27 January 2022
EMA/99325/2022
Committee for Medicinal Products for Human Use (CHMP)

CHMP group of variations including an extension of indication assessment report

Invented name: Briviact

International non-proprietary name: brivaracetam

Procedure No. EMEA/H/C/003898/II/0032/G

Marketing authorisation holder (MAH) UCB Pharma S.A.

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List of abbreviations

ADR	Adverse Drug Reaction
AEs	Adverse Events
AED	Antiepileptic drug
AHEG	Ad-Hoc Expert Group
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AUC	Area Under the Curve
bid	Twice daily
BRV	Brivaracetam
Cav	Average concentration over 24h
(CA)1	Cornu Ammonis
CBZ	Carbamazepine
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL	Clearance
CNS	Central Nervous System
CYP	Cytochrome P450
DBP`	Diastolic Blood Pressure
DRC	Daily Record Card
DRESS	Drug Rash with Eosinophilia and Systemic Symptoms
ED50	Median Effective Dose
EEG	Electroencephalogram
EM	Extensive metabolizer
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FAS	Full-Analysis Set
FDA	Food and Drug Administration
HVA	High Voltage Activated
IC50	Half Maximal Inhibitory Concentration
IIB	Initiating IV BRV
IOB	Initiating Oral BRV
IV	Intravenous(ly)
LEV	Levetiracetam
LTFU	Long-term follow-up
LTG	Lamotrigine
MAA	Marketing Authorization Application
MAHD	Maximal Approved Human Dose
MoA	Mechanism of Action
NOAEL	No-observed-adverse-effect level
NONMEN	Nonlinear mixed effects modelling
OLB	Open-Label BRV
PB	Phenobarbital /Primidone
PCA	Post-conceptional age
PD	Pharmacodynamic(s)
PDSs	Paroxysmal Depolarization Shifts
PHT	Phenytoin
PIP	Paediatric investigation plan
PK	Pharmacokinetic(s)
PGS	Primary Generalized Seizures
PM	Poor metabolizer
PND	Post-natal day
popPK	Population pharmacokinetics
POS	Partial-onset seizures
PTs	Preferred terms
RxB	Prescribed-BRV
SA	Scientific Advice
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SCAR	Severe Cutaneous Adverse Reaction
SOC	System Organ Class
SUDEP	Sudden Unexpected Death in Epilepsy
SV2A	Synaptic vesicle protein 2A

TPM	Topiramate
t½	Terminal half-life
TEAE	Treatment-Emergent Adverse Event
VPA	Valproate
(pp)VPCs	(prediction-corrected) Visual predictive checks

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 1 February 2021 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
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 and IIIB
B.II.f.1.b.2	Stability of FP - Extension of the shelf life of the finished product - After first opening (supported by real time data)	Type IB	I, IIIA and IIIB
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 IB	I, IIIA, IIIB and A

- Extension of indication to include patients from 1 month to 4 years of age for the Briviact treatment, as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The RMP version 8.0 has also been submitted. Furthermore, the PI is brought in line with the latest QRD template version 10.2 and the MAH took the opportunity to implement minor editorial updates.
- Extension of the shelf life after the first opening of Briviact Oral Solution (supported by real time data) (B.II.f.1.b.2 QUALITY CHANGES - FINISHED PRODUCT - Stability - Change in the shelf-life or storage conditions of the finished product - Extension of the shelf life of the finished product)
- Addition of a 1ml oral syringe and its adaptor for the paediatric population. (B.IV.1.a.1 - QUALITY CHANGES - Medical Devices - 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)

The Package Leaflet and Labelling are updated in accordance.

The group of variations requested 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(s) P/0324/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0324/2020 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 MAH 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 MAH received Scientific Advice (SA) from the CHMP on 30 April 2020 (EMEA/H/SA/681/11/2020/PA/PED/III). The SA pertained to quality and clinical aspects and in relation to paediatric development of the dossier.

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: N/A

Timetable	Actual dates
Submission date	1 February 2021
Start of procedure:	27 March 2021
CHMP Rapporteur Assessment Report	25 May 2021
PRAC Rapporteur Assessment Report	26 May 2021
PRAC Outcome	10 June 2021
CHMP members comments	14 June 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	17 June 2021
1st Request for supplementary information (RSI)	24 June 2021
MAH's responses to RSI	15 July 2021
CHMP Rapporteur Assessment Report	27 August 2021
PRAC Rapporteur Assessment Report	27 August 2021
PRAC Outcome	2 September 2021
CHMP members comments	8 September 2021
Updated CHMP Rapporteur Assessment Report	9 September 2021
2nd Request for supplementary information (RSI)	16 September 2021
Ad Hoc Expert Group meeting to address questions raised by the CHMP	7 October 2021
MAH's responses to RSI	11 October 2021
CHMP Rapporteur Assessment Report	28 October 2021
CHMP members comments	03 November 2021
Updated CHMP Rapporteur Assessment Report	05 November 2021
3rd Request for supplementary information (RSI)	11 November 2021
MAH's responses to RSI	21 December 2021
PRAC Rapporteur assessment report	28 December 2021
CHMP Rapporteur assessment report	12 January 2022
PRAC Outcome	13 January 2022

Timetable	Actual dates
CHMP members comments	20 Janaury 2022
Updated CHMP Rapporteur assessment report	21 January 2022
CHMP opinion	27 January 2022

2. Scientific discussion

2.1. Introduction

Brivaracetam (Briviact) is indicated as adjunctive treatment of partial onset seizures in adults, adolescents and children from 4 years of age with epilepsy.

In this variation, the MAH is proposing to extend the indication to the paediatric population from 1 month to 4 years of age.

2.1.1. Problem statement

An application for the extension of indication to the paediatric population from 4 years of age in the EU (adjunctive) and the US (adjunctive and monotherapy) based on the concept of extrapolation of efficacy data from the adult population was approved in 2018.

During the Epilepsy Foundation Research Roundtable for Epilepsy in May 2020 with FDA representatives in attendance, paediatric epileptologists and researchers shared data demonstrating that the underlying pathophysiology of partial onset seizures (POS), seizure characteristics and symptoms, electroencephalogram (EEG) features, disease progression, and treatment response are similar in patients ≥1 month to <2 years to those in older children (2020 Research Roundtable for Epilepsy). These data support the possibility that no separate efficacy studies (which would be very difficult to accomplish) would be needed for these young children as efficacy can be extrapolated in children ≥1 month to <2 years of age.

2.1.2. About the product

Brivaracetam (BRV) is indicated as adjunctive therapy in the treatment of POS in patients 4 years of age and older with epilepsy. BRV 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.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

In April 2020, the MAH received a scientific advice from the Committee for Medicinal Products for Human Use (CHMP) regarding UCB's proposed extrapolation strategy (EMA/CHMP/SAWP/203707/2020):

- For patients ≥2 to <4 years: extrapolation of efficacy from data in adults receiving BRV as adjunctive treatment
- For patients ≥1 month to <2 years: extrapolation of efficacy from data in adults and children receiving adjunctive levetiracetam (LEV), and efficacy data from adults receiving BRV as adjunctive treatment

The CHMP supported, in principle, a model-informed extrapolation-based approach to support the extension of indication in patients ≥2 to <4 years of age. This approach was previously agreed with the Paediatric Committee in the frame of the BRV PIP