kg bid with 100 mg bid maximum dose. The blue shaded area encompasses 90% of the simulated paediatric patients, the blue line is the median simulated paediatric Css. The horizontal grey bar is the predicted 90% CI Css of the adults receiving 100 mg bid with the same AED background therapy as the pediatric groups.

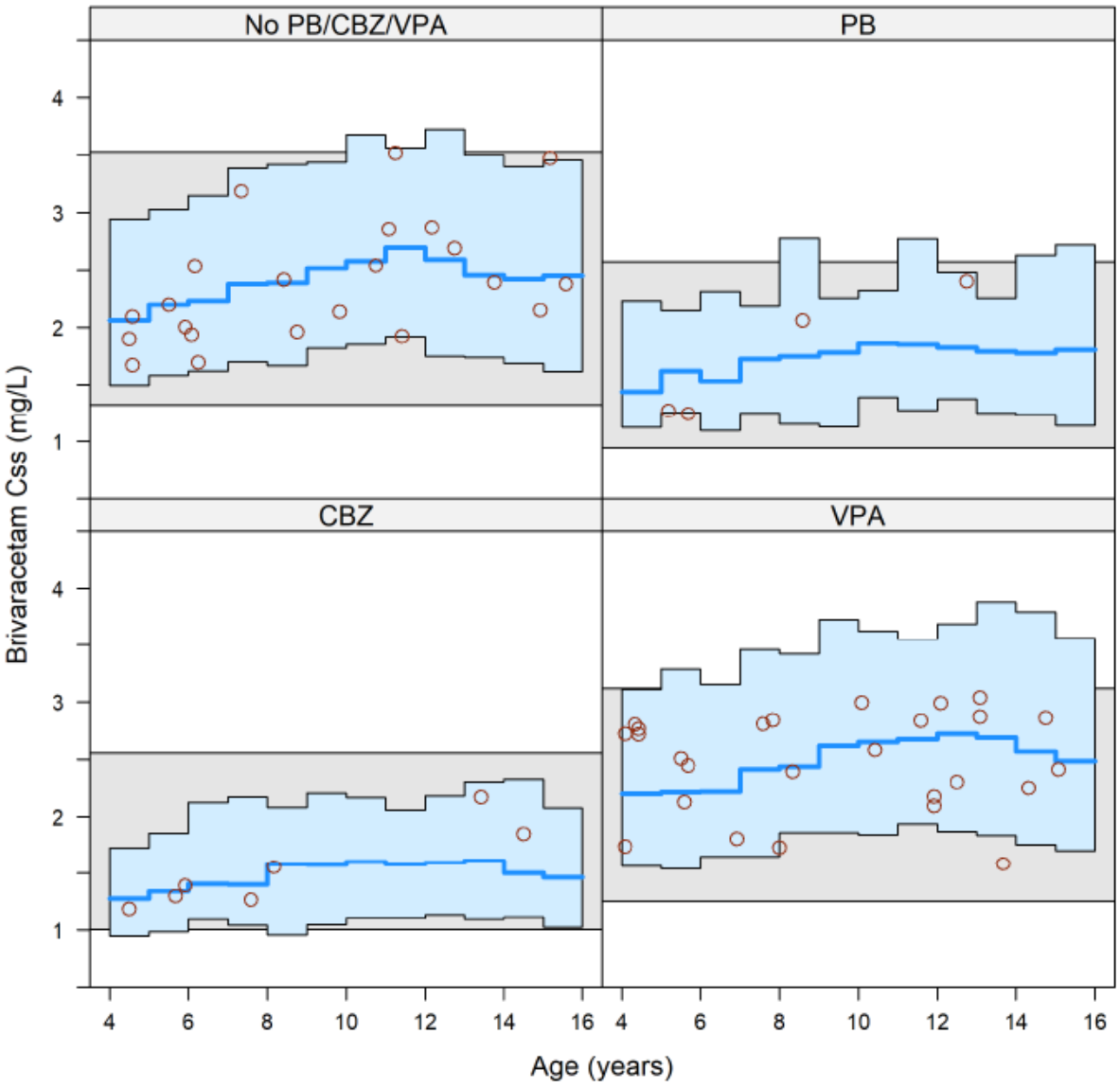
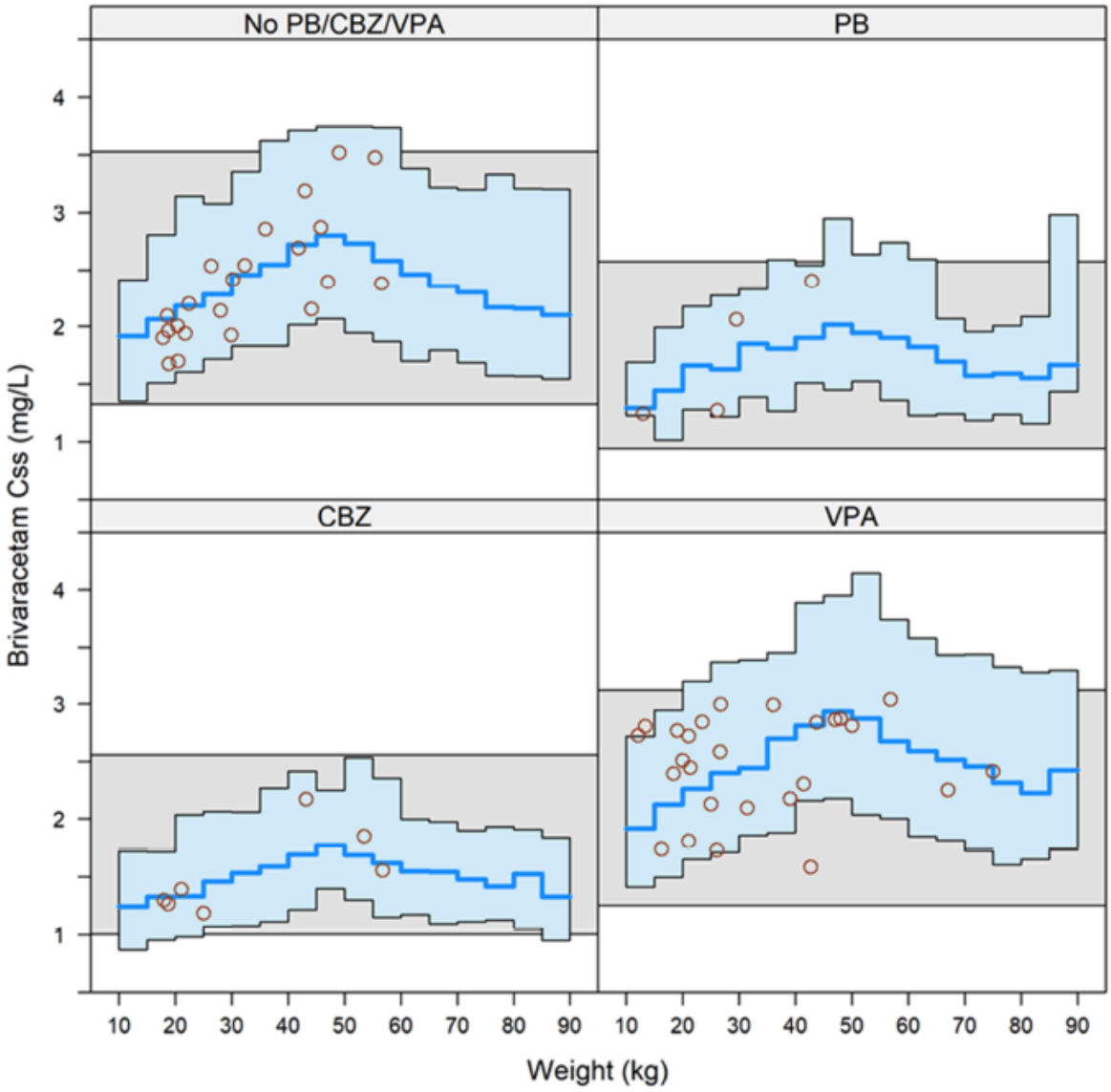


Figure 9. Predicted Css by weight split by co-administration with PB, CBZ and VPA or absence of PB/CBZ/VPA using the final paediatric population PK model but excluding patients <4 years (red circles: individual predictions) and predicted ranges for children from the NHANES database (with a maximum of 90kg) using 2 mg/kg bid with 100 mg bid maximum dose. The blue shaded area encompasses 90% of the simulated paediatric patients, the blue line is the median simulated paediatric Css. The horizontal grey bar is the predicted 90% CI Css of the adults receiving 100 mg bid with the same AED background therapy as the pediatric groups.



These graphs indicate that predicted Css for pediatric patients correspond well with AEDspecific adult reference sub-ranges, with the possible exception of VPA regarding the upper 95th percentile of the prediction interval which slightly exceeds the adult reference in the weight region of 40 to 60 kg. The adult population PK model estimated a slight increase in BRV clearance associated with VPA co-administration (typical value: +11.1%; 95%CI: +6.8%, +15.7%) which was not retained in the original final model, while the paediatric population PK model estimated a decrease in BRV clearance with VPA co-administration (typical value: -10.1%; 95%CI: -18.5%, -0.81%).

There is no strong rationale for suspecting a potential PK interaction of VPA on BRV. The modest and opposite changes estimated on BRV clearance in adults and children may be considered as chance effects, and their clinical relevance is insignificant.

The MAH concludes that the widths of the 90%CI of the paediatric predictions reflect at least in part the limited data available and the imprecision of the model while individual observations (red

circles in Fig. 17-2 and Fig 17-3) are contained within the respective adult reference sub-ranges. Overall, paediatric dosing adaptations provide a good match to adults with the same AED co-medication patterns.

2.4.4. Simulations to establish dosing recommendations for iv administration

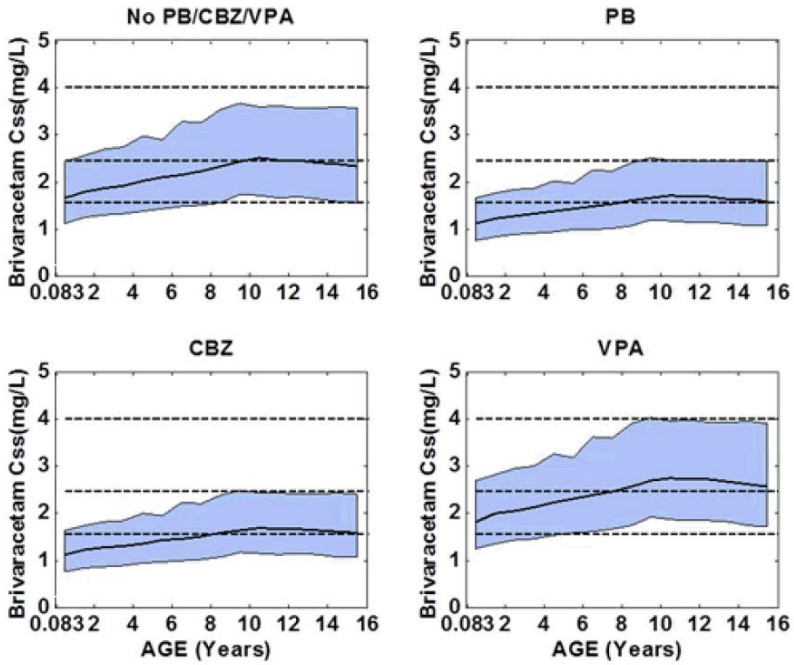
Data from an iv study in healthy volunteers (N01256) and a paediatric population PK model following oral administration (CL0187 derived from paediatric study N01263) were used to perform simulations to support the iv dosing recommendation in children. N01256 included 48 male and female healthy volunteers. In the part I of the study subjects received either a single oral or iv bolus or iv infusion of 10 mg BRV. In part II of the study the subjects were dosed with a single iv bolus or iv infusion of 10, 25, 50, 100, 150 mg BRV. Rich PK data was collected in the study.

A 1-compartment model with linear elimination adequately described the healthy volunteer iv data. The model included estimates of CL and V and inter-individual variability on CL and V. The residual error was described by a proportional model. The population estimates of CL and V were 2.96L/h (26.8%) and 36.2L (22.4%), respectively.

A paediatric iv model was derived by combining the adult iv model and model parameters from CL0187, a paediatric population PK model following oral administration (see section “Population PK modelling” above). The paediatric intravenous PK model was a one compartment model with linear elimination. The volume of distribution was 36.2 L. The CL was 3.61 L/h. Lean body weight was assumed to be a covariate on CL and V. Allometric scaling with fixed exponents of 1 and 0.75 were used as covariates on V and CL respectively. The effect of concomitant AEDs on CL was taken from paediatric oral population PK analysis.

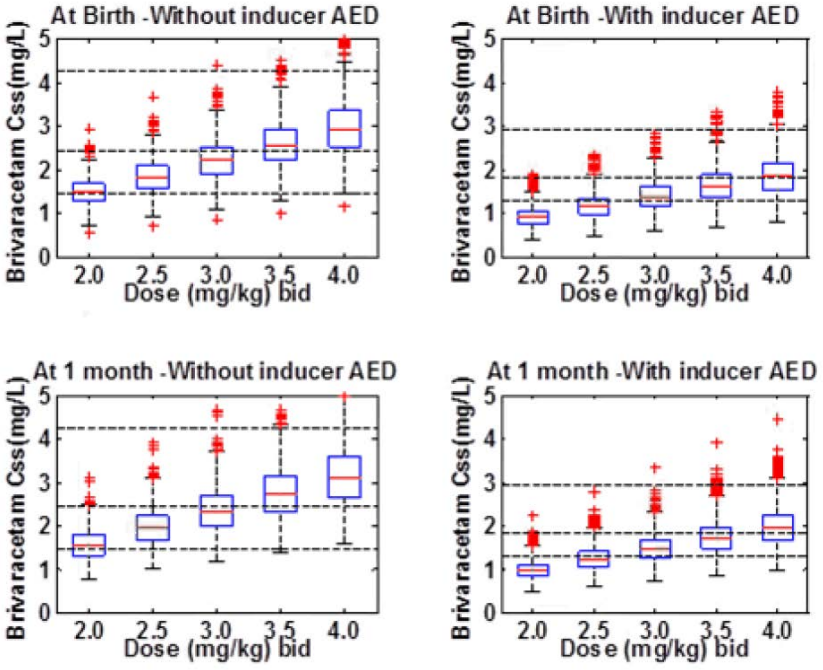
Simulations were performed to calculate the predicted steady state concentration (Css) of BRV at different dosage regimens. Two different age groups were simulated. The first age group consisted on subjects in the age range of 1 month to <17 years. The second age group included neonates (age between 0 to <28 days). Weight instead of lean body weight was used as a covariate when simulating steady state concentrations in neonates. The simulated Css were compared with the predicted Css in adults at 100 mg bid dosage regimen. The results of simulations in the age group of 1 month to <17 years are presented in Figure 10. Simulations suggested that in the age group of 1 month to <17 years a dosage regime of 2.0 mg/kg BID with a maximum of 100 mg BID would result in profiles comparable to simulated average steady state concentrations in the range of adult 100 mg BID which is the expected maximum therapeutic dose in adults.

Figure 10. Predicted steady state concentrations (Css) in the age group of 1 month to <17 years at 2 mg/kg iv BID with maximum of 100 mg BID.



The iv PK model for neonates was a one compartment model with linear elimination. The V was 36.2 L. The CL was 3.81 L/h. Weight instead of lean body weight was assumed to be a covariate on CL. Allometric scaling with fixed exponents of 1 and 0.75 were used as covariates on V and CL respectively. The effect of concomitant inducers on CL, taken from paediatric oral population PK analysis, was assumed to be 0.46. Figure 11. below shows the simulation results in the age group of 0 to <28 days. As presented in the figure below the simulations indicate that the Css at 2 and 2.5 mg/kg concentrations in neonates may be lower when compared to the predicted steady state concentrations in adults at 100 mg bid.

Figure 11. Predicted steady state concentrations (Css) in neonates (0 to <28 days) at different doses



The boxplots show the distribution of Css at different doses and the dashed lines represent the predicted Css for 95% of the adult patients and the median receiving 100 mg bid.

2.4.5. Pharmacodynamics

No specific studies have been performed to evaluate BRV PD effects in paediatric subjects which was found acceptable by the CHMP.

2.4.6. PK/PD modelling

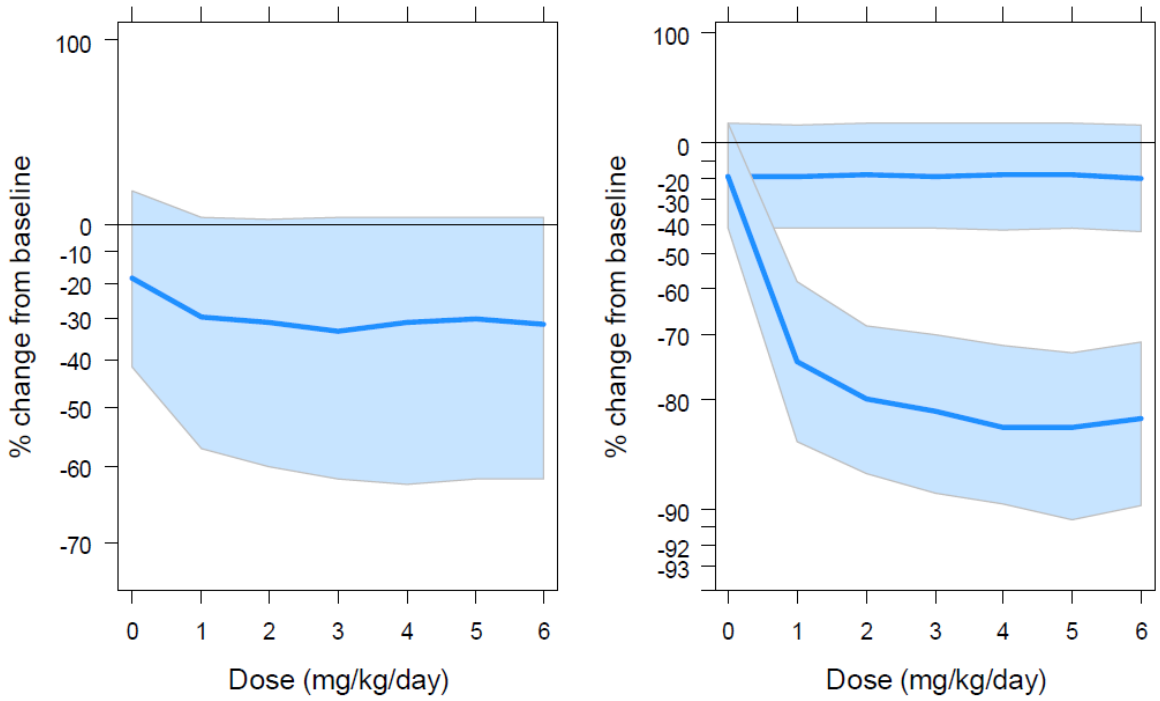
An exposure-response modelling study of BRV as adjunctive therapy in children ≥ 4 to <16 years of age with POS, was conducted to support the proposed dosing scheme as well as dosing in future paediatric studies. The modelling was based on Phase 3 PK/PD data from adults and children who received Levetiracetam, and on Phase 2 and 3 PK/PD data from adults who received BRV, as well as PK data from children in N01263.

A population PK/PD model was previously developed to describe the relationship between concentrations of BRV and daily seizure frequency in adult subjects. In order to support the extrapolation of PD in BRV to subjects 4 to 16 years of age, , a LEV adult/paediatric PK/PD model was built and subsequently used to scale the existing BRV adult PK/PD model to children. The developed LEV combined adult/paediatric PK model consisted of a first order absorption, single compartment distribution, and first order elimination population PK model. LEV CL and V were scaled as a function of body weight using allometric scaling, and the influence of coadministration with the hepatic enzyme-inducing AEDs CBZ, PHT, and PB was investigated for its effect on LEV CL.

The developed LEV combined adult/paediatric PK/PD model described seizure frequencies using a negative binomial distribution taking previous day seizure frequencies into account, and using a mixture model to separate a placebo (PBO)–like (ie, non-responder) and a responder subpopulation. The model was adapted to describe aggregated monthly seizure counts for the adult subjects in the LEV studies: daily seizure counts were only available for the children in the LEV studies. The LEV adult/paediatric PK/PD model was then used to support the scaling of the existing adult BRV PK/PD model into children. Pharmacokinetic and PD simulations for BRV were performed in children for a range of mg/kg doses to predict BRV effect in paediatric subjects.

The simulations conducted in CL0258 allowed characterization of the paediatric BRV dose response curve and suggest that BRV 1mg/kg/day is an effective dose, see Figure 12. Furthermore, the maximum response is obtained at approximately BRV 4mg/kg/day dosing (for body weights <50kg, and with a maximum of 200mg/day for body weights ≥ 50kg) in paediatric patients ≥ 4 years of age. This range (1 to 4mg/kg/day) provides dosing consistent with adult dose range of 50 to 200mg/day.

Figure 12. Overall simulated BRV effect by daily dose (left) and split by mixture model population (right) in children ⩾4 to 16 years of age



Note: Median (blue line) and interquartile range (light blue area) of simulated individuals (pale blue area)

2.4.7. Discussion on clinical pharmacology

The scope of the present application is to support the expansion of the current approved indication to include the use of BRV as adjunctive therapy in patients ≥4 years of age with POS for tablet, oral solution, and solution for iv use dosage forms. The BRV dosing recommendations in adults and in children, as proposed by the Applicant, are provided in the following table:

Summary of pediatric BRV dosing adaptations

	Adults	Children ≥50kg	Children <50kg
Maximum recommended dose	200mg/day	200mg/day	4mg/kg/day
Therapeutic dose range	50 to 200mg/day	50 to 200mg/day	1 to 4mg/kg/day

The Applicant stated that children weighing <50kg who receive BRV 1 to 4 mg/kg/day achieve BRV steady state plasma concentrations in the range of adults (≥ 16 years of age) receiving BRV 50 to 200mg/day. Children weighing ≥ 50kg are dosed like adults.

Samples for all paediatric PK analyses of BRV included in this application were collected in study N01263, the initial study of BRV in children. The primary objectives of the completed paediatric BRV study N01263 were to characterize the steady-state PK of BRV and its metabolites in subjects from ≥ 1 month to <16 years of age, evaluate their relationship with physiological developmental variables, and develop dosing adaptations. Trough BRV plasma concentration increased proportionally with dose. Trough BRV plasma concentration increased with increasing age; for example, at the high dose, geometric mean trough BRV plasma concentration was 0.596, 0.827, and 1.065 μg/mL in ≥ 1 month to <2 years, ≥ 2 to <12 years and ≥ 12 to <16 years groups, respectively.

As acknowledged by the MAH, meaningful comparisons across age groups should be interpreted with caution and considered as preliminary, due to the limited sample size, particularly in the ≥ 12 to <16 years group. Baseline characteristics have been presented for the range ≥ 2 to <12 years, although the sought indication is for children from 4 years old onward, the presented data is considered applicable for the age range ≥4 to <12 years.

A population PK model including fixed allometric scaling adequately describes the BRV PK data in children of 4 to 17 years of age. Lean body weight was used as the covariate for body size due to a slightly better model fit; this is considered acceptable due to the strong correlation to body weight. Further, it is not perceived that lean body weight is more predictive in a clinical setting and the dosing recommendation on body weight is endorsed.

In the model development PK data from children down to 1 month of age were included although organ maturation could be expected to influence the PK in young children. However, age related metabolism was investigated in the model development and was found not to further improve the description of BRV PK in small children and hence not included in the model which is acceptable.

No effects of categorical covariates race, ethnicity, sex, CYP3A or CYP2C19 inhibitors were detected and no effects of age, post-conceptional age (PCA), or eGFR were detected for either a linear, an exponential, or a power relationship. Instead PB, CBZ and VPA were highly significant covariates and the aggregate effect of IND obscured the individual contributions. All three AEDs had significant effects on CL on their own, and in the combined estimation (run411) co-administration of PB was estimated to induce a 40.8% increase in CL (95%CI: 19.9%/ 65.2%), CBZ a 47.9% increase (27.8%/ 71.2%), and VPA a 10.1% (0.8%/18.5%) decrease. The comparison of the population PK estimates in adult vs paediatric subjects pointed out that the effect on CL of concomitant drugs is higher for children. However, the effect of enzyme-inducing AEDs is expected to be similar in children and adults and proposing the same dose adjustments in adults and children (≥ 4 years of age) is considered appropriate.

Apart from the effect of AEDs, the PK parameter estimates from the paediatric population are similar to those estimated in adult patients. The allometric exponents were freely estimated in adults, however concentrations simulated from both models versus body weight largely overlap indicating that the slight differences in parameter estimates between adult and paediatric models are negligible.

Visual predictive check plots were then presented by age category visit, however the age category 2 years -<6 years includes also an age range out of the scope of the present variation. However, visual predictive checks for BRV time profile relative to 4y - <6y category still showed an acceptable correspondence between observed and simulated data which support the adequacy of the population PK model.

Exposure ranges based on predicted steady state concentrations from individual clearance values are considered acceptable due an adequate population PK model and low parameter shrinkage in individual clearance estimates.

The exposure simulations given the dosing regimen with an age cut-off of 8 years indicate a paediatric exposure range that is overall more similar to the adult reference range. However, at the break point for dose adjustment (8 years) there is an instant reduction exposure that could potentially lead to an undesirable loss of effect. Hence, the proposed dosing recommendation of 2 mg/kg bid with maximum 100 mg bid is endorsed although the exposure range in children somewhat exceeds the adult range between 30-70 kg.

According to the MAH, after subdividing the simulations by AED co-administration, it became apparent that the deviations in the young age group were mainly attributable to the more frequent co-administration of PB in the younger age category, however also CBZ administration contributed

to this deviation. This observation does support the above mentioned issue regarding possible different dose adjustments required paediatric population.

Paediatric dosing by kg does not result in under-exposure in any condition, nor in over-exposure except for the upper tail of the VPA confidence interval in the region of 40 to 60kg. When using the upper limit of adult reference range without concomitant PB/CBZ/VPA treatment, the risk of over exposure in the paediatric population co-treated with VPA decreases. As there is no known mechanistic rationale supporting the effect of VPA on BRV clearance and its apparently opposite directions in adults and children, both being of small magnitude, it is agreed that the predicted difference in exposure is considered non-clinically relevant.

The approach of extrapolation of adult iv exposure to paediatric iv exposure is accepted. Standard methods were used in the development of the adult healthy volunteer iv population PK model. The goodness of fit diagnostic indicates that the model fit the data reasonably well. The WRES vs time after dose indicate a deviation at late time points, however the model is considered acceptable due to adequate individual model fits and that only the volume of distribution is used from the model which is mainly informed by early time points.

The CHMP noted that the comparison between adult and paediatric (i.v.) exposure ranges rely on an adult reference range which is based on data obtained in healthy volunteers without co-medication of other AEDs. However, considering that the relevant adult reference range for oral administration including co-medication of different AEDs is provided in the application and the iv exposure in children is very similar to the oral exposure considers that the absence of adult exposure ranges for i.v. administration in patients receiving other AEDs is acceptable and the presence of such data would not be expected to indicate a need of change in i.v. posology.

The predicted steady state concentrations in neonates indicate that the maximum dose of 4 mg/kg/day is on the low side without inducer AEDs and too low with inducer AEDs, compared to the adult reference range. It is acknowledged that there is much uncertainty in these predictions, in terms of BRV PK, the PK of AEDs and the magnitude of interaction in neonates. However, these findings suggest that further considerations regarding dose selection in neonates are warranted in order to inform the recommended posology in this age group.

CL0258, an exposure-response modelling study of BRV as adjunctive therapy in children with POS, was conducted to support the dosing scheme proposed in this application as well as dosing in future studies. CL0258 was based on Phase 3 PK/PD data from adults and children who received levetiracetam (LEV) and on Phase 2 and 3 PK/PD data from adults who received BRV as well as PK data from children in N01263. The LEV PK/PD model has been used to assess if and how the PK/PD relationship scales from adults to paediatric subjects. The existing BRV PK/PD model in adult subjects has been updated with a scaling component in order to predict PD (seizure count) changes in paediatric subjects receiving BRV.

The final objectives of the analysis was to scale an existing adult population PK/PD model for BRV into children, using the information from a combined adult-paediatric PK/PD model for LEV, a compound with the same primary mechanism of action, and to predict the effective dose of BRV in children aged 4 to 16 years.

Overall, the final PK model can be considered acceptable, also in the light of the GOF plots indicating virtual absence of systematic model misspecification regarding incorporation of the size covariate effect WT, and age and no apparent model misspecification regarding population predictions, TAD, or time in study.

VPCs generated from the final LEV PK/PD model, for median % from baseline and fraction responders, suggest a reasonable model performance, and furthermore prediction corrected VPCs of change from baseline versus Cav display an adequate model fit.

It is acknowledged that few patients have been treated with brivaracetam in study N01263, however, model diagnostics suggest a reasonable model fit which further support the dose selection in the paediatric population.

According to the MAH, the simulations conducted in CL0258 allowed characterization of the paediatric BRV dose-response curve and suggest that BRV 1mg/kg/day is an effective dose and that the maximum response is obtained at approximately BRV 4mg/kg/day dosing (for body weights <50kg, with a maximum of 200mg/day for body weights ≥50kg) in paediatric patients ≥4 years of age. This range (1-4mg/kg/day) ensures to reach BRV Css consistent with the ones observed in adult with the administration of BRV from 50 to 200mg/day. However analyzing the simulations the added benefit with the higher doses seems to be not showed. Simulated overall BRV effect by daily dose and age, in children aged 4-16 years, showed that only a slight further benefit is expected following 3 mg/kg/day vs. 2 mg/kg/day and no benefit seems to be simulated with the 4 mg/kg/day.

The simulated BRV% change in seizure count from baseline by daily dose and age, for mixture-model responder population in children aged 4-16 years, the change from baseline simulated following 3 mg/kg/day, 4 mg/kg/day 5 mg/kg/day appears to be the same. Given that the recommended adult dose is 50 to 200 mg/day, where 200 mg/day is considered to be near or at the plateau of the exposure-response relationship, a paediatric dose range of 1 to 4 mg/kg/day (WT<50kg) is therefore supported by the data.

The MAH has provided an in depth description of the similarities between BRV and LEV in support of the extrapolation of LEV PKPD relationship to BRV. Most importantly, BRV and LEV have a similar primary mechanism of action, through their affinity for synaptic vesicle protein 2A (SV2A). Compared with LEV, BRV displays a higher selectivity and affinity for SV2A and does not display any other relevant pharmacological mechanism of action, including absence of any relevant effect on voltage-gated sodium, calcium and potassium channels and an absence of a direct action on inhibitory and excitatory receptors including AMPA, glycine and GABA-A.

2.4.8. Conclusions on clinical pharmacology

Population PK modelling and simulations have been used to provide evidence for Briviact exposure similarity between adults and paediatric patients (≥4 years). The results support the proposed posology in the paediatric population which is appropriately described in section 4.2 of the SmPC.

2.5. Clinical efficacy

Brivaracetam's efficacy has been considered established as adjunctive treatment of partial-onset seizures with or without secondary generalisation in patients from 16 years of age with epilepsy based on a clinical development program including two dose-ranging studies, three pivotal studies and one supportive flexible-dose study. The applicant has provided support for efficacy of BRV in the treatment of POS at adjunctive doses of 50 mg/day to 200 mg/day.

The efficacy of brivaracetam in childhood POS is based on extrapolation of efficacy from currently approved adult clinical data previously submitted and adult data and PK bridging and no further clinical efficacy data is provided within this variation. This is in accordance with regulatory guidance and previous practice.

Doses of 1mg/kg/day to 4mg/kg/day are proposed for the treatment of children and adolescents <50kg, the adult dose range is proposed for adolescents 50kg or greater.

2.5.1. Conclusions on the clinical efficacy

Brivaracetam's efficacy as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in adolescents and children from 4 years of age with epilepsy is considered established based on PK data supporting a similar exposure as in adults, where clinical efficacy was directly studied.

2.6. Clinical safety

Introduction

The safety pool for pediatric subjects ⩾1 month to <17 years of age with epilepsy (Pool Paediatric Studies) included data from the completed open-label core study (N01263) and ongoing open-label, follow-up study (N01266). N01266 was initially designed as a long-term follow-up (LTFU) to N01263 (enrolled subjects with either focal epilepsy or generalized epilepsy), but was amended to allow direct enrollment of subjects ⩾4 to <17 years of age with focal epilepsy (Table 14.).

Subjects with POS in Pool Paediatric Studies were also summarized by POS summary groups: <4 years, ⩾4 to <16 years, and Total POS (included subjects who were 16 years of age at study entry). Paediatric subjects (who were <17 years of age at the time of study entry) enrolled in the adult studies were not included in Pool Paediatric Studies.

Subjects in the paediatric studies were given doses of BRV from 0.8 to 5.0mg/kg/day, not exceeding 200mg/day. For Pool Paediatric Studies, the calculation of BRV modal daily doses considered the administration of both oral solution and oral tablets, where oral solution was administered in mg/kg doses and tablets were administered in mg doses.

Table 14. Phase 2/3 studies of BRV in paediatric subjects with epilepsy:

Study number	Study description	Number of subjects receiving BRV		Maximum duration of treatment	Status
		Total	By age group: M/F		
N01263	Phase 2a, open-label, single-arm, multicenter, pharmacokinetic, safety, and efficacy study of adjunctive administration of BRV in subjects from ≥1mo to <16y old with epilepsy	99	≥1mo to <2y: 15/15 ≥2y to <12y: 26/25 ≥12y to <16y: 7/11	5 weeks	Complete
N01266	Phase 3, open-label, single-arm, multicenter, long-term, study to evaluate safety and efficacy of BRV used as adjunctive treatment in pediatric subjects with epilepsy	206	≥1mo to <2y: 12/13[a] ≥2y to <12y: 76/55[a] ≥12y to <17y: 27/23[a]	Na[b]	Ongoing

2.6.1. Main Studies

N01263*:* Brivaracetam oral solution was administered at weekly increasing doses of approximately 0.4, 0.8, and 1.6mg/kg twice-daily (bid) (0.8, 1.6, and 3.2mg/kg/day) for subjects ≥8 years of age and 0.5, 1.0, and 2.0mg/kg bid (1.0, 2.0, and 4.0mg/kg/day) for subjects <8 years of age. A total of 100 subjects were enrolled and 99 subjects received BRV, including 30 subjects who were 28 days to 23 months of age, 51 subjects who were 2 to 11 years of age, and 18 subjects who were 12 to <16 years of age. The final clinical study report (CSR) was submitted with the original application.

N01266*:* Still ongoing, initially designed as a (long-term follow-up) LTFU study to N01263 (enrolled subjects ≥1 month to <16 years of age with POS or generalized seizures), but was amended to allow direct enrolment of subjects ≥4 to <17 years of age with focal (herein called POS) epilepsy in order to have safety data for at least 100 subjects for 1 year to support the proposed indication as requested by the EU guidance on epilepsy. The age for enrolment of subjects from N01263 into N01266 was <17 years of age to allow for subjects who turned 16 during enrolment in N01263.

Dose adjustments of BRV and any concomitant AEDs are allowed at any time based on clinical judgment. Subjects who directly enrolled into N01266 participate in an Up-Titration Period of at least 7-days duration, after which such subjects enter the Evaluation Period and receive flexible dosing of BRV as described above.

Methods

Study periods and study participants

The Evaluation Visit (EV) corresponded to the first study visit for LTFU subjects, and for direct enrollers (DE) subjects to the visit at which they enter the Evaluation Period upon completion of the Screening Visit (ScrV) and at least 1 Titration Visit (TV), as shown below in Table 15.

Table 15. Schedule of all study assessments for LTFU subjects and assessments subsequent to the final TV for DE subjects:

Period	Screening [a]	Up-Titration		
Visit	Screening (ScrV)	Titration Visit 1 (TV1)	Titration Visit 2 (TV2)	Titration Visit 3 (TV3)
Assessment				
Hospital stays [a]		X	X	X

DE=directly enrolled; DTV=Down-Titration Visit; EDV=Early Discontinuation Visit; EV=Entry Visit; FEV= Full Evaluation Visit; FV=Final Visit; LTFU=long-term follow-up; MEV=Minimal Evaluation Visit; SV=Safety Visit; TV=Titration Visit; UV=Unscheduled Visit; V=Visit; YEV=Yearly Evaluation Visit

Source: Study CSR

The Up-Titration Period is only applicable to DE subjects, and the start date is the date of the first dose of BRV. The Evaluation Period extends from the EV to the Final Visit (FV) for subjects who continue in the study until it ends or until the Early Discontinuation Visit (EDV) for subjects who prematurely discontinue the study and down titrate BRV over a maximum of 4 weeks (Down-Titration Period) Table 16:

Table 16. All study assessments for LTFU subjects and assessments subsequent to the final TV for DE subjects:

Period	Evaluation						Down-Titration	Safety (Drug-free)
Visit	Entry Visit (EV)		Minimal Evaluation Visit (MEV)	Full Evaluation Visit (FEV)	Yearly Evaluation Visit/Final Visit (YEV/FV [b])	Unscheduled Visit (UV)	Early Discontinuation Visit (EDV)	Down-Titration Visit (DTV) [c]	Safety Visit (SV)
Subjects	LTFU [a]	DE	All						

DE=directly enrolled; DTV=Down-Titration Visit; EDV=Early Discontinuation Visit; EV=Entry Visit; FEV= Full Evaluation Visit; FV=Final Visit; LTFU=long-term follow-up; MEV=Minimal Evaluation Visit; SV=Safety Visit; TV=Titration Visit; UV=Unscheduled Visit; V=Visit; YEV=Yearly Evaluation Visit **Source: Study CSR**

After 2 weeks free of study drug (Safety Period), subjects will complete the Safety Visit (SV). During the Evaluation Period, Minimal Evaluation Visits (MEVs) and Full Evaluation Visits (FEVs) are performed alternatively every month during the first 3 months and every 3 months thereafter, with a Yearly Evaluation Visit (YEV) every 12 months. Both safety data and efficacy data (seizure data) are collected during the study. The Post-Baseline Period is defined as the Evaluation, Down-Titration, and Post-Treatment Periods combined.

Key inclusion criteria (main criteria presented here):

-LTFU subjects only

- Male or female subjects having participated in a previous paediatric study in epilepsy with BRV and for whom a reasonable benefit from long-term administration of BRV was expected.

-Direct enrollers subjects only

- Male or female ≥4 years to <17 years of age
- *clinical diagnosis of POS* according to the International League Against Epilepsy (ILAE) classification
- EEG compatible with the clinical diagnosis of POS
- Subject had been observed to have uncontrolled POS after an adequate course of treatment (in the opinion of the Investigator) with at least 1 AED (concurrently or sequentially)
- At least 1 seizure (POS) during the 3 weeks before the ScrV.
- Subject was taking at least 1 AED. All AEDs needed to be at a stable dose for at least 7 days before the ScrV. Vagal nerve stimulator stable for at least 2 weeks before the ScrV was allowed and was counted as a concomitant AED. Benzodiazepines taken more than once a week (for any indication) were considered as a concomitant AED.

Key exclusion criteria

- All subjects:

- pregnant or nursing female
- Severe medical, neurological, or psychiatric disorders or laboratory values, which may have an impact on the safety of the subject
- Poor compliance with the visit schedule or medication intake in the previous study, if applicable

-LTFU subjects only

- Subject had developed hypersensitivity to any components of the investigational medicinal product (IMP) or comparative drugs as stated in the protocol during the course of the previous BRV study.
- Poor compliance with the visit schedule or medication intake in the previous BRV study.

- Lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or had suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the C-SSRS at the EV.

-Direct enrollers subjects only

- Subject had previously received BRV.
- Concomitant use of LEV at the ScrV (LEV was prohibited for at least 4 weeks prior to the ScrV).
- Subject had epilepsy secondary to a progressive cerebral disease or tumour, or any other progressively neurodegenerative disease. Stable arteriovenous malformations, meningiomas, or other benign tumours may have been acceptable according to Investigator's opinion.
- History of primary generalized epilepsy.
- History of status epilepticus in the month immediately prior to the ScrV or during the Up-Titration Period.

Behaviour and cognition

The effect of BRV on behaviour was assessed using the Achenbach Child Behaviour Checklist (CBCL) in subjects ≥18 months of age.

The effect of BRV on cognition in subjects <18 months of age was assessed using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III®), applicable only to long-term follow-up [LTFU] subjects enrolled in English-speaking countries, whereas the effect of BRV on cognition in subjects ≥2 years of age (after Protocol Amendment 3, dated 26 Sep 2012) was explored using the Behaviour Rating Inventory of Executive Function®-Preschool Version/Behaviour Rating Inventory of Executive Function® (BRIEF-P/BRIEF).

The effect of BRV on health-related quality of life was explored using the Paediatric Quality of Life Inventory™ (PedsQL™) in subjects ≥1 month of age which after Protocol Amendment 3, was also added to the assessments for subjects ≥2 years of age.

Of note, full efficacy results, pharmacokinetics (PK), and direct cost parameters are not presented in this interim clinical study report (CSR), and will be fully reported only in the final CSR.

Treatments and dose selection

Brivaracetam oral solutions, at concentrations of 1.0mg/mL and 10mg/mL, are supplied in 150mL and 300mL glass bottles, respectively. Measuring devices are polypropylene syringes (1.0mL and 10mL) with an adaptor able to fit the 2 bottle sizes.

Brivaracetam oral tablets are provided in the following strengths: 10mg, 25mg, and 50mg.

Brivaracetam is administered twice daily (bid) in 2 equally divided doses approximately 12 hours apart. All LTFU subjects must be able to tolerate the minimum BRV dose specified in the previous study to be eligible for entry into the Evaluation Period of N01266. All DE subjects are screened and participate in up to 3 weeks of an Up-Titration Period during which are required to tolerate at least 1.0mg/kg/day prior to entering the Evaluation Period on that dose. Should a DE subject demonstrate, in the opinion of the Investigator, acceptable tolerability and seizure control on the same daily dose of BRV (no lower than the minimum specified dose) for 7±2 days during the Up-Titration Period, the subject attends the Entry Visit (EV) and enters the Evaluation Period on that dose.

With regards to the dose selection, the dosing scheme initially included in N01266 and gathered

from the PK analyses of study N01263 showed that the plasma concentrations approximating the concentrations for adults receiving BRV 200mg/day could not be achieved, hence the same doses were recommended in all paediatric subgroups, ≥1 month to <17 years of age. For all subjects, the approximate doses to be administered are 0.5, 1.0, and 2.0mg/kg bid (1.0, 2.0, and 4.0mg/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. This scheme was derived by the PK linearity of BRV in adults up to 1 order of magnitude above the therapeutic dose range, the expected efficacious dose to be from 50mg/day up to 200mg/day and by the faster BRV elimination observed in N01263 for paediatric subjects in respect with adults, resulting in a lower plasma concentration. Therefore, clearance of BRV was shown to be higher in paediatric subjects than in adult subjects.

Modal dose calculation

Modal daily dose is summarized by the following categories: 0.0 to <1.0, 1.0 to <2.0, 2.0 to <3.0, 3.0 to ≤4.0, and >4.0mg/kg/day, after conveniently convert the tablet doses (in mg/day) to mg/kg/day where appropriate and after considering both administration of oral solution and oral tablets.

Study Objectives

Primary objective: to document the long-term safety and tolerability of BRV.

Secondary objectives: to assess the efficacy of BRV during long-term exposure (with the final results for efficacy postponed to the final CSR)

Other objectives

- To assess the effect of BRV on behaviour using the Achenbach Child Behaviour Checklist (CBCL) in subjects ≥18 months of age

- To explore the effect of BRV on cognition using the Behaviour Rating Inventory of Executive Function®-Preschool Version/Behaviour Rating Inventory of Executive Function (BRIEF-P/BRIEF) in subjects ≥2 years of age

- To assess the effect of BRV on cognition using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) scales in subjects <18 months of age (applicable only to LTFU subjects enrolled in English-speaking countries)

– To explore the effect of BRV on health-related quality of life using the Paediatric Quality of Life Inventory™ (PedsQL™) in subjects ≥1 month of age.

Study variables

- *Efficacy and PK variables:* The interim report provided by the MAH does not include efficacy and PK assessments, that will be fully reported only once the final CSR will be available.

- *Safety variables*: -Adverse event (AE) reporting

- Safety laboratory tests (hematology, biochemistry, including hepatic monitoring of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, and gamma-glutamyltransferase, and endocrinology for all subjects, urinalysis for subjects ≥4 years of age, and pregnancy testing for female subjects with Tanner stage >1)

- Electrocardiogram (ECG)

- Physical examination (Tanner scale, if applicable depending on subject's developmental status) and neurological examination

- Psychiatric and mental status

- Vital signs (blood pressure, pulse rate, and body temperature)
- Body weight and height
- Assessment of suicidality

- *Other variables*: -Change from Baseline in the Achenbach CBCL score: the Achenbach CBCL/1½-5 for children from 1½ to 5 years old at the Baseline assessment and the Achenbach CBCL/6-18 for children 6 years and older at the Baseline assessment

- Change from Baseline in the BRIEF-P/BRIEF score for subjects ≥2 years of age.

Statistical methods

The data reported in the interim CSR included only subjects within the clinical cutoff date of 31 Aug 2016; after this date for the ongoing subjects were not included. All summaries are descriptive and no statistical hypothesis testing is planned.

For categorical parameters, the number and percentage of subjects in each category were presented. The denominator for percentages is based on the number of subjects appropriate for the purpose of analysis. For continuous parameters, descriptive statistics include number of subjects (n), mean, standard deviation, median, minimum, and maximum.

The **Safety Set** (SS) consists of all enrolled subjects who took at least 1 dose of BRV in this long-term study. The **Full Analysis Set** (FAS) consists of all subjects in the SS who have a Baseline and at least 1 completed post-Baseline daily record card or EEG. All safety analyses were performed on the SS.

Adverse events were tabulated by MeDRA SOC and PT. All AE summaries were presented by 3-month time intervals.

Results

Subject disposition

Table 17 summarizes the disposition and discontinuation reasons overall and by cohort for the SS:

Table 17. Summary of subject disposition and discontinuation reasons by cohort (SS):

Disposition	**LTFU Cohort N=86** n (%)	**DE Cohort N=120** n (%)	**All subjects N=206** n (%)
Started study	**86 (100)**	**120 (100)**	**206 (100)**
Completed study	0	0	0
Ongoing	41 (47.7)	85 (70.8)	126 (61.2)
Discontinued	45 (52.3)	35 (29.2)	80 (38.8)
Primary reason for discontinuation			
Lack of efficacy	12 (14.0)	16 (13.3)	28 (13.6)
Adverse event	13 (15.1)	5 (4.2)	18 (8.7)
Consent withdrawn	12 (14.0)	6 (5.0)	18 (8.7)
Other	4 (4.7)	4 (3.3)	8 (3.9)
Unknown [a]	2 (2.3)	2 (1.7)	4 (1.9)
Lost to follow up	2 (2.3)	1 (0.8)	3 (1.5)
Protocol violation	0	1 (0.8)	1 (0.5)

DE=directly enrolled; LTFU=long-term follow up; SS=Safety Set

Note: Percentages are based on the number of subjects in the SS.

[a] *Subjects 114-01839, 201-01581, 308-07715, and 308-07716 have missing primary reasons for discontinuation in the interim database.*

Data sources: Table 1.2 and Table 1.2.1

As of the clinical cut-off date of 31 Aug 2016, 213 subjects had enrolled in the study and after 7 screening failures from the DE group only, 206 subjects started the study and were included in the SS, comprehending 86 subjects and 120 subjects in the LTFU cohort and the DE cohort, respectively. According to age subgroups overall, in the ≥1 month to <2 years, the ≥2 to <12 years and the ≥12 to <17 years groups there are n=25, n=131 and n=50 subjects, respectively.

A total of 126 subjects (61.2%) are ongoing; of these, 41 subjects (47.7%) and 85 subjects (70.8%) are in the LTFU cohort and in the DE cohort, respectively. Overall, 80 subjects (38.8%) discontinued from the study, including 45 subjects (52.3%) in the LTFU cohort and 35 subjects (29.2%) in the DE cohort. Lack of efficacy was the most common primary reason for discontinuation (28 subjects [13.6%]), followed by adverse events and consent withdrawn (18 subjects [8.7%] each) both prevailing in the LTFU cohort.

Baseline data

Demographics

Overall, the mean age of subjects in the SS at the time of entry into the study was 8.32 years (range: 0.17 to 16.92 years). The mean age of subjects by age groups was 1.21, 7.53, and 13.92 years in the ≥1 month to <2 years, ≥2 to <12 years, and ≥12 to <17 years of age groups, respectively. The mean weight was 9.54, 27.12, and 51.91kg in the ≥1 month to <2 years, ≥2 to <12 years, and ≥12 to <17 years of age groups, respectively. LTFU subjects weighed ≥3kg (per Inclusion Criterion 8 of N01263). The mean height was 75.26, 123.77, and 158.41cm in the ≥1 month to <2 years, ≥2 to <12 years, and ≥12 to <17 years of age groups, respectively. The mean BMI was 16.27, 17.05, and 20.52kg/m2 in the ≥1 month to <2 years, ≥2 to <12 years, and ≥12 to <17 years of age groups, respectively. Overall, 115 subjects (55.8%) were male, and the majority of subjects were White (146 subjects [70.9%]) and not of Hispanic or Latino ethnicity (141 subjects [68.4%]).

Seizure classification history

Mean age at time of diagnosis was 0.52 years, 2.99 years and 6.02 years in the ≥1 month to <2 years group, the ≥2 to <12 years, and the ≥12 to <17 years of age groups, respectively, with a total of 10 subjects (4.9%) having a history of status epilepticus.

The majority of subjects presented type I (focal) seizures (176 subjects [85.4%]), whereas 47 subjects (22.8%) had type II (generalized) seizures, according to ILAE 1981 classification. In the former group, 120 subjects (58.3%) reported seizures at Baseline that were classified as belonging to group 1B (complex partial), followed by 92 subjects (44.7%) classified as having seizures of type 1C (partial evolving to secondary generalized). Among subjects of the latter group, the most frequently reported seizures at Baseline were type IIB (myoclonic) for 24 subjects (11.7%), followed by tonic (type IID) and tonic-clonic (type IIE) for 17 subjects (8.3%) each. A total of 7 subjects (3.4%) had an unclassifiable seizure profile.

Table 18 summarizes the classification of epileptic syndromes for the subject population:

Table 18. Baseline classification of epileptic syndromes (SS):

Classification	**≥1 month to <2 years N=25** n(%)	**≥2 to <12 years N=131** n(%)	**≥12 to <17 years N=50** n(%)	**All subjects N=206** n(%)
Localization-related	**13 (52.0)**	**101 (77.1)**	**40 (80.0)**	**154 (74.8)**
Idiopathic	1 (4.0)	4 (3.1)	1 (2.0)	6 (2.9)

Cryptogenic or symptomatic	12 (48.0)	97 (74.0)	39 (78.0)	148 (71.8)
Generalized	**9 (36.0)**	**24 (18.3)**	**10 (20.0)**	**43 (20.9)**
Idiopathic	1 (4.0)	6 (4.6)	6 (12.0)	13 (6.3)
Cryptographic or symptomatic	5 (20.0)	10 (7.6)	3 (6.0)	18 (8.7)
Symptomatic	3 (12.0)	10 (7.6)	1 (2.0)	14 (6.8)
Specific syndromes	**1 (4.0)**	**3 (2.3)**	**0**	**4 (1.9)**
Undetermined	6 (24.0)	7 (5.3)	1 (2.0)	14 (6.8)
Generalized and focal	**1 (4.0)**	**6 (4.6)**	**0**	**7 (3.4)**
Other	5 (20.0)	1 (0.8)	1 (2.0)	7 (3.4)
Special syndromes	0	3 (2.3)	0	3 (1.5)
Situation-related syndromes	0	3 (2.3)	0	3 (1.5)

DE=directly enrolled; eCRF=electronic Case Report Form; LTFU=long-term follow-up; SS=Safety Set

Note: Seizures experienced at any time prior to study entry were summarized.

Note: The history of epilepsy used eCRF information collected at the time of entry into the previous study for LTFU subjects or at the time of entry into N01266 for DE subjects.

Note: Subjects may have been classified under more than 1 epileptic syndrome at Baseline. Data source: Table 5.1.2

Previous and ongoing diseases (epilepsy excluded)

Excluding epilepsy, 188 subjects (90.3%) had at least 1 previous (resolved) or ongoing general medical condition at the ScrV of the previous study for LTFU subjects or at the ScrV of N01266 for DE subjects. In this category, the most common prior and concomitant medical conditions (≥30% of all subjects) were reported in the SOC of Nervous system disorders (108 subjects [52.4%]), followed by Infections and infestations (70 subjects [34.0%]) and Congenital, familial and genetic disorders (64 subjects [31.1%]), with developmental delay being the most common PT (32 subjects [15.5%).

Prior AEDs

Overall, 185 subjects (89.8%) had taken at least one AED prior to entry into the parent BRV study (LTFU subjects) and into N01266 (DE subjects). A total of 59 subjects (28.6%) had taken 0 to 1 prior AEDs, 83 subjects (40.3%) had taken 2 to 4 prior AEDs, and 64 subjects (31.1%) had taken 5 or more prior AEDs. Levetiracetam (LEV) was the most common prior AED (113 subjects [54.9%]). The proportions of subjects aged 2 to <12 years and 12 to <17 years were comparable in terms of prior AEDs (in descending order: LEV, DPA, TPM, CBZ, OXC, LTG, CLB, CNZ). Vigabatrin is most commonly used in subjects with West syndrome as expected by its highest incidence below 2 years of age.

AED medications taken at study entry

The proportions of the most common (≥10% of all subjects) AED medications taken at entry into the previous study for LTFU subjects and time of entry into N01266 for DE subjects are summarized in Table 19. .

Table 19. AEDs taken at study entry by ≥10% of all subjects (SS):

WHO-DRL Preferred drug name	**≥1 month to <2 years N=25 n (%)**	**≥2 to <12 years N=131 n (%)**	**≥12 to <17 years N=50 n (%)**	**All subjects N=206 n (%)**
At least 1 AED	25 (100)	131 (100)	50 (100)	206 (100)
Valproate	12 (48.0)	64 (48.9)	23 (46.0)	99 (48.1)
Topiramate	7 (28.0)	32 (24.4)	7 (14.0)	46 (22.3)
Lamotrigine	1 (4.0)	24 (18.3)	14 (28.0)	39 (18.9)
Oxcarbazepine	3 (12.0)	22 (16.8)	10 (20.0)	35 (17.0)
Clobazam	4 (16.0)	24 (18.3)	7 (14.0)	35 (17.0)

Carbamazepine	2 (8.0)	23 (17.6)	9 (18.0)	34 (16.5)
Diazepam	0	18 (13.7)	7 (14.0)	25 (12.1)

AED=antiepileptic drug; BRV=brivaracetam; DE=directly enrolled; LTFU=long-term follow-up; SS=Safety Set; WHO-DRL=World Health Organization Drug Reference List

Note: Only AEDs ongoing at the time of study entry are summarized.

Note: Study entry for LTFU subjects was defined as the time of entry into the previous BRV study and for DE subjects was time of entry into N01266.

Note: WHO-DRL Version Jun/2012 was used. Data source: Table 6.2.5

The totality of LTFU and DE subjects were taking at least 1 AED at entry into the previous study or at entry at N01266 study, respectively. Fifty-nine subjects (28.6%) reported taking 1 AED, 93 subjects (45.1%), and 54 subjects (26.2%) reported taking 2 AEDs and ≥3 AEDs at study entry, respectively. A total of 9 subjects (4.4%) were using VNS at the time of study entry, including 4 subjects (3.1%) in the 2 to <12 years age group and 5 subjects (10.0%) in the 12 to <17 years age group.

Concomitant AEDs

All 206 subjects were taking at least 1 concomitant AED. Valproate was the most commonly reported concomitant AED, taken by approximately half of all subjects (104 subjects [50.5%]), followed by diazepam (55 subjects [26.7%]), clobazam (53 subjects [25.7%]), topiramate (52 subject [25.2%]), lamotrigine (48 subjects [23.3%]), oxcarbazepine (39 subjects [18.9%]) and carbamazepine (38 subjects [18.4%]).

Non-AED medications at study entry

Most non-AEDs taken at study entry by ≥5 subjects were in the pharmacological groups of the Nervous system (44 subjects [21.4% of all subjects]) and alimentary tract and metabolism (40 subjects [19.4% of all subjects]). Paracetamol and risperidone were the most common non anticonvulsant drugs at study entry (9 subjects [4.4%] each), followed by colecalciferol and melatonin (7 subjects [3.4%] each), macrogol, ibuprofen, levothyroxine sodium, and pyridoxine hydrochloride (6 subjects [2.9%] each), and methylphenidate and folic acid (5 subjects [2.5%] each).

Concomitant non-AED medications

The majority of subjects (180 subjects [87.4%]) were taking at least 1 concomitant non-AED during the study, being anti-infectives for systemic use (139 subjects [67.5%]) and nervous system (126 subjects [61.2%]), the most commonly reported concomitant non-AEDs, followed by alimentary tract and metabolism (107 subjects [51.9%]), and respiratory system (105 subjects [51.0%]).

Adult Safety Pools (for comparison)

Pool S4

Pool S4 was originally defined for the original application and consisted of subjects with focal or generalized epilepsy who received BRV in core studies N01114, N01193, N01252, N01253, N01254, N01358, and N01395, and follow-up studies N01125, N01199, N01372, and N01379, excluding subjects who enrolled in N01372 from N01394. No new subjects were added to Pool S4 since the original application was reviewed. The clinical cutoff date for the current application includes approximately 2 years of additional exposure to BRV.

Subjects in N01258 were included in Pool S4 only if they received BRV in N01379. Only safety data collected during treatment with BRV in N01379 were included in the integrated summaries for Pool S4. N01114 included a Conversion Period during which subjects randomized to placebo (PBO)

started treatment with BRV prior to enrollment in follow-up study N01125. All subjects who received BRV during the Conversion Period were included in Pool S4.

Pool Monotherapy

Pool Monotherapy was originally defined for the original application and consisted of subjects who received BRV in core studies N01276 and N01306, and LTFU study N01315. No new subjects were added to Pool Monotherapy since the original application was reviewed. The clinical cutoff date for the current application includes approximately 2 years of additional exposure to BRV.

Except when noted, summaries for Pool Monotherapy presented results for all BRV doses combined and by modal dose categories 5, 20, 50, 100, 150, and 200mg/day.

Of 150 randomized subjects in N01276 or N01306, all 150 subjects received BRV and comprised Pool Monotherapy.

Pool ULD

Pool ULD consisted of subjects with ULD who received BRV in core studies N01187 and N01236 and follow-up study N01125. No new subjects were added to Pool ULD since the original application was reviewed. The clinical cutoff date for the current application includes approximately 2 years of additional exposure to BRV.

N01187 and N01236 included a Conversion Period during which subjects randomized to PBO started treatment with BRV prior to enrollment into follow-up study N01125. All subjects who received BRV during the Conversion Period were included in Pool ULD, including any subjects who did not receive BRV in N01125.

Patient exposure

In Pool Paediatric Studies, of the 219 paediatric subjects exposed to BRV, 168 were subjects with POS. Of these paediatric subjects with POS, 16 subjects were <4 years of age, 149 subjects were ≥ 4 to <16 years of age, and 3 subjects were 16 years of age. The total subject-years of exposure for all subjects in Pool Paediatric Studies was 399.5 years and for subjects ≥ 4 to <16 years with POS was 249.7 years. For paediatric subjects ≥ 4 to <16 years with POS, 116 subjects (77.9%) were exposed to BRV for ≥ 6 months, 104 subjects (69.8%) for ≥ 12 months, 58 subjects (38.9%) for ≥ 24 months, 14 subjects (9.4%) for ≥ 48 months, and 2 subjects (1.3%) for ≥ 60 months.

An overall summary of subject-years of exposure and duration of exposure to BRV in BRV Overall by paediatric summary group in Pool Paediatric Studies is presented in Table 20. .

Table 20. Overall BRV exposure by paediatric summary group in Pool Paediatric Studies

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

BRV=brivaracetam; ISS=Integrated Summary of Safety; POS=partial-onset seizures; y=years
Note: Pool Pediatric Studies consisted of subjects from N01263 and N01266.
Note: The Total POS summary group included subjects <4 years, ≥4 to <16 years, and subjects who were 16 years at the time of study entry.
Note: All pediatric subjects included subjects with POS and other seizure types.

As of the clinical cutoff date, a total of 206 subjects had been exposed to at least 1 dose of BRV in N01266 for a total of 393.7 subject-years. Of these, 145 subjects (70.4%) had been exposed to BRV for at least 12 months, 92 subjects (44.7%) had been exposed to BRV for at least 24 months, 50 subjects (24.3%) had been exposed to BRV for at least 36 months, and 32 subjects (15.5%) had been exposed to BRV for at least 48 months.

Overall, the highest percentage of subjects had BRV modal daily doses >4.0mg/kg/day (96 subjects [46.6%]), followed by >3.0 to 4.0mg/kg/day (63 subjects [30.6%]) and >2.0 to 3.0mg/kg/day (26 subjects [12.6%]). Few subjects (n=15) had modal doses below 2.0mg/kg/day.

Of the subjects with a BRV modal dose >4.0mg/kg/day, 4 subjects had a modal dose between 4.38 and 4.6mg/kg/day; 15 subjects had a modal dose of 5.0mg/kg/day; 3 subjects had a modal dose >5.0mg/kg/day (modal doses of 5.17, 6.0, and 6.0mg/kg/day); and 30 subjects weighed <50kg and had tablet doses ≥ 4mg/kg/day when converted to mg/kg/day. A total of 31 subjects were ever exposed to a dose of ≥ 5.0mg/kg/day.

The majority of subjects (53.1%) who had a modal dose >4.0mg/kg/day remained in the study for at least 24 months. For subjects who had modal doses of >3.0 to 4.0mg/kg/day and of >2.0 to 3.0mg/kg/day a majority (≥ 50%) remained on treatment for at least 21 months and 18 months, respectively.

A summary of subject disposition and discontinuation reasons in BRV Overall by paediatric summary group in Pool Paediatric Studies is presented in Table 21. .

Table 21. Disposition and discontinuation reasons in BRV Overall paediatric summary group in Pool Paediatric Studies

	BRV Overall			
	POS summary group			All pediatric subjects N=219 n (%)
	<4y N=16 n (%)	≥4 to <16y N=149 n (%)	Total POS N=168 n (%)	
Ongoing subjects [a]	7 (43.8)	97 (65.1)	105 (62.5)	126 (57.5)
Completed core study and did not enter long-term study	0	2 (1.3)	2 (1.2)	4 (1.8)
Discontinued [b]	9 (56.3)	50 (33.6)	61 (36.3)	89 (40.6)
Reason for discontinuation				
Adverse event	2 (12.5)	11 (7.4)	14 (8.3)	24 (11.0)
Lack of efficacy	3 (18.8)	16 (10.7)	20 (11.9)	29 (13.2)
Lost to follow up	0	2 (1.3)	2 (1.2)	3 (1.4)
Subject choice	1 (6.3)	12 (8.1)	13 (7.7)	19 (8.7)
Other	2 (12.5)	7 (4.7)	9 (5.4)	10 (4.6)
Missing	1 (6.3)	2 (1.3)	3 (1.8)	4 (1.8)

BRV=brivaracetam; ISS=Integrated Summary of Safety; POS=partial-onset seizures; y=years
Note: Subjects with more than 1 reason for discontinuation were summarized for all reported reasons.
Note: The Total POS summary group included subjects <4 years, ≥4 to <16 years, and subjects who were 16 years at the time of study entry.
Note: All pediatric subjects included subjects with POS and other seizure types.
[a] The number of ongoing subjects at the time of the clinical cutoff date (31 Aug 2016).
[b] Included subjects who discontinued the study but the reason for discontinuation was not available in the clinical database. Such subjects were counted in the Missing category.

An overall summary of subject disposition and discontinuation reasons for subjects ≥4 to <16 years with POS by BRV modal daily dose in Pool Paediatric Studies is presented in Table 22. .

Table 22. Subject disposition and discontinuation reasons for subjects ⩾4 to <16 years with POS by BRV modal daily dose in Pool Paediatric Studies

	BRV modal daily dose (mg/kg/day)[b]					BRV Overall N=149 n (%)
	0.0 to 1.0 N=15 n (%)	>1.0 to 2.0 N=10 n (%)	>2.0 to 3.0 N=19 n (%)	>3.0 to 4.0 N=79 n (%)	>4.0 N=26 n (%)	
Ongoing subjects [a]	7 (46.7)	5 (50.0)	10 (52.6)	54 (68.4)	21 (80.8)	97 (65.1)
Completed N01263 core study and did not enter long-term study	0	2 (20.0)	0	0	0	2 (1.3)
Discontinued [b]	8 (53.3)	3 (30.0)	9 (47.4)	25 (31.6)	5 (19.2)	50 (33.6)
Reason for discontinuation						
Adverse event	5 (33.3)	0	0	6 (7.6)	0	11 (7.4)
Lack of efficacy	1 (6.7)	0	5 (26.3)	8 (10.1)	2 (7.7)	16 (10.7)
Lost to follow up	1 (6.7)	0	1 (5.3)	0	0	2 (1.3)
Subject choice	1 (6.7)	2 (20.0)	1 (5.3)	7 (8.9)	1 (3.8)	12 (8.1)
Other	0	1 (10.0)	2 (10.5)	3 (3.8)	1 (3.8)	7 (4.7)
Missing	0	0	0	1 (1.3)	1 (3.8)	2 (1.3)

BRV=brivaracetam; ISS=Integrated Summary of Safety; POS=partial-onset seizures
Note: Subjects with more than 1 reason for discontinuation were summarized for all reported reasons.
[a] The number of ongoing subjects at the time of the clinical cutoff date (31 Aug 2016).
[b] Included subjects who discontinued the study but the reason for discontinuation was not available in the clinical database. Such subjects were counted in the Missing category.

The ≥4 to <16 years POS group in Pool Paediatric Studies included 149 subjects who received BRV. Of these subjects, 97 (65.1%) were still participating in the long-term study (ongoing) at the time of the clinical cutoff date (31 Aug 2016) in BRV Overall; 2 subjects (1.3%) completed the core study but did not enter the long-term study. A total of 50 subjects (33.6%) in BRV Overall discontinued from either the core study or long-term study; the most frequently reported primary reason for discontinuation was lack of efficacy (16 subjects [10.7%]).

Across BRV modal daily dose groups, in general, the results were similar and there were no dose-related trends. The exceptions were the BRV 0.0 to 1.0mg/kg/day group, where the most frequently reported primary reason for discontinuation was AE (5 subjects [33.3%]), and the BRV >1.0 to 2.0mg/kg/day group, where the most frequently reported primary reason for discontinuation was subject choice (2 subjects [20.0%]).

Adult/adolescent exposure

In addition to data from the paediatric BRV clinical studies included in this application, data are included for the adult BRV studies (see above). In Pool Monotherapy, 150 subjects were exposed to BRV; the total subject-years of exposure was 394.6 years. In Pool S4, of the 2437 subjects exposed to BRV, 2368 were subjects with POS; the total subject-years of exposure for all subjects in Pool S4 was 7878.9 years. In Pool ULD, 102 subjects were exposed to BRV; the total subject-years of exposure was 459.7 years.

Demographic and baseline characteristics

A summary of demographic and baseline characteristics in BRV Overall by paediatric summary group in Pool Paediatric Studies is presented in Table 23. .

Table 23. Demographic and baseline characteristics in BRV Overall by paediatric summary group in Pool Paediatric Studies

	BRV Overall			
	POS summary group			**All paediatric subjects**
	<4y	**≥4 to <16y**	**Total POS**	
	N=16	**N=149**	**N=168**	**N=219**
Age (years)				
n	16	149	168	219
Mean (SD)	0.8 (0.7)	9.0 (3.4)	8.4 (4.2)	7.7 (4.5)
Median	1.0	9.0	9.0	8.0
Min, max	0, 2	4, 15	0, 16	0, 16
Gender, n (%)				
Male	12 (75.0)	84 (56.4)	97 (57.7)	120 (54.8)
Female	4 (25.0)	65 (43.6)	71 (42.3)	99 (45.2)
Overall racial group, n (%)				
White	12 (75.0)	98 (65.8)	112 (66.7)	154 (70.3)
Black	0	4 (2.7)	4 (2.4)	4 (1.8)
Other	4 (25.0)	47 (31.5)	52 (31.0)	61 (27.9)
Racial group, n (%)				
Black	0	4 (2.7)	4 (2.4)	4 (1.8)
White	12 (75.0)	98 (65.8)	112 (66.7)	154 (70.3)
Other/Mixed	4 (25.0)	47 (31.5)	52 (31.0)	61 (27.9)
Weight (kg)				

n	16	149	168	219
Mean (SD)	10.3 (2.9)	34.9 (16.1)	32.9 (17.1)	30.6 (17.4)
Median	10.8	31.2	28.4	26.7
Min, max	5, 15	11, 104	5, 104	4, 104
Height (cm)				
n	16	149	168	219
Mean (SD)	77.1 (8.6)	135.1 (20.2)	130.1 (26.1)	125.3 (29.3)
Median	76.5	135.7	131.8	128.0
Min, max	59, 90	90, 181	59, 181	55, 181
BMI (kg/m2)				
n	16	149	168	219
Mean (SD)	16.8 (2.5)	18.2 (4.3)	18.1 (4.2)	17.8 (4.1)
Median	16.8	17.3	17.3	17.2
Min, max	13, 21	9, 40	9, 40	9, 40
Head circumference (cm)				
n	14	141	158	204
Mean (SD)	44.6 (3.1)	52.1 (3.0)	51.5 (3.7)	50.7 (4.4)
Median	45.4	52.1	52.0	51.6
Min, max	39, 48	44, 60	39, 60	36, 60
AED inducer status, n (%)				
Inducer at core study entry	7 (43.8)	78 (52.3)	87 (51.8)	100 (45.7)
No inducer at core study entry	9 (56.3)	71 (47.7)	81 (48.2)	119 (54.3)
Number of previous AEDs, n (%)				
0 to 1	8 (50.0)	41 (27.5)	49 (29.2)	65 (29.7)
2 to 4	7 (43.8)	61 (40.9)	70 (41.7)	86 (39.3)
≥5	1 (6.3)	47 (31.5)	49 (29.2)	68 (31.1)
Geographic region (FDA classification), n (%)				
North America	6 (37.5)	40 (26.8)	47 (28.0)	55 (25.1)
Latin America	6 (37.5)	48 (32.2)	55 (32.7)	63 (28.8)
Western Europe	2 (12.5)	19 (12.8)	21 (12.5)	33 (15.1)
Eastern Europe	2 (12.5)	42 (28.2)	45 (26.8)	68 (31.1)
Geographic region (CHMP classification), n (%)				
North America	6 (37.5)	40 (26.8)	47 (28.0)	55 (25.1)
Latin America	6 (37.5)	48 (32.2)	55 (32.7)	63 (28.8)
Europe (EU member states)	4 (25.0)	61 (40.9)	66 (39.3)	101 (46.1)

AED=antiepileptic drug; BMI=body mass index; BRV=brivaracetam; CHMP=Committee for Medicinal Products for Human Use; EU=European Union; FDA=Food and Drug Administration; ISS=Integrated Summary of Safety; max=maximum; min=minimum; POS=partial-onset seizures; SD=standard deviation; y=years

Note: The Total POS summary group included subjects <4 years, ≥4 to <16 years, and subjects who were 16 years at the time of study entry.

Note: All pediatric subjects included subjects with POS and other seizure types.

In Pool Paediatric Studies, the age ranged from 0 to 16 years, approximately half the subjects were male, and the majority of subjects were White. In the ≥ 4 to <16 years POS group in Pool Paediatric Studies, the mean age was 9.0 years (range: 4 to 15 years); other demographic and baseline characteristics were similar to all subjects in Pool Paediatric Studies. There were no notable differences in subject demographic characteristics across BRV modal daily dose groups.

The demographic and baseline characteristics of subjects with POS in Pool Paediatric Studies were comparable with Pool S4, with the exception of age, height, weight, and body mass index, as expected. In general, the demographic and baseline characteristics of Pool Monotherapy, Pool S4,

and Pool ULD were similar for gender (approximately half males and half females), mean age (ranged from 36.3 to 39.6 years), and overall racial group (majority were White). In Pool Monotherapy, the percentage of subjects who were taking an AED inducer at core study entry was higher (47.3%), compared with Pool S4 and Pool ULD (14.7% and 29.4%, respectively); and in Pool ULD, the majority of subjects took 2 to 4 previous AEDs (73.5%), compared with Pool Monotherapy and Pool S4 (44.7% and 43.4%, respectively). Though there are understandable differences between the populations (eg, POS vs ULD), the demographic and Baseline characteristics in the various pools were generally similar. In addition, to the previous adult subject exposures, an adequate number of paediatric subject exposures are included in this application to characterize the safety of BRV at doses 50 to 200mg/day for up to 60 months of exposure.

Medical history for studies in paediatric subjects with epilepsy (Pool Pediatric Studies)

Table 24. summarizes the most relevant pre-existing conditions that were deemed most representative in the relevant 4 to <16 years is age subgroup:

Table 24. Medical history by POS Summary Groups (POS subjects ≥4 to <16 years)

MedDRA (Version 15.0)	**BRV modal daily dose (mg/kg/day)**					**BRV Overall N=149**
Primary SOC / **PT**	**0.0 to 1.0 N=15 n (%)**	**>1.0 to 2.0 N=10 n (%)**	**>2.0 to 3.0 N=19 n (%)**	**>3.0 to 4.0 N=79 n (%)**	**>4.0 N=26 n (%)**	
At least 1 history	13 (86.7)	9 (90.0)	17 (89.5)	71 (89.9)	24 92.3)	134 (89.9)
Congenital, familial and genetic disorders	6 (40.0)	3 (30.0)	5 (26.3)	21 (26.6)	8 (30.8)	43 (28.9)
Cerebral palsy	2 (13.3)	2 (20.0)	3 (15.8)	5 (6.3)	4 (15.4)	16 (10.7)
Eye disorders	2 (13.3)	1 (10.0)	2 (10.5)	15 (19.0)	2 (7.7)	22 (14.8)
Strabismus	0	1 (10.0)	1 (5.3)	9 (11.4)	0	11 (7.4)
Gastrointestinal disorders	2 (13.1)	1 (10.0)	3 (15.8)	16 (20.3)	4 (15.4)	26 (17.4)
Constipation	1 (6.7)	0	0	5 (6.3)	3 (11.5)	9 (6.0)
General disorders and administration site conditions	4 (26.7)	0	4 (21.1)	15 (19.0)	3 (11.5)	26 (17.4)
Developmental delay	4 (26.7)	0	4 (21.1)	13 (16.5)	1 (3.8)	22 (14.8)
Infections and infestations	4 (26.7)	3 (30.0)	9 (47.4)	23 (29.1)	7 (26.9)	46 (30.9)
Injury, poisoning and procedural complications	1 (6.7)	1 (10.0)	4 (21.1)	15 (19.0)	3 (11.5)	24 (16.1)
Nervous system disorders	6 (40.0)	6 (60.0)	10 (52.6)	43 (54.4)	15	80 (53.7)
Mental retardation	0	1 (10.0)	1 (5.3)	7 (8.9)	2 (7.7)	11 (7.4)
Hemiparesis	2 (13.3)	2 (2.0)	1 (5.3)	1 (1.3)	2 (7.7)	8 (5.4)
Encephalitis	0	2 (2.0)	0	3 (3.8)	1 (3.8)	6 (4.0)
Psychiatric disorders	8 (53.3)	0	4 (21.1)	18 (22.8)	11	41 (27.5)
ADHD	3 (20.0)	0	2 (10.5)	10 (12.7)	6 (23.1)	21 (14.1)
Abnormal behaviour	1 (6.7)	0	0	4 (5.1)	1 (3.8)	6 (4.0)
Respiratory, thoracic and mediastinal disorders	1 (6.7)	0	3 (15.8)	15 (19.0)	6 (23.1)	25 (16.8)
Asthma	0	0	3 (15.8)	5 (6.3)	2 (7.7)	10 (6.7)

Skin and subcutaneous tissue disorders	2 (13.3)	1 (10.0)	0	9 (11.4)	5 (19.2)	17 (11.4)

Note: Medical history includes both conditions that resolved prior to study entry and conditions that were ongoing at study entry.

Note: Total daily doses for subjects taking tablets and weighing >=50kg at Baseline are converted to mg/kg/day by dividing the total daily dose in mg/day by 50kg.

Note: The Total POS subjects summary group includes subjects <4 years of age, 4 to <16 years of age, and subjects who were 16 years of age at the time of study entry. Source: ISS Table 3.2.1B

In Pool Paediatric Studies, pre-existing conditions or diseases were reported as medical history by the vast majority of subjects (n=196 [89.5%]). The most frequently reported conditions/diseases were developmental delay (34 subjects [15.5%]), attention deficit/hyperactivity disorder (24 subjects [11.0%]), cerebral palsy (20 subjects [9.1%]), constipation (19 subjects [8.7%]), and gastroesophageal reflux disease (18 subjects [8.2%]). The reported medical history in Pool Pediatric Studies is typical of pediatric subjects with epilepsy.

The vast majority of POS subjects in ≥the 4 to <16 years age group (n=134 [89.9%]) had at least one medical history including conditions that resolved prior or that were ongoing at study entry without relevant differences among modal daily dose categories (range: 86.7%-92.3%). The most frequently reported conditions/diseases by Preferred Term were developmental delay (22 subjects [14.8%]), attention deficit/hyperactivity disorder (21 subjects [14.1%]), cerebral palsy (16 subjects [10.7%]), and strabismus and mental retardation (11 subjects each [7.4%]). With respect to ADHD, there seemed to be a trend toward a dose-effect, from the >2 to 3 mg/kg/day modal dose (2 subjects [10.5%] towards >4 mg/kg/day modal daily dose (6 subjects [23.1%]). However the number seemed overall too small to draw definitive conclusions.

Concomitant medications

In Pool Paediatric Studies, all 219 subjects were taking AEDs at study entry and used concomitant AEDs during the studies. The use of LEV at study entry and for the 4 weeks prior to the Screening Visit was an exclusion criterion. The most frequently used concomitant AEDs during the studies were valproate, diazepam, clobazam, topiramate, and lamotrigine.

In the ≥ 4 to <16 years POS group in Pool Paediatric Studies, all 149 subjects were taking AEDs at study entry and used concomitant AEDs during the studies. The most frequently used concomitant AEDs during the studies were valproate, diazepam, lamotrigine, carbamazepine, topiramate, oxcarbazepine, and clobazam. There were no notable differences in concomitant AED use across BRV modal daily dose groups.

In Pool S4, 99.9% of subjects used concomitant AEDs during the studies; the most frequently reported concomitant AEDs were carbamazepine, lamotrigine, valproate, and topiramate. Concomitant AEDs used in Pool S4, Pool Monotherapy, and Pool ULD were representative of the target population (Table 25. and Table 26.).

Table 25. AEDs taken at study entry and concomitant AEDs used by ⩾5% of subjects in BRV Overall for all paediatric subjects

Preferred drug name	BRV Overall			
	POS summary group			All pediatric subjects N=219 n (%)
	<4y N=16 n (%)	≥4 to <16y N=149 n (%)	Total POS N=168 n (%)	
At least 1 medication	16 (100)	149 (100)	168 (100)	219 (100)
Valproate	5 (31.3)	66 (44.3)	72 (42.9)	109 (49.8)
Topiramate	4 (25.0)	31 (20.8)	36 (21.4)	47 (21.5)
Lamotrigine	0	30 (20.1)	31 (18.5)	40 (18.3)
Oxcarbazepine	3 (18.8)	31 (20.8)	34 (20.2)	37 (16.9)
Carbamazepine	2 (12.5)	32 (21.5)	36 (21.4)	36 (16.4)
Clobazam	2 (12.5)	23 (15.4)	25 (14.9)	35 (16.0)
Diazepam	1 (6.3)	21 (14.1)	23 (13.7)	28 (12.8)
Lacosamide	0	16 (10.7)	16 (9.5)	18 (8.2)
Phenobarbital	3 (18.8)	4 (2.7)	7 (4.2)	17 (7.8)
Zonisamide	1 (6.3)	11 (7.4)	12 (7.1)	14 (6.4)
Clonazepam	1 (6.3)	11 (7.4)	12 (7.1)	12 (5.5)
Vigabatrin	2 (12.5)	5 (3.4)	7 (4.2)	11 (5.0)

AED=antiepileptic drug; BRV=brivaracetam; ISS=Integrated Summary of Safety; POS=partial-onset seizures; WHO-DRL=World Health Organization Drug Reference List; y=years

Note: This table summarizes AEDs taken at study entry by ≥5% of all pediatric subjects in BRV Overall.

Note: Drugs were coded using WHO-DRL version Jun/2012.

Note: Valproate included valproate sodium, valproate semisodium, valproate bismuth, valproate magnesium, valpromide, Ergenyl Chrono, and valproic acid. Phenobarbital included phenobarbital sodium, methylphenobarbital, metharbital, Alepsal, phenobarbital, Kaneuron, Epanal. Benzodiazepine AEDs that could be grouped by diazepam group, clonazepam, and clobazam were considered the same AED at the group level. Combination AEDs were not considered for grouping.

Note: The Total POS summary group included subjects <4 years, ≥4 to <16 years, and subjects who were 16 years at the time of study entry.

Note: All pediatric subjects included subjects with POS and other seizure types.

Table 26. Concomitant AEDs used by more than 5% of subjects by pediatric summary group (pool pedicatric studies)

Preferred drug name	BRV Overall			
	POS summary group			All pediatric subjects N=219 n (%)
	<4y N=16 n (%)	≥4 to <16y N=149 n (%)	Total POS N=168 n (%)	
At least 1 medication	16 (100)	149 (100)	168 (100)	219 (100)
Valproate	6 (37.5)	68 (45.6)	75 (44.6)	114 (52.1)
Diazepam	6 (37.5)	38 (25.5)	45 (26.8)	58 (26.5)
Clobazam	4 (25.0)	32 (21.5)	36 (21.4)	54 (24.7)
Topiramate	6 (37.5)	34 (22.8)	41 (24.4)	53 (24.2)
Lamotrigine	0	37 (24.8)	38 (22.6)	49 (22.4)
Oxcarbazepine	4 (25.0)	33 (22.1)	37 (22.0)	41 (18.7)
Carbamazepine	2 (12.5)	36 (24.2)	40 (23.8)	40 (18.3)
Clonazepam	3 (18.8)	14 (9.4)	17 (10.1)	21 (9.6)
Lacosamide	0	19 (12.8)	19 (11.3)	21 (9.6)
Phenobarbital	4 (25.0)	5 (3.4)	9 (5.4)	20 (9.1)
Phenytoin	2 (12.5)	14 (9.4)	16 (9.5)	17 (7.8)
Zonisamide	1 (6.3)	13 (8.7)	14 (8.3)	16 (7.3)
Vigabatrin	2 (12.5)	6 (4.0)	8 (4.8)	14 (6.4)

AED=antiepileptic drug; BRV=brivaracetam; ISS=Integrated Summary of Safety; POS=partial-onset seizures; WHO-DRL=World Health Organization Drug Reference List; y=years

Note: This table summarizes concomitant AEDs used by ≥5% of all pediatric subjects in BRV Overall.

Note: Drugs were coded using WHO-DRL version Jun/2012.

Note: Valproate included valproate sodium, valproate semisodium, valproate bismuth, valproate magnesium, valpromide, Ergenyl Chrono, and valproic acid. Phenytoin included phenytoin sodium, phenytoin calcium, mephenytoin, Zentronal, metetoin, ethotoin, albutoin, Hydantal, Phelantin, Hydantol D, Anirrit, Dintoinale, fosphenytoin sodium, phenytoin, fosphenytoin, hydantoin derivatives, and hydantoin. Phenobarbital included phenobarbital sodium, methylphenobarbital, metharbital, Alepsal, phenobarbital, Kaneuron, Epanal. Benzodiazepine AEDs that could be grouped by diazepam group, clonazepam, and clobazam were considered the same AED at the group level. Combination AEDs were not considered for grouping.

Note: The Total POS summary group included subjects <4 years, ≥4 to <16 years, and subjects who were 16 years at the time of study entry.

Note: All pediatric subjects included subjects with POS and other seizure types.

Adverse events

In Pool Paediatric Studies, the incidences of any TEAE, deaths, and treatment-emergent SAEs in BRV Overall were similar to Pool S4 (Table 27.).

Table 27. Overview of TEAEs by age group

	≥1 mo. to <2 y N=25 n (%)	≥2 to <12 y N=131 n (%)	≥12 to <17y N=50 n (%)	All subjects N=206 n (%)
Any TEAE	**25 (100)**	**121 (92.4)**	**45 (90.0)**	**191 (92.7)**
Serious TEAEs	12 (48.0)	30 (22.9)	12 (24.0)	54 (26.2)
Discontinuation due to TEAE	4 (16.0)	8 (6.1)	7 (14.0)	19 (9.2)
Drug-related TEAEs	6 (24.0)	42 (32.1)	15 (30.0)	63 (30.6)
Severe TEAEs	9 (36.0)	15 (11.5)	3 (6.0)	27 (13.1)
Drug-related serious TEAEs	1 (4.0)	3 (2.3)	1 (2.0)	5 (2.4)
Deaths	2 (8.0)	1 (0.8)	1 (2.0)	4 (1.9)

There were higher incidences of severe TEAEs at the higher BRV modal daily doses (>3.0 to 4.0 and >4.0mg/kg/day, compared with the lower BRV modal daily doses. The most frequently reported common TEAEs were nasopharyngitis (24.2% of subjects); pharyngitis (20.1%); pyrexia, convulsion, headache (17.4%), vomiting (14.8%), diarrhea (12.1%) and somnolence (10.4%). The incidences of convulsion and headache were similar to Pool S4. There were higher incidences of nasopharyngitis, pharyngitis, pyrexia, and vomiting compared with Pool S4 (Table 28.).

The MAH reported a higher incidence of diarrhoea (13.9% vs 7.3%) in children with the POS ⩾4-<12 years compared to POS ⩾12-<16 years group. Concerns were raised regarding the oral solution formulation of brivaracetam contains sorbitol. The most common ADRs known to be related to sorbitol are diarrhoea, flatulence and abdominal pain. The incidence of diarrhea was higher in the paediatric subjects with POS aged ⩾4 to <16 years compared with the adult (Pool S4) (12.1% vs 8.4%). All the events (18) occurred in the paediatric population were considered non-serious and not related with BRV treatment. The MAH specified that with the updated data on Pool Pediatric Studies up to 15 Mar 2017 no additional event of diarrhea was reported.

It is acknowledged that diarrhoea is one of the events consistent with the higher frequency of infectious diseases in the paediatric population. This AE is usually associated with gastrointestinal viruses or bacteria-related infections, antibiotic therapy, nutritional aspects. All cases of diarrhea were non-serious, the majority were mild in intensity (moderate diarrhea was reported in only 5 patients), did not lead to BRV discontinuation, and were not considered as related to BRV treatment. No specific pattern in terms of temporal relationship with BRV treatment was observed. The median duration of the event was relatively short (3 days). Most cases were related to antibiotic therapy. Moreover, all subjects received concomitant antiepileptic medications, some of them associated with diarrhea as adverse drug reaction.

As regard to the potential impact of sorbitol excipient on the occurrence of diarrhea, in the POS ⩾4 to <12 years group, 8 of 15 patients with diarrhea were receiving BRV oral solution. However, no specific pattern in terms of temporal relationship with the treatment was observed and when the dosage was increased in 4 subjects, this was not associated with diarrhea recurrence. Moreover, the MAH specify that the amount of sorbitol (95.92mg/kg/day) present if the maximal recommended dose for BRV (4 mg/kg/day) is given, is lower than the amount (140 mg/kg/day) reported as potentially associated with gastrointestinal discomfort and mild laxative effect.

Given the above, no definite conclusion can be drawn on the causal relationship between the excipient sorbitol and the occurrence of diarrhea.

Table 28. Most frequently reported common TEAEs (≥2% of all paediatric subjects in BRV Overall) by paediatric summary group in Pool Paediatric Studies

Primary SOC PT	BRV Overall			
	POS summary group			All pediatric subjects N=219 n (%)
	<4y N=16 n (%)	≥4 to <16y N=149 n (%)	Total POS N=168 n (%)	
Ear and labyrinth disorders				
Ear pain	1 (6.3)	4 (2.7)	5 (3.0)	6 (2.7)
Eye disorders				
Conjunctivitis	2 (12.5)	2 (1.3)	4 (2.4)	8 (3.7)
Gastrointestinal disorders				
Vomiting	8 (50.0)	22 (14.8)	32 (19.0)	43 (19.6)
Diarrhoea	3 (18.8)	18 (12.1)	21 (12.5)	33 (15.1)
Abdominal pain	3 (18.8)	11 (7.4)	14 (8.3)	15 (6.8)
Abdominal pain upper	0	9 (6.0)	10 (6.0)	13 (5.9)
Constipation	3 (18.8)	6 (4.0)	9 (5.4)	13 (5.9)
Nausea	3 (18.8)	4 (2.7)	7 (4.2)	9 (4.1)
Gastrooesophageal reflux disease	3 (18.8)	1 (0.7)	4 (2.4)	8 (3.7)
Toothache	1 (6.3)	3 (2.0)	4 (2.4)	8 (3.7)
General disorders and administration site conditions				
Pyrexia	11 (68.8)	26 (17.4)	37 (22.0)	51 (23.3)
Irritability	4 (25.0)	15 (10.1)	19 (11.3)	25 (11.4)
Fatigue	0	8 (5.4)	9 (5.4)	13 (5.9)
Asthenia	1 (6.3)	3 (2.0)	4 (2.4)	5 (2.3)

Primary SOC PT	BRV Overall			
	POS summary group			All pediatric subjects N=219 n (%)
	<4y N=16 n (%)	≥4 to <16y N=149 n (%)	Total POS N=168 n (%)	
Infections and infestations				
Nasopharyngitis	7 (43.8)	36 (24.2)	44 (26.2)	58 (26.5)
Pharyngitis	3 (18.8)	30 (20.1)	33 (19.6)	41 (18.7)
Upper respiratory tract infection	7 (43.8)	10 (6.7)	17 (10.1)	29 (13.2)
Pharyngotonsillitis	3 (18.8)	19 (12.8)	22 (13.1)	27 (12.3)
Gastroenteritis	5 (31.3)	11 (7.4)	16 (9.5)	26 (11.9)
Rhinitis	3 (18.8)	13 (8.7)	16 (9.5)	21 (9.6)
Bronchitis	4 (25.0)	8 (5.4)	12 (7.1)	19 (8.7)
Influenza	3 (18.8)	9 (6.0)	12 (7.1)	18 (8.2)
Ear infection	3 (18.8)	5 (3.4)	8 (4.8)	14 (6.4)
Otitis media	4 (25.0)	4 (2.7)	8 (4.8)	12 (5.5)
Pneumonia	0	3 (2.0)	3 (1.8)	12 (5.5)
Pharyngitis streptococcal	2 (12.5)	7 (4.7)	9 (5.4)	11 (5.0)
Viral infection	3 (18.8)	6 (4.0)	9 (5.4)	11 (5.0)
Urinary tract infection	1 (6.3)	3 (2.0)	4 (2.4)	10 (4.6)
Varicella	2 (12.5)	6 (4.0)	8 (4.8)	10 (4.6)
Laryngitis	2 (12.5)	3 (2.0)	5 (3.0)	9 (4.1)
Sinusitis	2 (12.5)	5 (3.4)	7 (4.2)	8 (3.7)
Acute tonsillitis	0	3 (2.0)	3 (1.8)	7 (3.2)
Respiratory tract infection	1 (6.3)	3 (2.0)	4 (2.4)	7 (3.2)
Otitis media acute	1 (6.3)	2 (1.3)	3 (1.8)	6 (2.7)
Pharyngitis bacterial	1 (6.3)	3 (2.0)	4 (2.4)	6 (2.7)
Viral pharyngitis	1 (6.3)	3 (2.0)	4 (2.4)	5 (2.3)

Primary SOC PT	BRV Overall			
	POS summary group			All pediatric subjects N=219 n (%)
	<4y N=16 n (%)	≥4 to <16y N=149 n (%)	Total POS N=168 n (%)	
Injury, poisoning, and procedural complications				
Fall	1 (6.3)	12 (8.1)	13 (7.7)	17 (7.8)
Laceration	0	3 (2.0)	3 (1.8)	6 (2.7)
Contusion	0	2 (1.3)	2 (1.2)	5 (2.3)
Head injury	0	4 (2.7)	4 (2.4)	5 (2.3)
Investigations				
Weight decreased	1 (6.3)	8 (5.4)	9 (5.4)	13 (5.9)
GGT increased	0	5 (3.4)	5 (3.0)	7 (3.2)
Creatinine renal clearance decreased	3 (18.8)	2 (1.3)	5 (3.0)	5 (2.3)
Metabolism and nutrition disorders				
Decreased appetite	3 (18.8)	15 (10.1)	19 (11.3)	26 (11.9)
Dehydration	4 (25.0)	0	4 (2.4)	7 (3.2)
Nervous system disorders				
Convulsion	6 (37.5)	26 (17.4)	34 (20.2)	46 (21.0)
Headache	0	26 (17.4)	27 (16.1)	35 (16.0)
Somnolence	3 (18.8)	16 (10.7)	19 (11.3)	26 (11.9)
Dizziness	0	9 (6.0)	10 (6.0)	10 (4.6)
Psychomotor hyperactivity	0	7 (4.7)	7 (4.2)	7 (3.2)
Status epilepticus	1 (6.3)	5 (3.4)	6 (3.6)	6 (2.7)
Psychiatric disorders				
Aggression	1 (6.3)	7 (4.7)	8 (4.8)	13 (5.9)
Insomnia	3 (18.8)	7 (4.7)	10 (6.0)	13 (5.9)
Suicidal ideation	0	7 (4.7)	8 (4.8)	9 (4.1)
Abnormal behaviour	1 (6.3)	3 (2.0)	5 (3.0)	6 (2.7)
Reproductive system and breast disorders				
Dysmenorrhoea	0	5 (3.4)	5 (3.0)	5 (2.3)

Respiratory, thoracic, and mediastinal disorders				
Cough	4 (25.0)	19 (12.8)	23 (13.7)	26 (11.9)
Oropharyngeal pain	1 (6.3)	6 (4.0)	7 (4.2)	10 (4.6)
Rhinitis allergic	1 (6.3)	8 (5.4)	9 (5.4)	10 (4.6)
Epistaxis	1 (6.3)	2 (1.3)	3 (1.8)	6 (2.7)
Rhinorrhoea	3 (18.8)	2 (1.3)	5 (3.0)	5 (2.3)
Skin and subcutaneous tissue disorders				
Rash	2 (12.5)	5 (3.4)	7 (4.2)	8 (3.7)

BRV=brivaracetam; GGT=gamma-glutamyltransferase; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; POS=partial-onset seizures; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event; y=years

Note: Adverse events were coded using MedDRA version 15.0.

Note: This table summarizes TEAEs reported in ≥2% of all pediatric subjects in BRV Overall.

Note: The Total POS summary group included subjects <4 years, ≥4 to <16 years, and subjects who were 16 years at the time of study entry.

Note: All pediatric subjects included subjects with POS and other seizure types.

In the existing adult and adolescent indication, the most frequently reported adverse reactions for brivaracetam were somnolence (14.3%) and dizziness (11%) usually in mild to moderate intensity. Somnolence and fatigue (8.2%) were reported at a higher incidence with increasing dose.

A higher TEAEs incidence Dysmenorrhea (7.3%vs 1.9%) and Gynaecomastia (4.9% vs 0) were reported in the POS ≥12-<16 years group than in the POS ≥4-<12 years group. The MAH specified that with the updated data on Pool Pediatric Studies up to 15 Mar 2017 no additional event of dysmenorrhea was reported. The explanation provided by the MAH; whereby the small number of patients in the BRV POS ≥12-<16 years group (dysmenorrhea n=3; gynaecomastia n=2) and the prevalence reported in the literature suggest that the findings from the BRV Pediatric Pools do not differ from the global pediatric population, is acceptable.

The incidences of severe TEAEs in the ⩾4 to <16 years POS group in Pool Paediatric Studies were lower than in Pool Monotherapy, Pool S4, and Pool ULD.

In the ⩾4 to <16 years POS group in Pool Paediatric Studies, most subjects reported TEAEs with a maximum intensity of mild (57 subjects [38.3%]) or moderate (69 subjects [46.3%]); severe TEAEs were reported by 12 subjects (8.1%) in BRV Overall. Severe TEAEs were most frequently reported in the Nervous system disorders System Organ Class (SOC) (3.4%); the most frequently reported severe TEAEs were convulsion (2.0%), and status epilepticus and pneumonia (1.3% each). The incidence of severe TEAEs was lower compared with Pool S4 (22.2%); the incidences of the most frequently reported TEAEs of convulsion and status epilepticus were similar to Pool S4.

Dose-relation

The TAEs of nasopharyngitis and headache tended to have increasing incidences with increasing doses (Table 29.).

Table 29. Most frequently reported common TEAEs (≥2% of subjects) for subjects ≥4 to <16 years with POS by BRV modal daily dose in BRV Overall in Pool Paediatric Studies

Primary SOC PT	BRV modal daily dose (mg/kg/day)					BRV Overall N=149 n (%)
	0.0 to 1.0 N=15 n (%)	>1.0 to 2.0 N=10 n (%)	>2.0 to 3.0 N=19 n (%)	>3.0 to 4.0 N=79 n (%)	>4.0 N=26 n (%)	
Ear and labyrinth disorders						
Ear pain	0	0	0	3 (3.8)	1 (3.8)	4 (2.7)
Gastrointestinal disorders						
Vomiting	0	2 (20.0)	1 (5.3)	14 (17.7)	5 (19.2)	22 (14.8)
Diarrhoea	1 (6.7)	0	5 (26.3)	8 (10.1)	4 (15.4)	18 (12.1)
Abdominal pain	1 (6.7)	0	1 (5.3)	6 (7.6)	3 (11.5)	11 (7.4)
Abdominal pain upper	0	0	1 (5.3)	8 (10.1)	0	9 (6.0)
Constipation	0	0	1 (5.3)	2 (2.5)	3 (11.5)	6 (4.0)
Nausea	0	1 (10.0)	2 (10.5)	1 (1.3)	0	4 (2.7)
Dental caries	0	1 (10.0)	1 (5.3)	1 (1.3)	0	3 (2.0)
Enterocolitis	0	1 (10.0)	0	2 (2.5)	0	3 (2.0)
Toothache	0	0	0	3 (3.8)	0	3 (2.0)
General disorders and administration site conditions						
Pyrexia	1 (6.7)	2 (20.0)	1 (5.3)	18 (22.8)	4 (15.4)	26 (17.4)
Irritability	1 (6.7)	0	3 (15.8)	10 (12.7)	1 (3.8)	15 (10.1)
Fatigue	0	0	1 (5.3)	5 (6.3)	2 (7.7)	8 (5.4)
Asthenia	0	1 (10.0)	0	2 (2.5)	0	3 (2.0)
Infections and infestations						
Nasopharyngitis	1 (6.7)	0	4 (21.1)	23 (29.1)	8 (30.8)	36 (24.2)
Pharyngitis	1 (6.7)	1 (10.0)	1 (5.3)	26 (32.9)	1 (3.8)	30 (20.1)
Pharyngotonsillitis	0	1 (10.0)	6 (31.6)	10 (12.7)	2 (7.7)	19 (12.8)
Rhinitis	0	0	1 (5.3)	9 (11.4)	3 (11.5)	13 (8.7)
Gastroenteritis	0	0	4 (21.1)	5 (6.3)	2 (7.7)	11 (7.4)
Upper respiratory tract infection	0	0	2 (10.5)	8 (10.1)	0	10 (6.7)
Influenza	0	1 (10.0)	1 (5.3)	5 (6.3)	2 (7.7)	9 (6.0)
Bronchitis	0	0	3 (15.8)	3 (3.8)	2 (7.7)	8 (5.4)
Pharyngitis streptococcal	1 (6.7)	0	0	4 (5.1)	2 (7.7)	7 (4.7)
Varicella	0	0	0	5 (6.3)	1 (3.8)	6 (4.0)
Viral infection	0	1 (10.0)	1 (5.3)	3 (3.8)	1 (3.8)	6 (4.0)
Ear infection	0	0	1 (5.3)	3 (3.8)	1 (3.8)	5 (3.4)
Sinusitis	0	1 (10.0)	0	2 (2.5)	2 (7.7)	5 (3.4)
Otitis media	0	0	1 (5.3)	3 (3.8)	0	4 (2.7)
Acute tonsillitis	0	0	1 (5.3)	1 (1.3)	1 (3.8)	3 (2.0)
Laryngitis	0	0	0	3 (3.8)	0	3 (2.0)
Oral herpes	0	0	1 (5.3)	2 (2.5)	0	3 (2.0)
Pharyngitis bacterial	0	1 (10.0)	1 (5.3)	1 (1.3)	0	3 (2.0)
Pneumonia	0	0	0	2 (2.5)	1 (3.8)	3 (2.0)

Respiratory tract infection	0	0	0	2 (2.5)	1 (3.8)	3 (2.0)
Tonsillitis	0	0	0	2 (2.5)	1 (3.8)	3 (2.0)
Urinary tract infection	0	0	1 (5.3)	1 (1.3)	1 (3.8)	3 (2.0)
Viral pharyngitis	0	0	0	3 (3.8)	0	3 (2.0)
Injury, poisoning, and procedural complications						
Fall	0	0	2 (10.5)	8 (10.1)	2 (7.7)	12 (8.1)
Head injury	0	0	3 (15.8)	1 (1.3)	0	4 (2.7)
Arthropod bite	0	0	1 (5.3)	2 (2.5)	0	3 (2.0)
Laceration	0	0	1 (5.3)	2 (2.5)	0	3 (2.0)
Thermal burn	0	0	1 (5.3)	1 (1.3)	1 (3.8)	3 (2.0)
Investigations						
Weight decreased	0	0	0	7 (8.9)	1 (3.8)	8 (5.4)
GGT increased	0	2 (20.0)	0	3 (3.8)	0	5 (3.4)
Blood triglycerides increased	0	1 (10.0)	0	2 (2.5)	0	3 (2.0)
Metabolism and nutrition disorders						
Decreased appetite	1 (6.7)	1 (10.0)	3 (15.8)	8 (10.1)	2 (7.7)	15 (10.1)
Musculoskeletal and connective tissue disorders						
Arthralgia	0	0	1 (5.3)	2 (2.5)	0	3 (2.0)
Neck pain	0	0	1 (5.3)	1 (1.3)	1 (3.8)	3 (2.0)
Pain in extremity	0	0	0	3 (3.8)	0	3 (2.0)
Nervous system disorders						
Convulsion	3 (20.0)	1 (10.0)	3 (15.8)	14 (17.7)	5 (19.2)	26 (17.4)
Headache	1 (6.7)	1 (10.0)	3 (15.8)	15 (19.0)	6 (23.1)	26 (17.4)
Somnolence	1 (6.7)	0	3 (15.8)	9 (11.4)	3 (11.5)	16 (10.7)
Dizziness	0	0	2 (10.5)	5 (6.3)	2 (7.7)	9 (6.0)
Psychomotor hyperactivity	1 (6.7)	1 (10.0)	0	3 (3.8)	2 (7.7)	7 (4.7)
Status epilepticus	0	0	1 (5.3)	4 (5.1)	0	5 (3.4)
Psychiatric disorders						
Aggression	2 (13.3)	1 (10.0)	1 (5.3)	2 (2.5)	1 (3.8)	7 (4.7)
Insomnia	0	1 (10.0)	3 (15.8)	3 (3.8)	0	7 (4.7)
Suicidal ideation	0	0	2 (10.5)	3 (3.8)	2 (7.7)	7 (4.7)
Anxiety	0	0	1 (5.3)	2 (2.5)	1 (3.8)	4 (2.7)
Sleep disorder	1 (6.7)	0	0	3 (3.8)	0	4 (2.7)
Abnormal behaviour	1 (6.7)	0	1 (5.3)	0	1 (3.8)	3 (2.0)
Affect lability	0	0	1 (5.3)	0	2 (7.7)	3 (2.0)
Attention deficit/hyperactivity disorder	0	0	1 (5.3)	2 (2.5)	0	3 (2.0)
Confusional state	0	0	0	3 (3.8)	0	3 (2.0)
Renal and urinary disorders						
Enuresis	0	1 (10.0)	0	2 (2.5)	1 (3.8)	4 (2.7)
Reproductive system and breast disorders						
Dysmenorrhoea	0	0	2 (10.5)	2 (2.5)	1 (3.8)	5 (3.4)
Respiratory, thoracic, and mediastinal disorders						
Cough	1 (6.7)	0	2 (10.5)	13 (16.5)	3 (11.5)	19 (12.8)
Rhinitis allergic	0	1 (10.0)	0	7 (8.9)	0	8 (5.4)
Oropharyngeal pain	0	0	1 (5.3)	3 (3.8)	2 (7.7)	6 (4.0)
Nasal congestion	0	0	0	3 (3.8)	0	3 (2.0)
Skin and subcutaneous tissue disorders						
Rash	0	0	0	4 (5.1)	1 (3.8)	5 (3.4)
Eczema	0	0	0	3 (3.8)	0	3 (2.0)

BRV=brivaracetam; GGT=gamma-glutamyltransferase; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; POS=partial-onset seizures; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event

Note: Adverse events were coded using MedDRA version 15.0.

Note: This table summarizes TEAEs reported in >2% of subjects >4 to <16 years with POS in BRV Overall.

In the ⩾4 to <16 years POS group in Pool Paediatric Studies, most subjects reported TEAEs with a maximum intensity of mild (57 subjects [38.3%]) or moderate (69 subjects [46.3%]); severe TEAEs were reported by 12 subjects (8.1%) in BRV Overall. In general, the intensity of TEAEs in subjects ⩾4 to <16 years with POS is consistent with the intensity of TEAEs in adults.

Drug-related TEAEs (as determined by the Investigator)

In the ≥4 to <16 years POS group in Pool Paediatric Studies, 36.9% of subjects in BRV Overall reported TEAEs that were considered drug-related by the Investigator. Drug-related TEAEs were reported most frequently in the Psychiatric disorders SOC (16.8%) and Nervous system disorders SOC (16.1%); the most frequently reported drug-related TEAEs were somnolence (6.0%) and decreased appetite (4.7%).

The incidence of drug-related TEAEs in Pool Paediatric Studies was lower than in Pool S4 (38.8% vs 57.0%, respectively). The incidence of somnolence was lower than in Pool S4 (6.8% vs 13.0%, respectively) and the incidence of decreased appetite was higher than in Pool S4 (6.4% vs 2.5%, respectively).

Adverse events by safety time interval for studies in paediatric subjects with epilepsy (Pool Paediatric Studies)

In the ≥4 to <16 years POS group in Pool Paediatric Studies, the incidence of TEAEs was highest during the first 3-month safety time interval, and was lower and relatively stable at all subsequent safety time intervals. No TEAE SOCs or PTs increased in frequency over time. In the ≥4 to <16 years POS group in Pool Paediatric Studies, the most frequently reported TEAEs (reported by more than 1 subject and ≥5% of subjects) in any safety time interval were vomiting, diarrhoea, pyrexia, irritability, nasopharyngitis, pharyngitis, pharyngotonsillitis, decreased appetite, headache, convulsion, somnolence, cough, and dysmenorrhoea.

Adverse events during the first 7 days of the Treatment Period for studies in paediatric subjects with epilepsy (Pool Paediatric Studies)

In Pool Paediatric Studies, 71 subjects (32.4%) in BRV Overall reported TEAEs during the first 7 days of treatment; TEAEs were most frequently reported in the General disorders and administration site conditions SOC (21 subjects [9.6%]), Nervous system disorders SOC and Psychiatric disorders SOC (15 subjects each [6.8%]), and Infections and infestations SOC (14 subjects [6.4%]). The most frequently reported TEAEs were irritability (11 subjects [5.0%]) and decreased appetite (7 subjects [3.2%]).

In the ≥4 to <16 years POS group in Pool Paediatric Studies, 46 subjects (30.9%) in BRV Overall reported TEAEs during the first 7 days of treatment; TEAEs were most frequently reported in the Psychiatric disorders SOC (12 subjects [8.1%]), General disorders and administration site conditions SOC (11 subjects [7.4%]), and Nervous system disorders SOC (10 subjects [6.7%]). The most frequently reported TEAEs were irritability (6 subjects [4.0%]), decreased appetite (5 subjects [3.4%]), and cough (5 subjects [3.4%]).

Laboratory findings

Hematology and blood chemistry assays

Within Appendix 12 of the SAP that accompanied the initial MAA for Brivaracetam, the MAH had defined the criteria for hematology and biochemistry Parameters to be considered possibly clinically significant treatment-emergent (PCST).

Overall, most of mean values for hematology parameters for the total population were within standard laboratory normal ranges at baseline and showed slight post-baseline values changes that did not show a clear prevalence in a particular age group.

Overall, PCST hematology values in the Evaluation Period were noticed for neutrophils (35 subjects [17.5%] with PCST low value) and leukocytes (26 subjects [12.9%] with PCST low value). The main differences observed between the POS ⩾4 to <12 and ⩾12 to <16 years populations were related to the higher incidence (>25) of PCST High Hematocrit and Leukocytes in the last group (Hematocrit: 17.5% vs 2.9%; Leucocytes: 10.0% vs 3.8%). In the overall POS paediatric population ⩾4 to <16, PCST AEs High hematocrit occurred with an incidence of 6.7%. The MAH provided clarifications: as regard to the hematocrit high PCST values, none of them was considered by the Investigators as related to BRV treatment, no trend in the BRV dosage or the time to onset was observed and no changes of BRV dose was made for these patients. Values returned to normal at subsequent visits. For 9 out of 10 patients, the high PCST values were within normal range according to the laboratory where the samples were analyzed. As regard to leukocytes high PCST values, eight patients (4 in each age group) showed high PCST values of leukocytes that were potentially related to infections concomitantly reported and, therefore, were not considered related to BRV treatment by the Investigators. No changes in BRV dosage was made. For 6 of these patients, values returned within the normal range at the subsequent visits, for only one patients high leukocytes values were observed at last visit.

With regard to blood chemistry results, in the Evaluation Period the highest incidences of PCST blood chemistry results were reported for creatinine clearance (52 subjects [26.3%] with low value), GGT (26 subjects [12.9%] with PCST high value) and triglycerides (20 subjects [10.0%] with PCST high value). For DE subjects during the Up-Titration Period, the only reported PCST chemistry value was high GGT (7 subjects [6.4%]), whereas 10 subjects (29.4%) reported PCST low creatinine clearance. Overall, 3 subjects discontinued from the study due to TEAEs associated with blood chemistry values (1 subject due to a TEAE of GGT increased, 1 subject due to TEAEs of ALT increased, AST increased, and GGT increased, and 1 subject due to a TEAE of hepatic enzyme increased. The main differences observed between the POS ≥4 to <12 and ≥12 to <16 years populations were related to the higher incidence (>2%) of PCST ALT and Glucose in the ≥12 to <16 years population (ALT: 10.0% vs 0.9%; Glucose: 4.9% vs 0) and of PCST hypernatremia in the ≥4 to <12 years population (Hypernatremia: 4.7% vs 2.5%). In the overall POS pediatric population ≥4 to <16, PCST AEs high ALT (3.3%), GGT (10.9%), sodium (4.1%), and urate (3.3%) occurred with a relatively high incidence. The PCST high ALT occurred during the first months (first 9 months) of treatments and no specific trend over the different visits was observed. The increase of transaminase was also observed in the BRV adult population (Pool S4).

As regard to the higher proportion of PCST related to Hypernatremia in POS ⩾4 to <12 years group, this AE was not observed in the BRV adult population. The MAH stated that it could be potentially linked to episodes of fever or dehydration that are expected to be more frequent in the ⩾4 to <12 years population. This could be considered plausible. Unfortunately, in the absence of a control group and due to the open-label study design and the limited numbers, it is difficult to conclude on the relationship between the occurrence of an AE and BRV treatment. However, the MAH reassures that the AEs related to hepatic and renal disorders will continue to be monitored through routine pharmacovigilance activities.

Endocrinology and Tanner stage

Mean values for the endocrinology parameters (FSH, LH, TSH, FT3, FT4) remained substantially within the normal ranges. No clear effect of BRV upon the sexual maturation process could be observed.

Evaluation of Potential Hepatotoxicity

An evaluation of potential cases of hepatoxicity was performed for all subjects in the study pools. The evaluation required medical review of laboratory data and TEAEs potentially associated with hepatotoxicity for all subjects.

In the ⩾4 to 16 years POS group in Pool Paediatric Studies, TEAEs potentially associated with hepatotoxicity were reported in 4.7% of subjects; the most frequently reported TEAE was GGT increased (3.4%). The incidences of TEAEs potentially associated with hepatotoxicity in the ⩾4 to 16 years POS group was not higher than in the adult population.

Vital signs

Overall, there were no clinically meaningful mean changes from Baseline over time in vital sign results in Pool Paediatric Studies or the adult analysis pools (Pool Monotherapy, Pool S4, and Pool ULD).

Body weight

In Pool Pediatric Studies, there was a steady increase in mean change from Baseline over time in body weight in BRV Overall. According to the Applicant, this is expected, since the pediatric subjects are growing.

In the ≥4 to <16 years POS group in Pool Pediatric Studies, there was a steady increase in mean change from Baseline over time in body weight in BRV Overall; the mean increase from Baseline was 3.6kg at Month 12, 6.4kg at Month 24, 11.9kg at Month 36, and 19.1kg at Month 48. According to the Applicant, this is expected, since the pediatric subjects are growing.

In Pool Pediatric Studies, the incidence of any PCST body weight result at any time point was 68 subjects (31.3%) in BRV Overall; 49 subjects (22.6%) had PCST low body weight and 19 subjects (8.8%) had PCST high body weight at any time point. There did not appear to be any trends over time in the incidence of PCST body weight results.

In the ≥4 to <16 years POS group in Pool Pediatric Studies, the incidence of any PCST body weight result at any time point was 41 subjects (27.9%) in BRV Overall; 25 subjects (17.0%) had PCST low body weight and 16 subjects (10.9%) had PCST high body weight at any time point. The incidence of PCST low and high body weight results over time was similar; there did not appear to be any trends over time in the incidence of PCST low or high body weight results.

In the ≥4 to <16 years POS group in Pool Pediatric Studies, body weight changes reported as TEAEs in BRV Overall were weight decreased (8 subjects [12.1%]), and weight increased and overweight (1 subject each [0.7%]). None of these events led to permanent discontinuation of study drug.

The incidence of TEAE "weight decrease" was relatively high in the ⩾4 to <16 years POS group in the Pool Pediatric Studies. This could be related to decreased appetite that is one of the established ADR to BRV in adult patients, and is now proposed by the MAH as an ADR for the pediatric patients as well. It is reassuring that none of the TEAEs "weight decrease" led to permanent discontinuation of study drug. However, the MAH was asked to clarify how many of the TEAEs related to body weight decrease presented also decreased appetite or weight decrease represents a standalone TEAE. It was apparent that a relationship between weight decrease and decreased appetite, that is a known ADR of BRV treatment, cannot be established in POS patients aged ⩾4 to <16 years. Moreover, weight decrease occurred in a minority of these patients and can be considered plausibly related to the severity of the underlying disease or to concomitant TEAEs. In most cases the event recovered and in no patient it led to BRV treatment discontinuation. This was considered reassuring.

<u>Pool S4</u>

In Pool S4, there were no clinically meaningful mean changes from Baseline over time to the Last Value in BRV Overall in body weight.

In Pool S4, the incidence of any PCST body weight result at any time point in BRV Overall was 1175 subjects (48.5%). The incidence of PCST low body weight and PCST high body weight at any time point were similar (605 subjects [25.0%] and 680 subjects [28.1%], respectively). There did

not appear to be a trend over time in the incidence of PCST body weight results.

Serious adverse event / deaths / other significant events

The incidences of treatment-emergent SAEs in the ⩾4 to <16 years POS group in Pool Paediatric Studies were similar to the incidence in Pool S4.

Severe TEAEs were most frequently reported in the Nervous system disorders System Organ Class (SOC) (3.4%); the most frequently reported severe TEAEs were convulsion (2.0%), and status epilepticus and pneumonia (1.3% each). The incidence of severe TEAEs was lower compared with Pool S4 (22.2%); the incidences of the most frequently reported TEAEs of convulsion and status epilepticus were similar to Pool S4. A summary of treatment-emergent SAEs reported in >1 subject in BRV Overall by paediatric group in Pool Paediatric Studies is presented in Table 30. .

In Pool Paediatric Studies, 59 subjects (26.9%) in BRV Overall reported treatment-emergent SAEs (Table 31.). In all paediatric subjects, treatment-emergent SAEs were most frequently reported in the Nervous system disorders SOC (28 subjects [12.8%]), and Infections and infestations SOC (15 subjects [6.8%]). The most frequently reported treatment-emergent SAEs in all paediatric subjects were convulsion (16 subjects [7.3%], status epilepticus (6 subjects [2.7%], pyrexia (5 subjects [2.3%]), and pneumonia and dehydration (4 subjects each [1.8%]). No other SAEs were reported in more than 3 subjects.

In the ⩾4 to <16 years POS group in Pool Paediatric Studies, treatment-emergent SAEs were reported in 30 subjects (20.1%) in BRV Overall. Treatment-emergent SAEs were most frequently reported in BRV Overall in the Nervous system disorders SOC (17 subjects [11.4%]). The most frequently reported SAEs in BRV Overall were convulsion (9 subjects [6.0%]) and status epilepticus (5 subjects [3.4%]). No other SAEs were reported in more than 2 subjects.

Table 30. Treatment-emergent SAEs reported in >1 subject in BRV Overall by paediatric group in Pool Paediatric Studies

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

BRV=brivaracetam; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; POS=partial-onset seizures; PT=preferred term; SAE=serious adverse event; SOC=system organ class; y=years

Note: Adverse events were coded using MedDRA version 15.0.

Note: n=number of subjects reporting a treatment-emergent SAE in any study period.

Note: The Total POS summary group included subjects <4 years, ≥4 to <16 years, and subjects who were 16 years at the time of study entry.

Note: All pediatric subjects included subjects with POS and other seizure types.

Note: This table summarizes treatment-emergent SAEs reported in >1 subject in BRV Overall for all pediatric subjects.

Table 31. Treatment-emergent SAEs reported in >1 subject ⩾4 to <16 years with POS by BRV modal daily dose in Pool Paediatric Studies

Primary SOC PT	BRV modal daily dose (mg/kg/day)					BRV Overall N=149 n (%)
	0.0 to 1.0 N=15 n (%)	>1.0 to 2.0 N=10 n (%)	>2.0 to 3.0 N=19 n (%)	>3.0 to 4.0 N=79 n (%)	>4.0 N=26 n (%)	
At least 1 treatment-emergent SAE	**3 (20.0)**	**1 (10.0)**	**3 (15.8)**	**17 (21.5)**	**6 (23.1)**	**30 (20.1)**
Infections and infestations						
Pneumonia	0	0	0	1 (1.3)	1 (3.8)	2 (1.3)
Nervous system disorders						
Convulsion	1 (6.7)	1 (10.0)	1 (5.3)	5 (6.3)	1 (3.8)	9 (6.0)
Status epilepticus	0	0	1 (5.3)	4 (5.1)	0	5 (3.4)
Somnolence	0	0	0	2 (2.5)	0	2 (1.3)
Respiratory, thoracic, and mediastinal disorders						
Respiratory distress	0	0	0	1 (1.3)	1 (3.8)	2 (1.3)

BRV=brivaracetam; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SAE=serious adverse event; SOC=system organ class
Note: Adverse events were coded using MedDRA version 15.0.
Note: n=number of subjects who reported a treatment-emergent SAE in any study period.
Note: This table summarizes treatment-emergent SAEs reported in >1 subject ≥4 to <16 years with POS in BRV Overall.

Discontinuation due to adverse events

Summary of AEs leading to permanent discontinuation of study drug

In Pool Paediatric Studies and the ≥4 to <16 years POS group, the incidences of TEAEs leading to permanent discontinuation of study drug were lower than in Pool S4, and the incidences of TEAEs leading to permanent discontinuation of study drug during the first 7 days of treatment were similar to Pool S4.

In Pool Paediatric Studies, 25 subjects (11.4%) in BRV Overall reported TEAEs leading to permanent discontinuation of study drug, and were most frequently reported in the Psychiatric disorders SOC (4.1%) and Nervous system disorders SOC (3.2%). The most frequently reported TEAEs leading to permanent discontinuation of study drug were aggression and suicidal ideation (1.4%), and convulsion, decreased appetite, pneumonia, and circulatory collapse (0.9%). The incidence of TEAEs leading to permanent discontinuation of study drug during the first 7 days of treatment was low (4 subjects [1.8%]).

In the ≥4 to <16 years POS group in Pool Paediatric Studies, 11 subjects (7.4%) in BRV Overall reported TEAEs leading to permanent discontinuation of study drug, and were most frequently reported in the Psychiatric disorders SOC (4.0%) and Nervous system disorders SOC (2.0%).

The most frequently reported TEAE leading to permanent discontinuation of study drug in BRV Overall was aggression (2.0%). In the ≥4 to <16 years POS group in Pool Paediatric Studies, the incidence of TEAEs leading to permanent discontinuation of study drug during the first 7 days of treatment was low (3 subjects [2.0%]).

Deaths

In Pool Paediatric Studies, a total of 4 subjects had TEAEs with fatal outcome during the BRV clinical development program as of the clinical cutoff date of 31 Aug 2016. Three subject deaths were reviewed with the original application and 1 subject died since the original application was reviewed.

TEAEs of interest

Treatment-emergent AEs identified by the MAH to be of special interest included TEAEs potentially associated with seizure worsening, behavioral disorders, suicidality, falls, accidents and injuries, blood dyscrasias, SCARs, abuse potential, renal injury, psychosis, and malignancies. For the paediatric population, additional TEAEs of interest included TEAEs potentially associated with growth, endocrine function/sexual maturation, neurodevelopment, cognitive impairment, anxiety, and depression (Table 32.).

Table 32. Exposure-adjusted IRs for TEAEs of interest by category and paediatric summary group in BRV Overall in Pool Paediatric Studies

TEAE of interest category	BRV Overall			
	POS summary group			All pediatric subjects
	<4y N=16 n (%) IR [95% CI]	≥4 to <16y N=149 n (%) IR [95% CI]	Total POS N=168 n (%) IR [95% CI]	N=219 n (%) IR [95% CI]
Seizure worsening	7 (43.8) 29.39 [11.82, 60.55]	32 (21.5) 14.91 [10.20, 21.06]	41 (24.4) 16.98 [12.19, 23.04]	58 (26.5) 17.74 [13.47, 22.93]
Behavioral disorder	8 (50.0) 44.67 [19.28, 88.01]	36 (24.2) 17.78 [12.45, 24.61]	45 (26.8) 20.21 [14.74, 27.04]	58 (26.5) 18.87 [14.33, 24.39]
Suicidality	0 0 [0.00, 9.99]	7 (4.7) 2.86 [1.15, 5.90]	8 (4.8) 2.81 [1.21, 5.54]	9 (4.1) 2.28 [1.04, 4.33]
Hepatotoxicity	1 (6.3) 2.72 [0.07, 15.14]	7 (4.7) 2.88 [1.16, 5.94]	8 (4.8) 2.82 [1.22, 5.57]	11 (5.0) 2.83 [1.41, 5.07]
Falls	3 (18.8) 9.97 [2.06, 29.12]	27 (18.1) 12.40 [8.17, 18.05]	31 (18.5) 12.37 [8.41, 17.56]	41 (18.7) 11.95 [8.58, 16.21]
Accidents and injuries	2 (12.5) 6.04 [0.73, 21.83]	31 (20.8) 14.59 [9.91, 20.71]	34 (20.2) 13.69 [9.48, 19.13]	42 (19.2) 12.32 [8.88, 16.65]
Blood dyscrasias	0 0 [0.00, 9.99]	2 (1.3) 0.83 [0.10, 2.98]	2 (1.2) 0.71 [0.09, 2.56]	4 (1.8) 1.03 [0.28, 2.63]
SCARs	0 0 [0.00, 9.99]	0 0 [0.00, 1.48]	0 0 [0.00, 1.27]	0 0 [0.00, 0.92]
Abuse potential	0 0 [0.00, 9.99]	0 0 [0.00, 1.48]	0 0 [0.00, 1.27]	1 (0.5) 0.25 [0.01, 1.41]
Renal injury	2 (12.5) 6.45 [0.78, 23.29]	0 0 [0.00, 1.48]	2 (1.2) 0.70 [0.09, 2.54]	2 (0.9) 0.51 [0.06, 1.83]
Psychosis	0 0 [0.00, 9.99]	2 (1.3) 0.81 [0.10, 2.94]	2 (1.2) 0.70 [0.08, 2.53]	3 (1.4) 0.76 [0.16, 2.22]
Malignancy	0 0 [0.00, 9.99]	0 0 [0.00, 1.48]	0 0 [0.00, 1.27]	0 0 [0.00, 0.92]
Growth	1 (6.3) 2.70 [0.07, 15.07]	0 0 [0.00, 1.48]	1 (0.6) 0.34 [0.01, 1.92]	3 (1.4) 0.76 [0.16, 2.21]
Endocrine/sexual maturation	2 (12.5) 6.14 [0.74, 22.16]	7 (4.7) 2.89 [1.16, 5.95]	9 (5.4) 3.23 [1.48, 6.14]	10 (4.6) 2.60 [1.25, 4.78]
Neurodevelopment	3 (18.8) 9.94 [2.05, 29.05]	10 (6.7) 4.26 [2.04, 7.83]	13 (7.7) 4.84 [2.58, 8.28]	16 (7.3) 4.30 [2.46, 6.98]
Cognitive impairment	2 (12.5) 6.41 [0.78, 23.14]	9 (6.0) 3.78 [1.73, 7.18]	11 (6.5) 4.04 [2.01, 7.22]	13 (5.9) 3.42 [1.82, 5.85]
Anxiety	0 0 [0.00, 9.99]	6 (4.0) 2.51 [0.92, 5.46]	6 (3.6) 2.15 [0.79, 4.68]	7 (3.2) 1.80 [0.73, 3.72]
Depression	0 0 [0.00, 9.99]	4 (2.7) 1.61 [0.44, 4.11]	4 (2.4) 1.38 [0.38, 3.54]	5 (2.3) 1.27 [0.41, 2.96]

BRV=brivaracetam; CI=confidence interval; IR=(exposure-adjusted) incidence rate; ISS=Integrated Summary of Safety; POS=partial-onset seizures; SCARs=severe cutaneous adverse reactions; TEAE=treatment-emergent adverse event; y=years

Note: n=number of subjects who reported a TEAE in any study period.

Note: Exposure-adjusted IRs were adjusted to a 100-year duration.

Note: Subject-years of exposure only considered exposure to BRV from the first dose of BRV to the onset of the earliest TEAE within the specified category for subjects with a TEAE in that category.

Note: The Total POS summary group included subjects <4 years, ≥4 to <16 years, and subjects who were 16 years at the time of study entry.

Note: All pediatric subjects included subjects with POS and other seizure types.

A summary of exposure-adjusted IRs for TEAEs of interest by category in subjects ≥4 to <16 years with POS in Pool Paediatric Studies is presented by BRV modal daily dose in Table 33. .

Table 33. Exposure-adjusted IRs for TEAEs of interest by category in subjects ≥4 to <16 years with POS in Pool Paediatric Studies is presented by BRV modal daily dose

TEAE of interest category	BRV modal daily dose (mg/kg/day)					BRV Overall N=149 n (%) IR [95% CI]
	0.0 to 1.0 N=15 n (%) IR [95% CI]	>1.0 to 2.0 N=10 n (%) IR [95% CI]	>2.0 to 3.0 N=19 n (%) IR [95% CI]	>3.0 to 4.0 N=79 n (%) IR [95% CI]	>4.0 N=26 n (%) IR [95% CI]	
Seizure worsening	3 (20.0) 23.01 [4.74, 67.23]	1 (10.0) 8.03 [0.20, 44.73]	4 (21.1) 15.95 [4.34, 40.83]	18 (22.8) 14.25 [8.44, 22.52]	6 (23.1) 15.95 [5.85, 34.71]	32 (21.5) 14.91 [10.20, 21.06]
Behavioral disorder	5 (33.3) 38.49 [12.50, 89.82]	2 (20.0) 16.29 [1.97, 58.86]	6 (31.6) 26.25 [9.63, 57.13]	17 (21.5) 14.25 [8.30, 22.82]	6 (23.1) 17.09 [6.27, 37.19]	36 (24.2) 17.78 [12.45, 24.61]
Suicidality	0 0 [0.00, 28.19]	0 0 [0.00, 29.62]	2 (10.5) 7.72 [0.93, 27.88]	3 (3.8) 2.00 [0.41, 5.84]	2 (7.7) 4.66 [0.56, 16.83]	7 (4.7) 2.86 [1.15, 5.90]
Hepatotoxicity	0 0 [0.00, 28.19]	2 (20.0) 17.66 [2.14, 63.80]	0 0 [0.00, 12.44]	4 (5.1) 2.74 [0.75, 7.01]	1 (3.8) 2.34 [0.06, 13.04]	7 (4.7) 2.88 [1.16, 5.94]
Falls	1 (6.7) 8.10 [0.21, 45.15]	0 0 [0.00, 29.62]	5 (26.3) 21.49 [6.98, 50.15]	18 (22.8) 13.81 [8.18, 21.82]	3 (11.5) 7.64 [1.58, 22.34]	27 (18.1) 12.40 [8.17, 18.05]
Accidents and injuries	1 (6.7) 8.10 [0.21, 45.15]	0 0 [0.00, 29.62]	6 (31.6) 26.95 [9.89, 58.66]	18 (22.8) 13.77 [8.16, 21.76]	6 (23.1) 17.30 [6.35, 37.66]	31 (20.8) 14.59 [9.91, 20.71]
Blood dyscrasias	0 0 [0.00, 28.19]	0 0 [0.00, 29.62]	0 0 [0.00, 12.44]	2 (2.5) 1.40 [0.17, 5.04]	0 0 [0.00, 8.46]	2 (1.3) 0.83 [0.10, 2.98]
SCARs	0 0 [0.00, 28.19]	0 0 [0.00, 29.62]	0 0 [0.00, 12.44]	0 0 [0.00, 2.44]	0 0 [0.00, 8.46]	0 0 [0.00, 1.48]
Abuse potential	0 0 [0.00, 28.19]	0 0 [0.00, 29.62]	0 0 [0.00, 12.44]	0 0 [0.00, 2.44]	0 0 [0.00, 8.46]	0 0 [0.00, 1.48]
Renal injury	0 0 [0.00, 28.19]	0 0 [0.00, 29.62]	0 0 [0.00, 12.44]	0 0 [0.00, 2.44]	0 0 [0.00, 8.46]	0 0 [0.00, 1.48]
Psychosis	1 (6.7) 7.74 [0.20, 43.13]	0 0 [0.00, 29.62]	0 0 [0.00, 12.44]	1 (1.3) 0.68 [0.02, 3.79]	0 0 [0.00, 8.46]	2 (1.3) 0.81 [0.10, 2.94]
Malignancy	0 0 [0.00, 28.19]	0 0 [0.00, 29.62]	0 0 [0.00, 12.44]	0 0 [0.00, 2.44]	0 0 [0.00, 8.46]	0 0 [0.00, 1.48]
Growth	0 0 [0.00, 28.19]	0 0 [0.00, 29.62]	0 0 [0.00, 12.44]	0 0 [0.00, 2.44]	0 0 [0.00, 8.46]	0 0 [0.00, 1.48]
Endocrine/sexual maturation	0 0 [0.00, 28.19]	0 0 [0.00, 29.62]	2 (10.5) 7.50 [0.91, 27.10]	4 (5.1) 2.69 [0.73, 6.89]	1 (3.8) 2.41 [0.06, 13.41]	7 (4.7) 2.89 [1.16, 5.95]
Neurodevelopment	1 (6.7) 7.65 [0.19, 42.64]	2 (20.0) 16.32 [1.98, 58.95]	0 0 [0.00, 12.44]	5 (6.3) 3.58 [1.16, 8.34]	2 (7.7) 5.00 [0.61, 18.07]	10 (6.7) 4.26 [2.04, 7.83]
Cognitive impairment	0 0 [0.00, 28.19]	1 (10.0) 8.05 [0.20, 44.87]	1 (5.3) 3.40 [0.09, 18.95]	6 (7.6) 4.26 [1.56, 9.27]	1 (3.8) 2.37 [0.06, 13.19]	9 (6.0) 3.78 [1.73, 7.18]
Anxiety	0 0 [0.00, 28.19]	0 0 [0.00, 29.62]	1 (5.3) 3.38 [0.09, 18.86]	3 (3.8) 2.10 [0.43, 6.14]	2 (7.7) 4.85 [0.59, 17.52]	6 (4.0) 2.51 [0.92, 5.46]
Depression	1 (6.7) 7.65 [0.19, 42.62]	0 0 [0.00, 29.62]	1 (5.3) 3.50 [0.09, 19.50]	2 (2.5) 1.32 [0.16, 4.78]	0 0 [0.00, 8.46]	4 (2.7) 1.61 [0.44, 4.11]

BRV=brivaracetam; CI=confidence interval; IR=(exposure-adjusted) incidence rate; ISS=Integrated Summary of Safety; SCARs=severe cutaneous adverse reactions; TEAE=treatment-emergent adverse event
Note: n=number of subjects who reported a TEAE in any study period.
Note: Exposure-adjusted IRs were adjusted to a 100-year duration

In the ≥4 to <16 years POS group in Pool Paediatric Studies, TEAEs of interest were reported most frequently in the following categories: behavioural disorder (36 subjects [24.2%]; IR=17.78 per 100 subject-years), seizure worsening (32 subjects [21.5%]; IR=14.91 per 100 subject-years), accidents and injuries (31 subjects [20.8%]; IR=14.59 per 100 subject-years), and falls (27 subjects [18.1%]; IR=12.40 per 100 subject-years).

TEAEs potentially associated with seizure worsening (Pool Paediatric Studies)

In Pool Paediatric Studies, TEAEs potentially associated with seizure worsening were reported in 58 subjects (26.5%) in BRV Overall; the most frequently reported TEAEs were convulsion (46 subjects

[21.0%]), and status epilepticus (6 subjects [2.7%]). In the ⩾4 to <16 years POS group in Pool Paediatric Studies, TEAEs potentially associated with seizure worsening were reported in 32 subjects (21.5%); the most frequently reported TEAEs were convulsion (17.4%) and status epilepticus (3.4%). In the majority of cases, the events did not lead to adjustment of BRV dose or discontinuation. Convulsion (9 subjects [6.0%]), status epilepticus (5 subjects [3.4%]), and epilepsy and partial seizure with secondary generalisation (1 subject each [0.7%]) were reported as treatment emergent SAEs.

The exposure-adjusted IRs (95% CI) for TEAEs potentially associated with seizure worsening were higher in the ⩾4 to <16 years POS group in Pool Paediatric Studies compared with Pool S4 (14.91 [10.20, 21.06] and 6.01 [5.45, 6.62] per 100 subject-years), respectively (Table 34. and Table 35.).

Table 34. TEAEs potentially associated with seizure worsening in BRV Overall by paediatric summary group in Pool Paediatric Studies

Primary SOC PT	BRV Overall			
	POS summary group			All pediatric subjects N=219 n (%)
	<4y N=16 n (%)	≥4 to <16y N=149 n (%)	Total POS N=168 n (%)	
At least 1 event	**7 (43.8)**	**32 (21.5)**	**41 (24.4)**	**58 (26.5)**
Nervous system disorders	**7 (43.8)**	**32 (21.5)**	**41 (24.4)**	**58 (26.5)**
Convulsion	6 (37.5)	26 (17.4)	34 (20.2)	46 (21.0)
Status epilepticus	1 (6.3)	5 (3.4)	6 (3.6)	6 (2.7)
Grand mal convulsion	1 (6.3)	0	1 (0.6)	4 (1.8)
Complex partial seizures	1 (6.3)	1 (0.7)	2 (1.2)	2 (0.9)
Epilepsy	0	1 (0.7)	1 (0.6)	2 (0.9)
Petit mal epilepsy	0	2 (1.3)	2 (1.2)	2 (0.9)
Tonic convulsion	0	0	0	2 (0.9)
Clonic convulsion	0	1 (0.7)	1 (0.6)	1 (0.5)
Myoclonic epilepsy	0	0	0	1 (0.5)
Partial seizures with secondary generalisation	0	1 (0.7)	1 (0.6)	1 (0.5)
Postictal state	0	1 (0.7)	1 (0.6)	1 (0.5)
Seizure cluster	0	1 (0.7)	1 (0.6)	1 (0.5)

BRV=brivaracetam; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; POS=partial-onset seizures; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event; y=years

Note: Adverse events were coded using MedDRA version 15.0.

Note: n=number of subjects who reported a TEAE for the specified category.

Note: The Total POS summary group included subjects <4 years, ≥4 to <16 years, and subjects who were 16 years at the time of study entry.

Note: All pediatric subjects included subjects with POS and other seizure types.

Table 35. TEAEs potentially associated with seizure worsening in subjects ⩾4 to <16 years with POS in Pool Paediatric Studies is presented by BRV modal daily dose

Primary SOC PT	BRV modal daily dose (mg/kg/day)					BRV Overall N=149 n (%)
	0.0 to 1.0 N=15 n (%)	>1.0 to 2.0 N=10 n (%)	>2.0 to 3.0 N=19 n (%)	>3.0 to 4.0 N=79 n (%)	>4.0 N=26 n (%)	
At least 1 event	**3 (20.0)**	**1 (10.0)**	**4 (21.1)**	**18 (22.8)**	**6 (23.1)**	**32 (21.5)**
Nervous system disorders	**3 (20.0)**	**1 (10.0)**	**4 (21.1)**	**18 (22.8)**	**6 (23.1)**	**32 (21.5)**
Convulsion	3 (20.0)	1 (10.0)	3 (15.8)	14 (17.7)	5 (19.2)	26 (17.4)
Status epilepticus	0	0	1 (5.3)	4 (5.1)	0	5 (3.4)
Petit mal epilepsy	0	0	1 (5.3)	0	1 (3.8)	2 (1.3)
Clonic convulsion	0	0	1 (5.3)	0	0	1 (0.7)
Complex partial seizures	0	0	0	0	1 (3.8)	1 (0.7)
Epilepsy	0	0	0	1 (1.3)	0	1 (0.7)
Partial seizures with secondary generalisation	0	0	0	1 (1.3)	0	1 (0.7)
Postictal state	0	0	0	0	1 (3.8)	1 (0.7)
Seizure cluster	0	0	0	1 (1.3)	0	1 (0.7)

BRV=brivaracetam; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; POS=partial-onset seizures; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event
Note: Adverse events were coded using MedDRA version 15.0.
Note: n=number of subjects who reported a TEAE for the specified category.

The incidence of reports of TEAEs potentially associated with seizure worsening was highest during Months 1 to 3 (12 subjects [8.1%]), and decreased thereafter (during Months 4 to 12 [range: 5 to 6 subjects; 4.6% to 5.2%], during Months 13 to 24 [range: 2 to 5 subjects; 2.8% to 6.1%], and after Month 25 [0 or 1 subject]). No TEAEs potentially associated with seizure worsening were reported during the Down-Titration Period.

Treatment-emergent AEs potentially associated with suicidality

In the ⩾4 to <16 years POS group in Pool Paediatric Studies, 7 subjects (4.7%) reported suicidal ideation, including 1 subject (0.7%) who attempted suicide 10 days after discontinuing BRV. Six of the 7 subjects were >10 years of age at onset and 1 subject was 8 years of age.

In 4 of the 7 subjects, the TEAE of suicidal ideation occurred within the first 3 months of BRV initiation. All events were mild and nonserious, except 1 event that was a severe SAE. Six of the 7 events resolved and were considered not related to BRV by the Investigator. Five of the TEAEs of suicidal ideation started the same day (±1 day) the Columbia-Suicide Severity Rating Scale assessment was performed, which could suggest that the assessment contributed to the identification and the reporting of these events. No subject completed suicide.

The overall incidence on suicidality in the ⩾4 to <16 years POS group in Pool Paediatric Studies was 4.7% while it was 3.2% in the Pool S4. The exposure-adjusted incidence in the ⩾4 to <16 years POS group in Pool Paediatric Studies was 2.86% [1.15 - 5.90] versus 1.02% [0.8 – 1.27] in Pool S4 (Table 36. and Table 37.).

Table 36. TEAEs potentially associated with suicidality in BRV Overall by paediatric summary group in Pool Paediatric Studies

Primary SOC PT	BRV Overall			
	POS summary group			All pediatric subjects N=219 n (%)
	<4y N=16 n (%)	≥4 to <16y N=149 n (%)	Total POS N=168 n (%)	
At least 1 event	**0**	**7 (4.7)**	**8 (4.8)**	**9 (4.1)**
Psychiatric disorders	**0**	**7 (4.7)**	**8 (4.8)**	**9 (4.1)**
Suicidal ideation	0	7 (4.7)	8 (4.8)	9 (4.1)
Self-injurious behaviour	0	0	0	1 (0.5)
Suicide attempt	0	1 (0.7)	1 (0.6)	1 (0.5)

BRV=brivaracetam; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; POS=partial-onset seizures; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event; y=years
Note: Adverse events were coded using MedDRA version 15.0.
Note: n=number of subjects who reported a TEAE for the specified category.
Note: The Total POS summary group included subjects <4 years, ≥4 to <16 years, and subjects who were 16 years at the time of study entry.
Note: All pediatric subjects included subjects with POS and other seizure types.

Table 37. Paediatric subjects reporting TEAEs potentially associated with suicidality

Subject number	Age (y)/ gender	BRV dose at onset	Preferred term	Causality per Investigator	Serious/Led to discontinuation of BRV	Study day of TEAE onset
Subjects ≥4 to <16 years with POS						
N01263-603-01774 N01266-603-01774	4/F	4mg/kg/day	Suicidal ideation	Not related	N/N	1119
N01266-101-07504	11/F	1.0mg/kg/day	Suicidal ideation	Not related	N/N	1
N01266-101-07505	15/F	200mg/day	Suicidal ideation	Not related	N/N	77
N01266-103-07511	15/M	NA [a]	Suicidal ideation	Not related	Y/N	72
N01266-105-07541	12/F	200mg/day	Suicidal ideation	Not related	N/N	960
N01266-113-07601	13/F	150mg/day	Suicidal ideation	Related	N/Y	70
		NA [b]	Suicide attempt	Not related	Y/NA	88
N01266-603-07780	10/F	150mg/day	Suicidal ideation	Not related	N/N	39
Subject 16 years with POS						
N01266-603-07818	16/F	100mg/day	Suicidal ideation	Not related	N/Y	50
Subject with other seizure type (not POS)						
N01263-301-01721	13/F	0mg/day	Suicidal ideation	Not related	Y/Y	104
N01266-301-01721			Self-injurious behaviour	Not related	N/N	

BRV=brivaracetam; F=female; M=male; NA=not applicable; POS=partial-onset seizures; TEAE=treatment-emergent adverse event; y=years
[a] Event onset was 8 days posttreatment.
[b] Event onset was 10 days posttreatment.

One event of suicidal ideation was considered related to study drug by the Investigator:
Subject N01266-113-07601, a 13-year-old white female, experienced an event of depression, 66 days after the first study drug dose. The event was considered mild in intensity and related to study drug by the Investigator. The subject experienced an event of suicidal ideation, 4 days after the onset of depression. The event occurred 70 days after the first study drug dose in N01266. The event was considered mild in intensity and related to study drug by the Investigator. The subject received venlafaxine hydrochloride and escitalopram oxalate as treatment for the suicidal ideation. The subject experienced an event of suicide attempt during the Post-Treatment Period, 18 days after the onset of suicidal ideation. The event occurred 88 days after the first study drug dose in

N01266. The event was considered moderate in intensity and not related to study drug by the Investigator. At the time of the suicide attempt, the subject was not taking the study drug and had been off study drug for 10 days.

Treatment-emergent AEs potentially associated with behavior disorders

In the ⩾4 to <16 years POS group in Pool Paediatric Studies, TEAEs potentially associated with behavioral disorders were reported in 36 subjects (24.2%); the most frequently reported TEAEs were irritability (10.1%), and aggression and psychomotor hyperactivity (4.7% each). The events were reported most frequently during the first 3 months of treatment.

Of the 15 subjects reporting irritability, the events were mild in intensity in 14 subjects and moderate in 1 subject. None of the events of irritability were serious and none led to discontinuation of BRV. In 1 subject, the BRV dose was decreased, while in all other subjects the BRV dose was unchanged. In 6 of the 15 subjects, irritability was considered drug-related by the investigator.

Among 7 subjects for whom aggression was reported, most cases were mild or moderate in intensity. One subject had aggression reported as severe. This event was the 1 case of aggression (0.7%) reported as an SAE (N01266-103-07511). The event was considered not related to BRV by the investigator and led to discontinuation of BRV. In total, 3 subjects (2.0%) discontinued BRV due to the TEAE of aggression. In 4 of the 7 subjects, the investigator considered the aggression drug-related.

In the 7 subjects with psychomotor hyperactivity, all events were mild or moderate in intensity. None of the events was serious. One subject (0.7%) discontinued BRV because of psychomotor hyperactivity. None of the other events of psychomotor hyperactivity led to a change in BRV dose. In 4 of the 7 subjects, the investigator considered psychomotor hyperactivity drug-related.

The exposure-adjusted incidence rates (IRs) (95% CI) for TEAEs potentially associated with behavioral disorders were higher in the ⩾4 to <16 years POS group in Pool Paediatric Studies compared with Pool S4 (17.78 [12.45, 24.61] and 5.22 [4.70, 5.78] per 100 subject-years), respectively.

In addition to the analysis of TEAEs potentially associated with behavioral disorders, the effect of BRV on behavior and cognition was assessed using the age-appropriate Achenbach Child Behavior Checklist (CBCL) and Behavior Rating Inventory of Executive Function (BRIEF)/Behavior Rating Inventory of Executive Function®-Preschool Version (BRIEF-P).

In summary, behavioral disorders were reported more frequently in the ⩾4 to 16 years POS group in Pool Paediatric Studies compared with the established BRV safety profile in adults.

The initially assessed interim results of the Achenbach CBCL/1½-5 and CBCL/6-18 and BRIEF/BRIEF-P questionnaires showed small improvements (decreases) from baseline for most subscale scores and large variability. Following the request of further clarification regarding the interpretation of the outcomes from the scales adopted by the MAH, the listings provided resulted heavily biased by the low numbers and by a remarkable heterogeneity of the scores gathered by the parents among visits. They seemed to coherently show highly statistically significant differences (LSM estimates) at the MMRM analysis for the following scales and domains:

-Achenbach P (CBCL 11/2-5): The majority of subscales showed statistically unsignificant results from Baseline (e.g., Anxious/Depressed; Attention problems; Emotionally reactive; Sleep

problems; Withdrawn). Few statistically significant differences were found late in the study only for the subscale Somatic complaints (p=0.019 at Visit 13 and p=0.0002 at Visit 15).

-CBCL 6-18 scale: With the exception of the subscale/syndrome Withdrawn/Depressed for which no significant changes were reported, all the following subscales were statistically significant: aggressive behavior (p<0.003 from Visit 7 through Visit 15); anxious/depressed (p value ranging from 0.0033 at Visit 3 to 0.02 at Visit 15; Attention problems (p ranging from 0.0014 at Visit 3 to <.0001 at Visit 15); Rule-breaking behavior (p ranging from p=0.004 at Visit 7 to 0.027 at Visit 15); Social problems (p ranging from p=0.0024 at Visit 3 to p=0.0015 at Visit 15); Somatic complaints (p<0.0001 from Visit 3 through Visit 15, with the exception of p=.0003 at Visit 5); Thought problems (p=0.0031 at Visit 3 through p=0.0032 at Visit 15.

-BRIEF scale: The majority of subscales did not show statistically unequivocal results from Baseline, particularly regarding the domains Behavioral Regulation, Metacognition, GEC, Shift, Emotional Control, Initiate, Plan/Organize, Monitor. On the other hand, the following domains showed more consistently statistically significant differences from Baseline: Inhibit (p=0.009 at Visit 7, p=0006 at Visit 11 and p=0.02 at Visits 13 and 15), Working memory (p value ranging from 0.0195 at Visit 3 to 0.0012 at Visit 11), Organization of Materials (p ranging from 0.04 at Visit 5 to 0.0055 at Visit 13).

Further information about the outcome/reversibility of the TEAEs leading to discontinuation, in particular those in the SOC of Nervous System Disorders and Psychiatric Disorders, was required to the MAH. The MAH provided additional and updated (120-Day Safety Update (120DSU) Report; data lock point 15 Mar 2017) information on the outcome/reversibility of the AEs leading to discontinuation, with special attention to those occurred in the SOC of Nervous System disorders and Psychiatric disorders. Moreover, the MAH further investigated the increased risks of suicidality and behavioral disorders in the pediatric population in two SSARs and neither of these signals was confirmed.

In the updated Pool Pediatric Studies up to 15 Mar 2017, 2 additional subjects had AEs leading to permanent discontinuation of study drug due to astrocytoma (low grade) and pregnancy. Overall 37 AEs leading to permanent discontinuation were reported in 27 (12.3%) subjects, more frequently in the SOCs of Psychiatric disorders (4.1%) and Nervous System disorders (3.2%). The most common AEs leading to permanent discontinuation were aggression and suicidal ideation (1.4% each) (particularly in the ⩾12 to <16 years group), and convulsion decreased appetite, pneumonia, and circulatory collapse (0.9% each).

Most these events (21 AEs in 16 subjects) resolved. In the updated data, no additional fatal outcome was reported other than the 4 cases (aspiration [aspiration/acute respiratory failure/circulatory collapse], septic shock/pneumonia, pneumonia, and circulatory collapse) already reported in the previous assessment report. None of these fatal cases was considered related to BRV. One AE was reported as resolving, 2 as resolved with sequelae and 6 AEs not resolved in 5 subjects (4 in study N01266 and 1 in study N01263): limited information could be obtained on these patients because they were lost to follow-up or had withdrawn consent.

In the SOC of Psychiatric disorders: 3/10 events (Aggression, Depression, and Suicidal ideation) were not resolved; 2/10 events (Abnormal behavior and Aggression) resolved with sequelae (worsening of Abnormal behavior and Aggression that remained stable). The average duration of these AEs was <1 month.

As regard to the AEs in the SOC of Nervous System disorders, all of them resolved and their average duration was <2 months.

In the SSARs on suicidality, that include comprehensive review of the available data from clinical studies, published literature and spontaneous postmarketing reports, due to the several methodological limitations, an increased risk of suicidality in the pediatric population treated with BRV beyond what is already documented in the SmPC could not be established.

In conclusion, most AEs leading to study drug discontinuation resolved without sequelae, most of these occurred as per the PTs in the SOC of Psychiatric disorders and Nervous System disorders that are already reported as ADRs in section 4.8 of the current BRV SmPC. However, due to the several methodological limitations of pediatric studies, these AEs should continue to be monitored through pharmacovigilance activities.

TEAEs potentially associated with growth, endocrine function/sexual maturation, neurodevelopment, cognitive impairment, anxiety, and depression (Pool Paediatric Studies)

Table 38. Paediatric TEAEs of interest, which included TEAEs potentially associated with growth, endocrine function or sexual maturation, neurodevelopment, cognitive impairment, anxiety, and depression, in BRV Overall by paediatric summary group in Pool Paediatric Studies

TEAE of interest category Primary SOC PT	BRV Overall			
	POS summary group			All pediatric subjects
	<4y N=16 n (%)	≥4 to <16y N=149 n (%)	Total POS N=168 n (%)	N=219 n (%)
Growth				
At least 1 event	**1 (6.3)**	**0**	**1 (0.6)**	**3 (1.4)**
Metabolism and nutrition disorders	1 (6.3)	0	1 (0.6)	3 (1.4)
Underweight	0	0	0	2 (0.9)
Failure to thrive	1 (6.3)	0	1 (0.6)	1 (0.5)
Endocrine function or sexual maturation				
At least 1 event	**2 (12.5)**	**7 (4.7)**	**9 (5.4)**	**10 (4.6)**
Congenital, familial and genetic disorders	**1 (6.3)**	**1 (0.7)**	**2 (1.2)**	**2 (0.9)**
Cryptorchism	1 (6.3)	1 (0.7)	2 (1.2)	2 (0.9)
Endocrine disorders	**0**	**2 (1.3)**	**2 (1.2)**	**3 (1.4)**
Hypothyroidism	0	2 (1.3)	2 (1.2)	3 (1.4)
Investigations	**1 (6.3)**	**1 (0.7)**	**2 (1.2)**	**2 (0.9)**
Blood testosterone decreased	1 (6.3)	0	1 (0.6)	1 (0.5)
Blood TSH increased	**0**	**1 (0.7)**	**1 (0.6)**	**1 (0.5)**
Metabolism and nutrition disorders	1 (6.3)	0	1 (0.6)	1 (0.5)
Hypoglycaemia	1 (6.3)	0	1 (0.6)	1 (0.5)
Reproductive system and breast disorders	**0**	**3 (2.0)**	**3 (1.8)**	**3 (1.4)**
Gynaecomastia	0	2 (1.3)	2 (1.2)	2 (0.9)
Amenorrhoea	0	1 (0.7)	1 (0.6)	1 (0.5)
Skin and subcutaneous tissue disorders	**1 (6.3)**	**0**	**1 (0.6)**	**1 (0.5)**
Hair growth abnormal	1 (6.3)	0	1 (0.6)	1 (0.5)

TEAE of interest category Primary SOC PT	BRV Overall			
	POS summary group			All pediatric subjects N=219 n (%)
	<4y N=16 n (%)	≥4 to <16y N=149 n (%)	Total POS N=168 n (%)	
Neurodevelopment				
At least 1 event	**3 (18.8)**	**10 (6.7)**	**13 (7.7)**	**16 (7.3)**
General disorders and administration site conditions	**0**	**0**	**0**	**1 (0.5)**
Developmental delay	0	0	0	1 (0.5)
Nervous system disorders	**2 (12.5)**	**7 (4.7)**	**9 (5.4)**	**10 (4.6)**
Psychomotor hyperactivity	0	7 (4.7)	7 (4.2)	7 (3.2)
Disturbance in attention	0	0	0	1 (0.5)
Speech disorder	1 (6.3)	0	1 (0.6)	1 (0.5)
Speech disorder developmental	1 (6.3)	0	1 (0.6)	1 (0.5)
Psychiatric disorders	**1 (6.3)**	**3 (2.0)**	**4 (2.4)**	**4 (1.8)**
Bradyphrenia	0	2 (1.3)	2 (1.2)	2 (0.9)
Autism spectrum disorder	0	1 (0.7)	1 (0.6)	1 (0.5)
Neurodevelopmental disorder	1 (6.3)	0	1 (0.6)	1 (0.5)
Social circumstances	**0**	**1 (0.7)**	**1 (0.6)**	**2 (0.9)**
Learning disability	0	0	0	1 (0.5)
Mental disability	0	1 (0.7)	1 (0.6)	1 (0.5)
Cognitive impairment				
At least 1 event	**2 (12.5)**	**9 (6.0)**	**11 (6.5)**	**13 (5.9)**
Nervous system disorders	**1 (6.3)**	**0**	**1 (0.6)**	**2 (0.9)**
Disturbance in attention	0	0	0	1 (0.5)
Speech disorder developmental	1 (6.3)	0	1 (0.6)	1 (0.5)

TEAE of interest category Primary SOC PT	BRV Overall			
	POS summary group			All pediatric subjects N=219 n (%)
	<4y N=16 n (%)	≥4 to <16y N=149 n (%)	Total POS N=168 n (%)	
Psychiatric disorders	**1 (6.3)**	**9 (6.0)**	**10 (6.0)**	**11 (5.0)**
Attention deficit/hyperactivity disorder	0	3 (2.0)	3 (1.8)	4 (1.8)
Confusional state	0	3 (2.0)	3 (1.8)	3 (1.4)
Oppositional defiant disorder	0	2 (1.3)	2 (1.2)	2 (0.9)
Autism spectrum disorder	0	1 (0.7)	1 (0.6)	1 (0.5)
Conduct disorder	0	1 (0.7)	1 (0.6)	1 (0.5)
Neurodevelopmental disorder	1 (6.3)	0	1 (0.6)	1 (0.5)
Anxiety				
At least 1 event	**0**	**6 (4.0)**	**6 (3.6)**	**7 (3.2)**
Psychiatric disorders	**0**	**6 (4.0)**	**6 (3.6)**	**7 (3.2)**
Anxiety	0	4 (2.7)	4 (2.4)	4 (1.8)
Nervousness	0	2 (1.3)	2 (1.2)	3 (1.4)
Panic attack	0	1 (0.7)	1 (0.6)	1 (0.5)
Depression				
At least 1 event	**0**	**4 (2.7)**	**4 (2.4)**	**5 (2.3)**
Psychiatric disorders	**0**	**4 (2.7)**	**4 (2.4)**	**5 (2.3)**
Depression	0	2 (1.3)	2 (1.2)	3 (1.4)
Depressed mood	0	2 (1.3)	2 (1.2)	2 (0.9)

BRV=brivaracetam; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; POS=partial-onset seizures; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event; TSH=thyroid-stimulating hormone; y=years

Note: Adverse events were coded using MedDRA version 15.0.

Note: n=number of subjects who reported a TEAE for the specified category.

Note: The Total POS summary group included subjects <4 years, ≥4 to <16 years, and subjects who were 16 years at the time of study entry.

Note: All pediatric subjects included subjects with POS and other seizure types.

In Pool Paediatric Studies, TEAEs of interest for the paediatric population were reported most frequently in BRV Overall in the following categories: neurodevelopment (16 subjects [7.3%]), cognitive impairment (13 subjects [5.9%]), and endocrine function or sexual maturation (10 subjects [4.6%]). No TEAEs were reported in the category of growth (Table 39.).

Table 39. TEAEs potentially associated with growth, endocrine function or sexual maturation, neurodevelopment, cognitive impairment, anxiety, and depression in subjects ≥4 to <16 years with POS in Pool Paediatric Studies

TEAE of interest category Primary SOC PT	BRV modal daily dose (mg/kg/day)					BRV Overall N=149 n (%)
	0.0 to 1.0 N=15 n (%)	>1.0 to 2.0 N=10 n (%)	>2.0 to 3.0 N=19 n (%)	>3.0 to 4.0 N=79 n (%)	>4.0 N=26 n (%)	
Endocrine function or sexual maturation						
At least 1 event	**0**	**0**	**2 (10.5)**	**4 (5.1)**	**1 (3.8)**	**7 (4.7)**
Congenital, familial and genetic disorders	**0**	**0**	**0**	**0**	**1 (3.8)**	**1 (0.7)**
Cryptorchism	0	0	0	0	1 (3.8)	1 (0.7)
Endocrine disorders	**0**	**0**	**0**	**2 (2.5)**	**0**	**2 (1.3)**
Hypothyroidism	0	0	0	2 (2.5)	0	2 (1.3)
Investigations	**0**	**0**	**0**	**1 (1.3)**	**0**	**1 (0.7)**
Blood TSH increased	0	0	0	1 (1.3)	0	1 (0.7)
Reproductive system and breast disorders	**0**	**0**	**2 (10.5)**	**1 (1.3)**	**0**	**3 (2.0)**
Gynaecomastia	0	0	2 (10.5)	0	0	2 (1.3)
Amenorrhoea	0	0	0	1 (1.3)	0	1 (0.7)
Neurodevelopment						
At least 1 event	**1 (6.7)**	**2 (20.0)**	**0**	**5 (6.3)**	**2 (7.7)**	**10 (6.7)**
Nervous system disorders	**1 (6.7)**	**1 (10.0)**	**0**	**3 (3.8)**	**2 (7.7)**	**7 (4.7)**
Psychomotor hyperactivity	1 (6.7)	1 (10.0)	0	3 (3.8)	2 (7.7)	7 (4.7)
Psychiatric disorders	**0**	**1 (10.0)**	**0**	**2 (2.5)**	**0**	**3 (2.0)**
Bradyphrenia	0	1 (10.0)	0	1 (1.3)	0	2 (1.3)
Autism spectrum disorder	0	0	0	1 (1.3)	0	1 (0.7)
Social circumstances	**0**	**0**	**0**	**1 (1.3)**	**0**	**1 (0.7)**
Mental disability	0	0	0	1 (1.3)	0	1 (0.7)
Cognitive impairment						
At least 1 event	**0**	**1 (10.0)**	**1 (5.3)**	**6 (7.6)**	**1 (3.8)**	**9 (6.0)**
Psychiatric disorders	**0**	**1 (10.0)**	**1 (5.3)**	**6 (7.6)**	**1 (3.8)**	**9 (6.0)**
Attention deficit/hyperactivity disorder	0	0	1 (5.3)	2 (2.5)	0	3 (2.0)
Confusional state	0	0	0	3 (3.8)	0	3 (2.0)
Oppositional defiant disorder	0	1 (10.0)	0	0	1 (3.8)	2 (1.3)
Autism spectrum disorder	0	0	0	1 (1.3)	0	1 (0.7)
Conduct disorder	0	0	0	1 (1.3)	0	1 (0.7)
Anxiety						
At least 1 event	**0**	**0**	**1 (5.3)**	**3 (3.8)**	**2 (7.7)**	**6 (4.0)**
Psychiatric disorders	**0**	**0**	**1 (5.3)**	**3 (3.8)**	**2 (7.7)**	**6 (4.0)**
Anxiety	0	0	1 (5.3)	2 (2.5)	1 (3.8)	4 (2.7)
Nervousness	0	0	0	1 (1.3)	1 (3.8)	2 (1.3)
Panic attack	0	0	1 (5.3)	0	0	1 (0.7)
Depression						
At least 1 event	**1 (6.7)**	**0**	**1 (5.3)**	**2 (2.5)**	**0**	**4 (2.7)**
Psychiatric disorders	**1 (6.7)**	**0**	**1 (5.3)**	**2 (2.5)**	**0**	**4 (2.7)**
Depressed mood	1 (6.7)	0	1 (5.3)	0	0	2 (1.3)
Depression	0	0	0	2 (2.5)	0	2 (1.3)

BRV=brivaracetam; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; POS=partial-onset seizures; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event
Note: Adverse events were coded using MedDRA version 15.0.
Note: n=number of subjects who reported a TEAE for the specified category.

In the neurodevelopment category, 1 subject (0.7%) discontinued study drug due to the TEAE of psychomotor hyperactivity. In the depression category, 1 subject (0.7%) had a treatment-emergent SAE of depression, and 1 subject (0.7%) discontinued study drug due to the TEAE of depression. No other TEAEs of interest specific to the paediatric population were treatment-emergent SAEs or resulted in discontinuation of study drug.

In the ≥4 to <16 years POS group in Pool Paediatric Studies, the incidence of TEAEs potentially associated with neurodevelopment was highest during Months 1 to 3 (7 subjects [4.7%]), and was lower at all subsequent safety time intervals (0% to 1.7%). For TEAEs potentially associated with cognitive impairment, the incidence was highest during Months 1 to 3 (7 subjects [4.7%]), and was lower at all other safety time intervals (0% to 1.9%).

TEAEs potentially associated with falls (Pool Paediatric Studies)

In Pool Paediatric Studies, TEAEs potentially associated with falls were reported in 41 subjects (18.7%) in BRV Overall; the most frequently reported TEAE was fall (7.8%).

Treatment-emergent AEs potentially associated with falls in BRV Overall were reported in 27 subjects (18.1%) in the ≥4 to <16 years POS group in Pool Paediatric Studies, the most frequently reported TEAE in BRV Overall was fall (8.1%). Clavicle fracture and forearm fracture (1 subject each [0.7%]) were reported as treatment-emergent SAEs. None of the TEAEs potentially associated with falls resulted in discontinuation of study drug.

In the ≥4 to <16 years POS group in Pool Paediatric Studies, the incidence of TEAEs potentially associated with falls was highest during Months 1 to 3 (11 subjects [7.4%]) and was lower during Months 4 to 24 (range: 0.9% to 6.3%); no falls were reported after Month 24 through Month 63.

In Pool Paediatric Studies, TEAEs potentially associated with falls and concurrent Type 1B or Type 1C seizures were reported in 13 subjects (5.9%) in BRV Overall; the most frequently reported TEAE was fall (3.2%).

Treatment-emergent AEs potentially associated with falls with concurrent Type 1B or Type 1C seizures in BRV Overall were reported in 9 subjects (6.0%) in the ≥4 to <16 years POS group in Pool Paediatric Studies (Table 40.). In the ≥4 to <16 years POS group in Pool Paediatric Studies, TEAEs potentially associated with falls without concurrent Type 1B or Type 1C seizures were reported in 20 subjects (13.4%) in BRV Overall; the most frequently reported TEAE was fall (6.0%) (Table 41.).

Table 40. TEAEs potentially associated with falls without concurrent Type 1B or Type 1C seizures reported in >1 subject in all paediatric subjects in BRV Overall by paediatric summary group in Pool Paediatric Studies

Primary SOC PT	BRV Overall			
	POS summary group			All pediatric subjects N=219 n (%)
	<4y N=16 n (%)	≥4 to <16y N=149 n (%)	Total POS N=168 n (%)	
At least 1 event	**3 (18.8)**	**20 (13.4)**	**23 (13.7)**	**32 (14.6)**
General disorders and administration site conditions				
Gait disturbance	1 (6.3)	0	1 (0.6)	2 (0.9)
Injury, poisoning and procedural complications				
Fall	0	9 (6.0)	9 (5.4)	12 (5.5)
Laceration	0	3 (2.0)	3 (1.8)	6 (2.7)
Contusion	0	2 (1.3)	2 (1.2)	5 (2.3)
Head injury	0	3 (2.0)	3 (1.8)	4 (1.8)
Excoriation	1 (6.3)	1 (0.7)	2 (1.2)	2 (0.9)
Hand fracture	0	2 (1.3)	2 (1.2)	2 (0.9)
Joint dislocation	0	2 (1.3)	2 (1.2)	2 (0.9)
Nervous system disorders				
Syncope	0	2 (1.3)	2 (1.2)	3 (1.4)
Balance disorder	0	0	0	2 (0.9)

BRV=brivaracetam; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; POS=partial-onset seizures; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event; y=years
Note: Adverse events were coded using MedDRA version 15.0.
Note: n=number of subjects who reported a TEAE for the specified category.
Note: This table summarizes TEAEs reported in >1 subject in all pediatric subjects in BRV Overall.
Note: TEAEs identified as potentially associated with a fall were summarized. TEAEs that coded to a PT of Fall or TEAEs with a verbatim term containing Fall or Fell that did not code to Fall were also included in the summary, with the exception of TEAEs that coded to Tooth loss, Initial insomnia, or Alopecia.
Note: The Total POS summary group included subjects <4 years, ≥4 to <16 years, and subjects who were 16 years at the time of study entry.
Note: All pediatric subjects included subjects with POS and other seizure types.

Table 41. TEAEs potentially associated with falls without concurrent Type 1B or Type 1C seizures reported in >1 subject ≥4 to <16 years with POS in Pool Paediatric Studies is presented by BRV modal daily dose

Primary SOC PT	BRV modal daily dose (mg/kg/day)					BRV Overall N=149 n (%)
	0.0 to 1.0 N=15 n (%)	>1.0 to 2.0 N=10 n (%)	>2.0 to 3.0 N=19 n (%)	>3.0 to 4.0 N=79 n (%)	>4.0 N=26 n (%)	
At least 1 event	**1 (6.7)**	**0**	**4 (21.1)**	**13 (16.5)**	**2 (7.7)**	**20 (13.4)**
Injury, poisoning and procedural complications						
Fall	0	0	2 (10.5)	5 (6.3)	2 (7.7)	9 (6.0)
Head injury	0	0	2 (10.5)	1 (1.3)	0	3 (2.0)
Laceration	0	0	1 (5.3)	2 (2.5)	0	3 (2.0)
Contusion	0	0	1 (5.3)	1 (1.3)	0	2 (1.3)
Hand fracture	0	0	1 (5.3)	1 (1.3)	0	2 (1.3)
Joint dislocation	0	0	1 (5.3)	1 (1.3)	0	2 (1.3)
Nervous system disorders						
Syncope	0	0	0	2 (2.5)	0	2 (1.3)

BRV=brivaracetam; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; POS=partial-onset seizures; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event
Note: Adverse events were coded using MedDRA version 15.0.
Note: n=number of subjects who reported a TEAE for the specified category.
Note: This table summarizes TEAEs reported in >1 subject ≥4 to <16 years with POS in BRV Overall.
Note: TEAEs identified as potentially associated with a fall were summarized. TEAEs that coded to a PT of Fall or TEAEs with a verbatim term containing Fall or Fell that did not code to Fall were also included in the summary, with the exception of TEAEs that coded to Tooth loss, Initial insomnia, or Alopecia.
Data source: ISS Table 5.14.4.5.1B

TEAEs potentially associated with accidents and injuries (Pool Paediatric Studies)

In Pool Paediatric Studies, TEAEs potentially associated with accidents and injuries were reported in 42 subjects (19.2%) in BRV Overall; the most frequently reported TEAE was fall (7.8%).

In the ≥4 to <16 years POS group in Pool Paediatric Studies, TEAEs potentially associated with accidents and injuries in BRV Overall were reported in 31 subjects (20.8%); the most frequently reported TEAE was fall (8.1%). Hypothermia, clavicle fracture, and forearm fracture (1 subject each [0.7%]) were reported as a treatment-emergent SAEs. None of the TEAEs potentially associated with accidents and injuries resulted in discontinuation of study Drug.

In the ≥4 to <16 years POS group in Pool Paediatric Studies, the incidence of TEAEs potentially associated with accidents and injuries was highest during Months 1 to 3 (12 subjects [8.1%]), was lower during Months 4 to 24 (range: 1.9% to 6.3%); no accidents or injuries were reported after Month 24 through Month 63.

In Pool Paediatric Studies, TEAEs potentially associated with accidents and injuries and concurrent Type 1B or Type 1C seizures were reported in 17 subjects (7.8%); the most frequently reported TEAE was fall (3.2%).

In the ≥4 to <16 years POS group in Pool Paediatric Studies, TEAEs potentially associated with accidents and injuries and concurrent Type 1B or Type 1C seizures in BRV Overall were reported in 13 subjects (8.7%); the most frequently reported TEAE was fall (3.4%). In Pool Paediatric Studies, TEAEs potentially associated with accidents and injuries without concurrent Type 1B or Type 1C seizures were reported in 30 subjects (13.7%) in BRV Overall; the most frequently reported TEAE was fall (5.5%).

In the ≥4 to <16 years POS group in Pool Paediatric Studies, TEAEs potentially associated with accidents and injuries without concurrent Type 1B or Type 1C seizures were reported in 21 subjects (14.1%) in BRV Overall; the most frequently reported TEAE was fall (6.0%).

TEAEs potentially associated with psychosis (Pool Paediatric Studies)

In Pool Paediatric Studies, TEAEs potentially associated with psychosis were reported in 3 subjects (1.4%) in BRV Overall; the reported TEAEs were hallucination (2 subjects [0.9%]) and hallucination, visual (1 subject [0.5%]).

In the ≥4 to <16 years POS group in Pool Paediatric Studies, TEAEs potentially associated with psychosis in BRV Overall were reported in 2 subjects (1.3%); the reported TEAE was hallucination. The TEAE of hallucination was not a treatment-emergent SAE and did not result in discontinuation of study drug.

Safety in special populations

Gender

Overall exposure: In the ≥4 to <16 years POS group in Pool Pediatric Studies, exposure to BRV in BRV Overall was higher for male subjects (84 subjects with 146.1 subject-years of exposure) compared with female subjects (65 subjects with 103.6 subject-years of exposure).

Subject disposition: In the ≥4 to <16 years POS group, 23 male subjects (27.4%) and 27 female subjects (41.5%) discontinued prematurely from the study. The most frequently reported reason for discontinuation for male subjects was lack of efficacy (10.7%), and for female subjects was lack of efficacy, AE, and subject choice (10.8% each).

Common TEAEs: In the ≥4 to <16 years POS group in Pool Pediatric Studies, the most frequently reported common TEAEs in BRV Overall were nasopharyngitis (24.2%); pharyngitis (20.1%); pyrexia, convulsion, and headache (17.4%); and vomiting (14.8%) (Section 6.2.1). The incidences of these most frequently reported common TEAEs in male and female subjects are as follows:

- Nasopharyngitis: Male subjects (21.4%) and female subjects (27.7%)

- Pharyngitis: Male subjects (19.0%) and female subjects (21.5%)

- Pyrexia: Male subjects (16.7%) and female subjects (18.5%)

- Convulsion: Male subjects (19.0%) and female subjects (15.4%)

- Headache: Male subjects (9.5%) and female subjects (27.7%)

- Vomiting: Male subjects (17.9%) and female subjects (10.8%)

In the ≥4 to <16 years POS group in Pool Pediatric Studies, in general, the incidences of the most frequently reported common TEAEs in BRV Overall were similar in male and female subjects. Male subjects, compared with female subjects, reported higher incidences of vomiting (17.9% vs 10.8%); fatigue (7.1% vs 3.1%); psychomotor hyperactivity (7.1% vs 1.5%); varicella (7.1% vs 0%); sinusitis (6.0% vs 0%); constipation (6.0% vs 1.5%); aggression (6.0% vs 3.1%); and head injury (4.8% vs 0%). Male subjects, compared with female subjects, reported lower incidences of dental caries and abnormal behaviour (0% vs 4.6% each); suicidal ideation (1.2% vs 9.2%); sleep disorder (1.2% vs 4.6%); rhinitis allergic (2.4% vs 9.2%); insomnia (3.6% vs 6.2%); abdominal pain and gastroenteritis (4.8% vs 10.8% each); abdominal pain upper (4.8% vs 7.7%); and headache (9.5% vs 27.7%).

The differences observed in the frequencies of some of common treatment emergent adverse events (TEAEs) between males and females, particularly those related to the system organ class (SOC) Nervous System Disorders and the SOC Psychiatric Disorders, were of concern. However, due to the small numbers and the lack of a control group, it is not possible to conclude on the significance of differences observed for some AEs between males and females. The requested data provided by the MAH were particularly reassuring regarding the sex-differences for some important AEs in the SOC of Nervous System disorders and Psychiatric disorders that appear to be unlikely related to BRV treatment but rather to the sex differences in the background population reported in literature.

Hematology: In the ≥4 to <16 years POS group in Pool Pediatric Studies, in both male and female subjects, there were no clinically meaningful mean changes from Baseline over time to the Last Value in BRV Overall for any hematology parameter. In the ≥4 to <16 years POS group in Pool Pediatric Studies, most subjects had normal values at both Baseline and Last Value for all hematology parameters. The incidence of shifts from normal at Baseline to low or high at Last Value was similar in male and female subjects for all hematology parameters. In the ≥4 to <16 years POS group in Pool Pediatric Studies, the incidence of PCST hematology results at any time point was low and was similar in male and female subjects for all hematology parameters; there were no trends over time.

Clinical chemistry: In the ≥4 to <16 years POS group in Pool Pediatric Studies, in both male and female subjects, there were no clinically meaningful mean changes from Baseline over time to the

Last Value in BRV Overall for any clinical chemistry parameter. In the ≥4 to <16 years POS group in Pool Pediatric Studies, most subjects had normal values at both Baseline and Last Value for all clinical chemistry parameters. The incidence of shifts from normal at Baseline to low or high at Last Value was similar in male and female subjects for almost all clinical chemistry parameters. In male subjects, compared with female subjects, there was a lower incidence of shifts from normal at Baseline to high at Last Value for GGT (6.0% vs 15.4%), and there was a higher incidence of shifts from normal at Baseline to high at Last Value for creatinine (8.3% vs 0%).

In the ≥4 to <16 years POS group in Pool Pediatric Studies, the incidence of PCST clinical chemistry results at any time point was low and was similar in male and female subjects for all clinical chemistry parameters; there were no trends over time.

Urinalysis: In the ≥4 to <16 years POS group in Pool Pediatric Studies, the incidence of PCST urinalysis results at any time point was low and was similar in male and female subjects for almost all urinalysis parameters; there were no trends over time. In male subjects, compared with female subjects, there were lower incidences of PCST results at any time point for occult blood (0% vs 17.9%) and leukocyte esterase (2.5% vs 17.9%).

Endocrinology: In the ≥4 to <16 years POS group in Pool Pediatric Studies, the results were similar in male and female subjects; there were no clinically meaningful mean changes from Baseline over time to the Last Value in BRV Overall for T3 free, T4 free, and thyrotropin; there were no trends over time. The small number of female subjects (N=0 or 1) with results for follicle stimulating hormone and luteinizing hormone at most time points does not allow for meaningful comparisons.

Vital signs: In the ≥4 to <16 years POS group in Pool Pediatric Studies, there were gender differences in the mean changes from Baseline in pulse rate; in male subjects the changes from Baseline were negative at almost all time points (during the first 24 months, when sample size is meaningful, range: -0.5 to -6.0bpm), while in female subjects the changes from Baseline tended to be positive (range: -0.6 to 4.6bpm). This gender difference did not raise clinical concern. In both male and female subjects there were no clinically meaningful mean changes from Baseline over time to the Last Value in BRV Overall for any vital sign parameter. The incidence of PCST vital sign results at any time point was similar in male and female subjects for all vital sign parameters; there were no trends over time.

Post marketing experience

No separate postmarketing data is provided. According to the exposure data from the RMP, cumulatively, 389,022,360 mg of product has been distributed worldwide from 01 Jan 2016 to 31 Dec 2016 contributing to approximately 10,651 patient-years (Table 42.).

Table 42. Patient exposure by formulation for the cumulative time interval (01 Jan 2016 to 31 Dec 2016)

Dosage form	Patient-years for the cumulative interval
Film-coated tablet	10,357
Oral solution	264
Solution for infusion	30
Total	10,651

2.6.2. Discussion on clinical safety

The safety data set presented in support of the current group of variations (II-10 G) is mainly based on an ad hoc pediatric Pool which included clinical safety data from all pediatric subjects enrolled in the completed Phase 2a study N01263 (an open-label, single-arm, multicenter, pharmacokinetic, safety, and efficacy study of adjunctive administration of brivaracetam in subjects from ≥ 1 month to <16 years old with epilepsy) and its ongoing Phase 3 LTFU N01266 (open-label, single-arm, multicenter, long-term study to evaluate safety and efficacy of brivaracetam used as adjunctive treatment in pediatric subjects with epilepsy), amended also to include (as direct enrollers) a relevant quote of subjects (at least 100) with a clinical diagnosis of partial onset seizures (POS). The clinical cut-off date for the current application is 31 Aug 2016. The responses to request for supplementary information included also safety data from the US 120 Day safety update for which the cut-off date is 15 March 2017.

A total of 149 subjects were 4 to 16 years old with 249.7 subject-years of exposure. Of them, 34 (22.8%) followed-up the parent study N01263, and 115 (77.2%) were directly enrolled into study N01266. A total of 104 subjects (69.8%) had ≥1 calendar year of exposure to brivaracetam, 97 subjects (65.1%) were ongoing and 50 subjects (33.6%) discontinued. Thus, the size of the safety database for this application is considered compliant to the current CHMP guideline for epilepsy.

With regards to the modal daily dose for the ≥4 to <16 years group with POS, the highest proportion was in the >3.0 to 4.0mg/kg/day overall (n=79 [53%]) with 151.0 subject-years, followed by the >4.0mg/kg/day (n=26 [17.4%]) with 43.6 subject-years exposure. As per those subjects with at least ≥12 months exposure to BRV, the highest proportion was again in the >3.0 to 4.0mg/kg/day modal daily dose (58 subjects [55.8%]), followed by the >4.0mg/kg/day group overall (n=22 [21.2%]). These data comply with the CHMP requirements for assessing the safety profile of brivaracetam as adjunctive therapy in subjects with POS down to 4 years of age.

In the ≥ 4 to <16 years POS group in Pool Paediatric Studies, the most frequently reported common TEAEs were nasopharyngitis (24.2% of subjects); pharyngitis (20.1%); pyrexia, convulsion, and headache (17.4%); and vomiting (14.8%). The majority of adverse events was reported as mild or moderate in intensity and non-serious, and did not lead to dose reduction or discontinuation of study drug. Higher incidences for nasopharyngitis, pharyngitis, pyrexia, vomiting, decreased appetite and psychomotor hyperactivity were reported in the paediatric population compared with adult Pool S4, while incidences of convulsion and headache were similar. The MAH presented analysis of the TEAEs in children divided to different age groups (4 to <12 and

12 to <16 years) and compared to the pool S4. In general, it is agreed that the reporting of TEAE was similar between both children groups and adult population.

The MAH reported that higher incidence of vomiting (21.3% vs 0), diarrhea (13.9% vs 7.3%), Pyrexia (24.1% vs 9.8%), Irritability (13.0% vs 4.9%), Pharyngitis (26.9% vs 9.8%), Rhinitis (11.1% vs 2.4%) and Varicella (5.6% vs 0) in children with the POS ≥4-<12 years compared to POS ≥12-<16 years group. It could be considered that Pyrexia, Pharyngitis and Rhinitis are common AEs observed in this children age group and could be difficult to establish direct causality to Briviact treatment. On the other hand, the ADRs of vomiting and irritability are already present in the Table of ADRs in section 4.8.

A higher TEAEs incidence of falls (3.7% vs 19.5%), Dysmenorrhea (1.9% vs 7.3%) and Gynaecomastia (0 vs 4.9%) were reported in the POS ≥12-<16 years group than in the POS ≥4-<12 years group and adults. However, the explanation provided by the MAH that considering the small number of patients in the BRV POS ≥12-<16 years group (dysmenorrhea n=3; gynaecomastia n=2) and the prevalence reported in the literature, the findings from the BRV Pediatric Pools do not differ from the global pediatric population is acceptable.

The incidence of TEAE "weight decrease" was relatively high in the ≥ 4 to <16 years POS group in the Pool Pediatric Studies. It is reassuring that none of the TEAEs "weight decrease" led to permanent discontinuation of study drug. It was apparent that a relationship between weight decrease and decreased appetite, that is a known ADR of BRV treatment, cannot be established in POS patients aged ≥ 4 to <16 years. Moreover, weight decrease occurred in a minority of these patients and can be considered plausibly related to the severity of the underlying disease or to concomitant TEAEs. In most cases the event recovered and in no patient it lead to BRV treatment discontinuation. This was considered reassuring.

In addition, there are higher incidences of PTs Headache (26.8%), Fatigue (9.8%), Dizziness (17.1%) and Suicidal ideation (9.8%) in POS ≥12-<16 years group. It is noted that ADRs of Headache, Fatigue and Dizziness were also the most common ADRs reported in adults (Pool S1 9.6%, 7.7% and 10.7% respectively). However, frequency of suicidality is substantially higher in children, especially teenagers, compared to the one reported for adults in the currently approved SmPC (0.3% in brivaracetam treated patients). The higher incidence observed in children is appropriately reflected in section 4.8 of the SmPC. No new safety signals were identified in the studied paediatric population except–psychomotor hyperactivity. Dose-relation was not observed in paediatric population for somnolence and dizziness as reported in the adult population. This may be explained by the fact that the paediatric population is quite wide in age range and hence positive or negative trends may not be observed clearly also due to flexible dosing schedule without unbiased dose comparison and by the relative small sample size of paediatric study population which doesn't allow drawing definitive conclusions.

The most frequently reported SAEs were in the SOC Nervous system disorders (17 subjects [11.4%]) and the most frequently reported PTs in BRV Overall were convulsion (9 subjects [6.0%]) and status epilepticus (5 subjects [3.4%]). The TEAEs of interest specific to the paediatric population (growth, endocrine function/sexual maturation, neurodevelopment, cognitive impairment, anxiety and depression) were reported the mostly in the category of neurodevelopment (6.7%), cognitive impairment (6%) and endocrine function or sexual

maturation (4.7%) in the ≥ 4 to <16 years POS group and were similar to what has been reported in paediatric populations with other AEDs. On the other hand, the available data concerning long-term consequences of brivaracetam treatment is limited and these should be evaluated in a larger population with longer exposure duration. Relevant data that is expected to be collected in the on-going study N01266.

The exposure-adjusted (100 subject-years) IR of the most frequent TEAEs of interest were in the categories behavioural disorder (24.2%; IR=17.78), seizure worsening (21.5%; IR=14.91), accidents and injuries (20.8%; IR=14.59), falls (18.1%; IR=12.40) and neurodevelopment (6.7%; IR=4.26).

The higher incidence of adverse events within the behavioral disorders can be expected in this age group in general and is reflected in section 4.8 of the SmPC.

In relation to accidents/injuries, in the updated data (cutoff date (15 Mar 2017), there were 4 additional subjects in the ≥4 to <16 age group reporting at least 1 of these AE that were mild to moderate, did not lead to BRV dose changes or discontinuation, and were not considered related to BRV treatment by the investigators. The same additional 4 subjects resulted when the PT falls was used in the searching strategy. For comparison purposes, the MAH provided also data on adult patients from the Pool Monotherapy, a safety pool for subjects ≥16 years of age enrolled in conversion to monotherapy studies with a sample size (N=150) smaller than that of the Pool S4 but comparable to that of the POS ≥4 to <16 year group (N=149). The MAH pointed out that the adjusted-incidence rates in the pediatric groups are in between Pool S4 and the Pool Monotherapy and hence that BRV appears not to have a specific effect on the paediatric population. Limitations of pediatric studies do not allow drawing definitive conclusions on accident/injuries or fall-related AEs, however, given the above, based on the comparison with the Monotherapy Pool data presented by the MAH, the CHMP considers that it is plausible to conclude that there is no increased risk of falls and accidents/injury in the pediatric population treated with BRV.

Concerning the TEAEs potentially associated with seizure worsening, higher exposure-adjusted IRs (95% CI) were reported in the ≥ 4 to <16 years POS group in Pool Paediatric Studies compared with adults Pool S4 (14.91 [10.20, 21.06] versus 6.01 [5.45, 6.62] per 100 subject-years). This more than doubled incidence in children is attributed by the applicant to the underlying disease and associated comorbidities in patients with difficult to treat childhood-onset epilepsies. The Applicant provided a review of the (few) available data regarding TEAEs potentially associated with seizure worsening in pediatric studies with brivaracetam N01263 and N01266 (Pool Pediatric Studies) as of the cut-off date 15 March 2017. The conclusion that the distribution of focal or generalized epilepsies was generally similar in patients for whom TEAEs potentially associated with seizure worsening were or were not reported, with a slightly higher frequency of epilepsies of undetermined origin in the former group, is acknowledged by the CHMP.

With respect to TEAEs potentially associated with seizure worsening, at least one event was reported in the ≥4 of <16 years age range for 43/149 (28.9%) subjects with POS and for 29/51 (34.5%) in non-POS subjects. Apparently, the onset of TEAEs potentially associated with seizure worsening was slightly higher in the first 3-month interval.

Regarding the effect of BRV on seizure frequency in patients with POS in the 4 to 16 years age range, no definitive conclusion can be drawn as only interim data are available and significant decrease in the number of patients, particularly beyond Visit 12 (month 24) was observed mainly due to premature discontinuation and the variable time of follow up depending on study entry.

A larger amount of EEG data was expected than those presented with the current application. However, it seems difficult at the present stage to get further data during the present procedure. Additional data is expected to be collected and made available in the final CSR of study N01266.

In the ≥4 to <16 years POS group, the most frequently observed AEs leading to treatment discontinuation were in the SOC Psychiatric disorders (6 subjects [4.0%] and Nervous system disorders SOC (3 subjects [2.0%]), with the most frequently reported PT being aggression (3 subjects [2.0%]), with a bimodal distribution for the vast majority of AEs being in the 0.0 to 1.0 and >3.0 to 4.0 modal daily dose categories. Most AEs leading to study drug discontinuation resolved without sequelae, most of these occurred as per the PTs in the SOC of Psychiatric disorders and Nervous System disorders that are already reported as ADRs in section 4.8 of the current BRV SmPC. However, due to the several methodological limitations of pediatric studies, these AEs should continue to be monitored through pharmacovigilance activities.

A higher overall incidence of TEAEs potentially associated with suicidality was reported in paediatric population compared to the adult Pool S4 with an exposure-adjusted incidence of 2.86% (95% CI; 1.15 - 5.90) in the ≥ 4 to <16 years POS group compared to 1.02% (0.8 – 1.27) in adult Pool S4. Seven subjects (7.4%) were in the ≥4 to <16y POS group and all events were in the SOC Psychiatric disorders, with PT suicidal ideation (n=7 [4.7%]) and suicidal attempt (n=1 [0.7%]) being the most frequent. The events mostly occurred in the dose range of BRV 150-200mg/day, showed variability either in duration or delay of onset from the subject's study entry and in some cases the onset was further to the suspension of the study drug. However, only one of the suicidality cases was judged to be related to brivaracetam treatment by the investigator. Definite conclusions on suicidal ideation in the pediatric population cannot be drawn due to several limitations of the pediatric studies presented by the MAH, including the lack of a control group, the small numbers, the open-label design which makes the drug relationship assessed by the investigators, the limitations of the tools used for the evaluation of psychiatric disorder related event. Moreover, the presence of several confounding factors should be taken into account, such as the potential effects of concomitant medications, including AEs, and concomitant medical and psychiatric conditions. However, it appears that the incidence of suicidality in the pediatric studies with BRV is higher than that observed in the adult population of Pool S4, particularly in the age category of ≥12 to <16 years, even after exposure-adjusted analysis. It is acknowledged that this can confirm literature data, but indirect comparison with available clinical data from other AEDs (lacosamide, levetiracetam and perampanel), seems to indicate a possibly higher incidence of suicidal ideation in BRV pediatric studies, although differences in studied-population, exposure and study design should be taken into account.

Large variation but no apparent worsening has been reported according to the interim results for cognition-related scales (Achenbach and BRIEF/BRIEF-P). Overall, data presented by the MAH did not show a trend towards a worsening of the responses to the adopted neurodevelopment and cognition scales. This is reassuring. However, due to the limitations of paediatric studies, including

the lack of a control group, the limited numbers, the open-label design, the limitations of the scales adopted, no definite conclusion can be drawn on the actual effects of BRV on cognition and neurodevelopment in POS paediatric patients. The MAH should continue to strictly monitor the occurrence of AEs related to cognition and neurodevelopment through pharmacovigilance activity.

Unexpectedly, in the ≥4 to <16 years POS patients of the Pool Pediatric Studies, some differences by gender were observed. The MAH explained these differences as mostly related to the differences in the background population reported in literature in terms of slightly lower incidence of epilepsy and unprovoked seizures in females than males. Males would tend to have a higher incidence of lesional epilepsy and acute symptomatic seizures while females would be more likely to have idiopathic generalized epilepsy. Moreover, the behavior of some common epilepsy syndromes such as mesial temporal sclerosis may differ between genders with isolated auras more common among females and secondary seizure spread more likely in males. The MAH pointed out that literature data report a higher prevalence of suicidal ideation in female adolescents than male.

Due to the small numbers and the lack of a control group, it is not possible to conclude on the significance of differences observed for some AEs between males and females. Data provided by the MAH are particularly reassuring regarding the sex-differences for some important AEs in the SOC of Nervous System disorders and Psychiatric disorders that appear to be unlikely related to BRV treatment but rather to the sex differences in the background population reported in literature. Finally, changes from Baseline of pulse rate were more frequently negative (decrease) in males and positive (increase) in females. However, it is reassuring that the incidence of PCST vital sign results was similar between the two sexes.

In the paediatric population of interest for this extension of indication, there were differences in the incidence of common TEAEs between AED inducer subjects and No AED inducer subjects. This is of particular concern mainly for Nervous System and Psychiatric Disorders which occurred more frequently in AED inducer subjects: headache (23.1% vs 11.3%); convulsion (19.2% vs 15.5%); somnolence (11.5% vs 9.9%); dizziness (10.3% vs 1.4%); syncope (2.6% vs 0); suicidal ideation (5 subjects, 6.4% vs 2 subjects, 2.8%); sleep disorders (3.8% vs 1.4%); aggression (2.6% vs 0). The majority of patients was under carboxamide derivatives (47.2% of patients in ≥4-<12 years group, and by 39% of patients in ≥12-<16 years group) and most AEs in the group of AED inducers occurred under concomitant treatment with carboxamide derivatives. Carbamazepine is known to decrease the BRV plasma concentration by 29%. However, the MAH pointed out that this change in exposure does not require a BRV dose adjustment in the pediatric population, similarly to the recommendation made in adults and this has been reflected in the SmPC section 4.5. Moreover, it should be considered that some patients could have taken more than 1 concomitant AED inducer.

The MAH provided additional information related to the analyses performed in the initial pediatric submission on the PCST values for hematology and blood chemistry parameters. The MAH pointed out that only possibly clinically significant treatment emergent (PCST) AEs and not treatment emergent markedly abnormal (TEMA) values were recorded in the frame of the BRV Pediatric clinical development program. High PCST values for hematocrit were observed in 10 patients (6.7%) (3 [2.9%] in the POS≥4 to <12 years group and 7 [17.5%] in the ≥12 to <16 years

group). For 3 of these patients, values returned within the normal range at the subsequent visits. For 2 patients the high PCST value was seen at the last visits. None of these PCST values were considered by the Investigators as related to BRV but as a stand-alone adverse event. No trend in the BRV dosage or the time to onset were observed and no changes of BRV dose was made for these patients. For 6 of these patients, values returned within the normal range at the subsequent visits, for only one patient high leukocytes values were observed at last visit. Given the above, the CHMP agreed that the reported increased hematocrit values are not related to brivaracetam treatment.

As regard to chemistry parameters, the main differences observed between the POS ≥4 to <12 and ≥12 to <16 years populations were related to the higher incidence (>2%) of PCST ALT and Glucose in the ≥12 to <16 years population (ALT: 10.0% vs 0.9%; Glucose: 4.9% vs 0) and of PCST hypernatremia in the ≥4 to <12 years population (Hypernatremia: 4.7% vs 2.5%). In the overall POS pediatric population ≥4 to <16, PCST AEs high ALT (3.3%), GGT (10.9%), sodium (4.1%), and urate (3.3%) occurred with a relatively high incidence. The PCST high ALT occurred during the first months (first 9 months) of treatments and no specific trend over the different visits was observed. Given the above and the low numbers it is not possible to draw definite conclusion on causal relationship between BRV treatment and increase of transaminases and hypernatraemia. The increase of transaminase was also observed in the BRV adult population (Pool S4). The MAH reassures that the AEs related to hepatic and renal disorders will continue to be monitored through routine pharmacovigilance activities.

2.6.3. Conclusions on clinical safety

Though the single arm study design constitutes a limitation in the ability to attribute side effects to drug exposure, it appears that no major safety issues were identified in paediatric patients when compared with the known safety profile in adults.

A higher frequency of suicidality, especially teenagers, and behavioural disorders compared to the ones reported for adults were observed. These higher incidences observed in children are appropriately reflected in section 4.8 of the SmPC.

Considering the age group, further characterization of the safety of brivaracetam treatment in paediatric patients is needed in terms of long-term effects on growth, endocrine function or sexual maturation, neurodevelopment, cognitive impairment, anxiety, and depression in paediatric patients. These will continue to be monitored through routine pharmacovigilance activities. In addition, relevant data are expected to be collected in the on-going study N01266.

Despite the uncertainties listed above, the safety profile of brivaracetam in the proposed paediatric population is considered acceptable.

2.6.4. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

According to these requirements the PSUR cycle should follow a half-yearly cycle until otherwise agreed by the CHMP.

2.7. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (RMP):
The PRAC considered that the risk management plan version 6.3 is acceptable.
The CHMP endorsed the Risk Management Plan version 6.3 without changes with the following content:

Safety concerns

Summary of safety concerns

Important identified risks	Suicidality (class label for anticonvulsant products) Aggression
Important potential risks	Neutropenia Worsening of seizures (as an anticonvulsant product) Abuse potential (as a CNS-active product)
Missing information	Data during pregnancy and lactation Data in patients with pre-existing hepatic impairment Data in patients with pre-existing end-stage renal impairment requiring dialysis Data in elderly Clinical outcomes after an overdose Long-term safety Long-term effects on growth, endocrine function or sexual maturation, neurodevelopment, cognitive and psychomotor development in pediatric patients

Pharmacovigilance plan

Ongoing and planned additional Pharmacovigilance activities in the PV plan

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Participation in and sponsorship of EURAP Ongoing	To collect data on pregnancy	Pregnancy and lactation	Start of data collection Completion of data collection Interim study report	Cumulative data appearing in these registries are discussed in PSURs

Ongoing and planned additional Pharmacovigilance activities in the PV plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Participation in and sponsorship of North American AED Pregnancy Registry Ongoing	To collect data on pregnancy	Pregnancy and lactation	Start of data collection Completion of data collection Interim study report	Cumulative data appearing in these registries are discussed in PSURs

Risk minimisation measures

Summary table of risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Suicidality (class label for anticonvulsant products)	Routine risk minimization measures: Available by prescription only SmPC Section 4.4 (Special warnings and precautions for use [class wording]), and SmPC Section 4.8 (Undesirable effects) Packaging Additional risk minimization measures: None	Routine PhV activities beyond adverse reactions reporting and signal detection: C-SSRS used in all clinical studies (in subjects <6 years symptoms and signs of depression are recorded) Additional PhV activity:None
Aggression	Routine risk minimization measures: Available by prescription only SmPC Section 4.8: Undesirable effects Additional risk minimization measures: None	Routine PhV activities beyond adverse reactions reporting and signal detection: None Additional PhV activity: None

Summary table of risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Neutropenia	Routine risk minimization measures: Available by prescription only SmPC Section 4.8: Undesirable effects Additional risk minimization measures: None	Routine PhV activities beyond adverse reactions reporting and signal detection: None Additional PhV activity: None
Worsening of seizures (as an anticonvulsant product)	Routine risk minimization measures: Available by prescription only Additional risk minimization measures: None	Routine PhV activities beyond adverse reactions reporting and signal detection: None Additional PhV activity: None
Abuse potential (as a CNS active product)	Routine risk minimization measures: Available by prescription only Additional risk minimization measures: None	Routine PhV activities beyond adverse reactions reporting and signal detection: None Additional PhV activity: None
Data during pregnancy and lactation	Routine risk minimization measures: Available by prescription only SmPC Section 4.6: Fertility, pregnancy and lactation Additional risk minimization measures: None	Routine PhV activities beyond adverse reactions reporting and signal detection: None Additional PhV activities: • Participation in and sponsorship of EURAP and North American AED Pregnancy Registry. Activities include provision of requested data from UCB to the registries and regular review of interim outputs from the registries.

Summary table of risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Data in patients with pre existing hepatic impairment	Routine risk minimization measures: Available by prescription only SmPC Section 4.2 (Posology and method of administration), SmPC Section 4.4 (Special warnings and precautions for use), and SmPC Section 5.2 (Pharmacokinetic properties) Additional risk minimization measures: None	Routine PhV activities beyond adverse reactions reporting and signal detection: None Additional PhV activity: None
Data in patients with pre existing end stage renal impairment requiring dialysis	Routine risk minimization measures: Available by prescription only SmPC Section 4.2 (Posology and method of administration), and SmPC Section 5.2 (Pharmacokinetic properties) Additional risk minimization measures: None	Routine PhV activities beyond adverse reactions reporting and signal detection: None Additional PhV activity: None
Data in elderly	Routine risk minimization measures: Available by prescription only SmPC Section 4.2 (Posology and method of administration) Additional risk minimization measures: None	Routine PhV activities beyond adverse reactions reporting and signal detection: None Additional PhV activity: None
Clinical outcomes after an overdose	Routine risk minimization measures: Available by prescription only SmPC Section 4.2: Posology and method of administration), and SmPC Section 4.9 (Overdose) Additional risk minimization measures: None	Routine PhV activities beyond adverse reactions reporting and signal detection: None Additional PhV activity: None

Summary table of risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Long-term safety	Routine risk minimization measures: Available by prescription only SmPC Section 4.8: Undesirable effects Additional risk minimization measures: None	Routine PhV activities beyond adverse reactions reporting and signal detection: None Additional PhV activity: None
Long-term effects on growth, endocrine function or sexual maturation, neurodevelopment, cognitive and psychomotor development in pediatric patients	Routine risk minimization measures: Available by prescription only Additional risk minimization measures: None	Routine PhV activities beyond adverse reactions reporting and signal detection: None Additional PhV activity: None

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

2.8. Update of the Product information

As a consequence of the extension of the indication in paediatric patients from to 4 years old to 16, sections 4.1, 4.2, 4.4, 4.8, 5.1. 5.2 and 6.5 of the SmPC have been updated. The Package Leaflet has been updated accordingly. The changes pertaining to SmPC sections 4.1, 4.2, 4.4 and 4.8 are indicated below (new text in bold, deleted text strikethrough). The remaining SmPC changes are highlighted in the attached Product Information (PI) document.

- Changes applicable for all presentations:

4.1 Therapeutic indications

Briviact is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adult**s** ~~and~~**,** adolescent**s** ~~patients from 16 years of age~~ **and children from 4 years of age** with epilepsy.

4.2 Posology and method of administration

Posology

Adults

[…]

Renal impairment

No dose adjustment is needed in patients with impaired renal function (see section 5.2). Brivaracetam is not recommended in end-stage renal disease patients undergoing dialysis due to lack of data.

Based on data in adults, no dose adjustment is necessary in paediatric patients with impaired renal function.

Hepatic impairment

Exposure to brivaracetam was increased in **adult** patients with chronic liver disease. ~~A~~**In adults, a** 50 mg/day starting dose should be considered. **In children and adolescents weighing 50 kg or greater, a 50 mg/day starting dose is recommended.** A maximum daily dose of 150 mg administered in 2 divided doses is recommended for all stages of hepatic impairment (see section 4.4 and 5.2).

In children and adolescents weighing less than 50 kg, a 1 mg/kg/day starting dose is recommended. The maximum dose should not exceed 3 mg/kg/day. No clinical data are available in paediatric patients with hepatic impairment.

Paediatric population

The physician should prescribe the most appropriate formulation and strength according to weight and dose.

The following table summarises the recommended posology for children from 4 years of age and adolescents. More details are provided below the table.

	Children (≥4 years) and adolescents ≥50 kg **Administered in 2 equally divided doses**	**Children (≥4 years) and adolescents <50 kg** **Administered in 2 equally divided doses**
Therapeutic dose range	**50 - 200 mg/day**	**1 - 4 mg/kg/day**
Recommended starting dose	**50 mg/day (or 100 mg/day)***	**1 mg/kg/day (or 2 mg/kg/day)***
Recommended maintenance dose	**100 mg/day**	**2 mg/kg/day**

*** Based on physician assessment of need for seizure control.**

Children (from 4 years of age) and adolescents weighing 50 kg or more
The recommended starting dose is 50mg/day. Brivaracetam may also be initiated at 100 mg/day based on physician assessment of need for seizure control. The dose should be administered in two equally divided doses, once in the morning and once in the evening. The recommended maintenance dose is 100 mg/day. Based on individual patient response, the dose may be adjusted in the effective dose range of 50 mg/day and 200 mg/day.

Children (from 4 years of age) and adolescents weighing less than 50 kg
The recommended starting dose is 1 mg/kg/day. Brivaracetam may also be initiated at 2 mg/kg/day based on physician assessment of need for seizure control. The dose should be administered in two equally divided doses, once in the morning and once in the evening.The recommended maintenance dose is 2 mg/kg/day. Based on individual patient response, the dose may be adjusted in the effective dose range of 1 mg/kg/day and 4 mg/kg/day.

Children less than 4 years

The safety and efficacy of brivaracetam in children aged less than~~16~~ **4** years have not yet been established.

Currently available data are described in section 4.8, 5.1, and 5.2 but no recommendation on a posology can be made.

- Changes applicable for oral solution presentation only:

4.2 Posology and method of administration

Paediatric population

[…]

The dose per intake for each patient should be calculated using the following formula:

Volume per administration (ml) = [weight (kg) x daily dose (mg/kg/day)] x 0.05

The table below provides examples of volumes of oral solution per intake depending on prescribed dose and body weight. The precise volume of oral solution is to be calculated according to the exact body weight of the child.

	Volumes of oral solution to be taken per administration			
Weight	***For a dose of 1 mg/kg/day*** **0.05 ml/kg/intake** **(corresponding to 0.5 mg/kg/intake)**	***For a dose of 2 mg/kg/day*** **0.1 ml/kg/intake** **(corresponding to 1 mg/kg/intake)**	***For a dose of 3 mg/kg/day*** **0.15 ml/kg/intake** **(corresponding to 1.5 mg/kg/intake)**	***For a dose of 4 mg/kg/day*** **0.2 ml/kg/intake** **(corresponding to 2 mg/kg/intake)**
10 kg	**0.5 ml (5 mg)**	**1 ml (10 mg)**	**1.5 ml (15 mg)**	**2 ml (20 mg)**
15 kg	**0.75 ml (7.5 mg)**	**1.5 ml (15 mg)**	**2.25 ml (22.5 mg)**	**3 ml (30 mg)**
20 kg	**1 ml (10 mg)**	**2 ml (20 mg)**	**3 ml (30 mg)**	**4 ml (40 mg)**
25 kg	**1.25 ml (12.5 mg)**	**2.5 ml (25 mg)**	**3.75 ml (37.5 mg)**	**5 ml (50 mg)**
30 kg	**1.5 ml (15 mg)**	**3 ml (30 mg)**	**4.5 ml (45 mg)**	**6 ml (60 mg)**
35 kg	**1.75 ml (17.5 mg)**	**3.5 ml (35 mg)**	**5.25 ml (52.5 mg)**	**7 ml (70 mg)**
40 kg	**2 ml (20 mg)**	**4 ml (40 mg)**	**6 ml (60 mg)**	**8 ml (80 mg)**
45 kg	**2.25 ml (22.5 mg)**	**4.5 ml (45mg)**	**6.75 ml (67.5 mg)**	**9 ml (90 mg)**
50 kg	**2.5 ml (25 mg)**	**5 ml (50 mg)**	**7.5 ml (75 mg)**	**10 ml (100 mg)**

[…]

Method of administration

Brivaracetam oral solution can be diluted in water or juice shortly before swallowing and may be taken with or without food (see section 5.2). A nasogastric tube or a gastrostomy tube may be used when administering brivaracetam oral solution.

Briviact oral solution is provided with a 5 ml and a 10 ml oral dosing syringe with their adaptor.

Oral dosing syringe (5 ml graduated every 0.1 ml) with an adaptor, recommended for use by patients weighing less than 20 kg or needing a maximum of 50 mg (5 ml) brivaracetam per administration.
The 5 ml oral syringe must be used in patients weighing less than 20 kg to ensure accurate dosing as the 10 ml oral syringe does not allow accurate measurements of volumes <1 ml.
One full 5 ml oral dosing syringe corresponds to 50 mg of brivaracetam. The minimum extractible volume is 0.25 ml which is 2.5 mg of brivaracetam. As from the 0.1 ml graduation mark, each graduation corresponds to 0.1 ml which is 1 mg of brivaracetam. Additional graduations at 0.25 ml and 0.75 ml starting at 0.25 ml up to 5 ml are shown.

Oral dosing syringe (10 ml graduated every 0.25 ml) with an adaptor, recommended for use by patients weighing more than 20 kg or needing a dose between 50 mg and 100 mg (5 ml to 10 ml) brivaracetam per administration.
One full 10 ml oral dosing syringe corresponds to 100 mg of brivaracetam. The minimum extractible volume is 1 ml which is 10 mg of brivaracetam. As from the 1 ml graduation mark, each graduation corresponds to 0.25 ml which is 2.5 mg of brivaracetam.

Instructions for use are provided in the package leaflet.

- **Changes applicable to all presentations:**

4.4 Special warnings and precautions for use

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic drugs (AEDs), including brivaracetam, in several indications. A meta-analysis of randomized placebo-controlled trials of AEDs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for brivaracetam.
Patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should any signs of suicidal ideation or behaviour emerge. **See also section 4.8, paediatric data.**

4.8 Undesirable effects

[…]

Tabulated list of adverse reactions

In the table below, adverse reactions, which were identified based on review of the **three placebo-controlled, fixed-dose** ~~full brivaracetam clinical~~ studies safety database **in subjects ⩾ 16 years of age,** are listed by System Organ Class and frequency.

The frequencies are defined as follows: very common (⩾ 1/10), common (⩾ 1/100 to < 1/10), uncommon (⩾ 1/1,000 to < 1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

[…]

Paediatric population

The safety profile of brivaracetam observed in children was consistent with the safety profile observed in adults. In the open label, uncontrolled, long-term studies suicidal ideation was reported in 4.7 % of paediatric patients (more common in adolescents) compared with 2.4 % of adults and behavioural disorders were reported in 24.8 % of paediatric patients compared with 15.1 % of adults. The majority of events were mild or

moderate in intensity, were non-serious, and did not lead to discontinuation of study drug. An additional adverse reaction reported in children was psychomotor hyperactivity (4.7 %).

There are limited safety data from open-label studies in children from 1 month to < ~~16~~ **4** years of age. ~~A total of 152 children (1 month to < 16 years of age) were treated with brivaracetam in a pharmacokinetic study and the related follow up study. From the limited available data, the most frequently reported TEAEs considered drug-related by the investigator were somnolence (10 %), decreased appetite (8 %), fatigue (5 %) and weight decreased (5 %).The safety profile appears to be consistent with that known in adults. No~~ **Limited** data are available on neurodevelopment **in children <4 years of age**. ~~Currently, n~~**N**o clinical data are available in neonates.

2.8.1. User consultation

The applicant has submitted a full user test for the oral solution and two bridging reports, one for the film-coated tablets and one for the solution for injection/infusion.

The results of the user consultation with target patient groups on the package leaflet show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use. The bridging reports submitted by the applicant have also been found acceptable

3. Benefit-Risk Balance

3.1. Favourable effects

The efficacy of brivaracetam has been established as adjunctive treatment of partial-onset seizures with or without secondary generalisation in adult and adolescent patients from 16 years of age with epilepsy. An extension of indication is proposed with the present application for children from 4 years of age. As stated in the CHMP Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders, focal epilepsies in children older than 4 years are expected to have a similar clinical expression to that of adolescents and adults. Therefore, extrapolation of efficacy from adults to children based on similar exposure is considered acceptable.

No study focusing on clinical efficacy in the paediatric population has been provided in the current application. Extrapolation of efficacy in adjunctive therapy of POS as established in adults was proposed with support of clinical pharmacology data. In a pharmacokinetic study with a 3-week evaluation period and weekly fixed 3-step up-titration scheme using the brivaracetam oral solution it was shown that plasma concentrations were dose-proportional in all age groups. Population pharmacokinetics modeling indicated that the dose of 2.0 mg/kg twice a day provides the same steady-state average plasma concentration as in adults receiving 100 mg twice daily. The estimated plasma clearance was 1.61 L/h, 2.18 L/h and 3.19 L/h for children weighing 20 kg, 30 kg and 50 kg, respectively. In comparison, plasma clearance was estimated at 3.58 L/h in adult patients (70 kg body weight). Similar exposure as in adults and dose recommendations are supported with popPK/PD modelling and simulation.

3.2. Uncertainties and limitations about favourable effects

The application is based on PK bridging of efficacy from adults to children, as is generally accepted in POS. Residual uncertainties on magnitude of effect are remaining but are considered minor to such extrapolation.

3.3. Unfavourable effects

The paediatric safety database consisting of 219 patients including 168 with POS is considered of adequate size as 104 patients aged 4-16 years were exposed to brivaracetam at least 12 months. In general the safety profile did not differ qualitatively from the safety profile in adults. The most frequently reported common TEAEs were nasopharyngitis (24.2% of subjects); pharyngitis (20.1%); pyrexia, convulsion, headache (17.4%), vomiting (14.8%), diarrhea (12.1%) and somnolence (10.4%) with highest incidences during the first 3-month period after dosing (78.5% of subjects), and ranging from 13.3% to 52.8% at all subsequent time intervals. The incidences of nasopharyngitis, pharyngitis, pyrexia, vomiting, psychomotor hyperactivity, decreased appetite and suicidality were higher in the paediatric patients compared to adults.

Higher incidences rates (corrected by 100-year exposure) were observed in the 4 to 16 years POS children with respect to the Pool S4) for seizure worsening (14.91 vs. 6.01, respectively), behavioral disorder (17.78 vs. 5.22, respectively), suicidality (2.86 vs. 1.02, respectively), accidents and injuries (14.59 vs. 10.29, respectively), and falls (12.40 and 10.08, respectively).

Weight decrease was frequently observed after brivaracetam treatment; however no permanent discontinuation of the study was registered.

Although 9 subjects (6%) in the ≥4 to <16y POS population met at least 1 laboratory criterion for drug-induced liver injury or reported at least 1 TEAE potentially associated with hepatotoxicity, no subject met Hy's Law for fatal drug-induced liver injury. Given the low numbers it is not possible to draw definite conclusion on causal relationship between BRV treatment and increase of transaminases and hypernatraemia. The increase of transaminase was also observed in the BRV adult population (Pool S4). The MAH reassures that the AEs related to hepatic and renal disorders will continue to be monitored through routine pharmacovigilance activities.

3.4. Uncertainties and limitations about unfavourable effects

The single arm open-label uncontrolled study design intrinsically makes specific attribution of causality of side effects fraught with uncertainty.

The available data on growth, endocrine function or sexual maturation, neurodevelopment, cognition and psychotomor status in paediatric patients is very limited currently as these aspects require longer duration of observation and larger study population. Moreover, higher proportions of behavioral disorders and suicidality were observed in adolescents compared to adults, however definite conclusions cannot be drawn given the open-label design of the clinical studies assessing safety in the extended indication of brivaracetam down to 4 years of age. Although this could be expected, indirect comparison with available clinical data from other antiepileptics (lacosamide, levetiracetam and perampanel), seems to indicate a possibly higher incidence of suicidal ideation in pediatric brivaracetam studies. Nevertheless, differences in studied-population, exposure and study design should be taken into account. Long-term safety is listed as missing information in the RMP and further characterization and monitoring of these safety concerns will be performed through routine pharmacovigilance.

Overall, there is yet no convincing evidence of the absence of seizure worsening with the exposure to BRV in patients with POS aged from 4 to 16 years and particularly in those for whom POS and

non-POS seizures could coexist. A larger amount of EEG data was expected than those presented with the current application. Additional data is expected to be collected and made available in the final CSR of study N01266.

3.5. Benefit-risk assessment and discussion

3.5.1. Importance of favourable and unfavourable effects

The effect of brivaracetam in the adjunctive treatment of partial onset seizures in children 4 to 16 years of age is extrapolated from the studies in patients 16 years and older. These studies showed clinically relevant reduction in seizure frequency with brivaracetam as add-on therapy. Weight-based paediatric dosing regimens have been established using population-PK modelling and simulations. The safety profile in the paediatric population of 4 to 16 years of age does not seem to significantly differ in the types of adverse events from that already known in the adult population of POS patients, however available data on neurodevelopment, cognition and psychotomor status are very limited and no useful information is derived from the results of the Achenbach CBCL and BRIEF scales due to missing data and lack of adequate analyses. Further, higher incidence rates of suicidal ideation, compared with the adult studies, as discussed above were observed particularly in the ≥12 to <16 years POS children. The risk of suicidal ideation was already known and appropriately described in the Warnings and Precautions section of the SmPC. However, a higher incidence of adverse events within the behavioral disorders was observed in children when compared to the one reported for adults. Although this can be expected in this age group in general, such a higher incidence is reflected in section 4.8 of the SmPC, given the uncertainties on causal relationship with brivaracetam treatment.

3.5.2. Balance of benefits and risks

The efficacy of brivaracetam in 4 to 16 years old patients with POS is considered established based on extrapolation of efficacy from the studies in adults and adolescents.

The safety profile of brivaracetam in the proposed paediatric population is considered sufficiently characterised to allow for an assessment of the benefit-risk balance.

In conclusion, the benefit-risk profile of Briviact in the paediatric population is deemed positive, and the extension of indication to include adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in *children* with epilepsy 4 years of age and older is approvable.

3.6. Conclusions

The overall B/R of Briviact is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation,

concerning the following changes:

Variations accepted		Type	Annexes affected
B.IV.1.a.1	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	Type IAin	IIIA
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I,A, IIIA and IIIB
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type IB	I

Extension of Indication to include adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy 4 years of age and older for Briviact.
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.5 of the SmPC are updated.
In addition, the Marketing authorisation holder (MAH) has provided a5 ml oral dosing syringe and adaptor for the 10mg/ml oral solution, for use in the paediatric population.

The Annex A, Package Leaflet and Labelling are updated in accordance.

The group of variations leads to amendments to the Summary of Product Characteristics, Annex A, Labelling, Package Leaflet and to the Risk Management Plan (RMP).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0048/2017 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy 4 years of age and older for Briviact.
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.5 of the SmPC are updated.
In addition, the Marketing authorisation holder (MAH) has provided a 5ml oral dosing syringe and adaptor for the 10mg/ml oral solution, for use in the paediatric population.

Summary

Please refer to the Scientific Discussion Briviact EMEA/H/C/003898/II/0010/G.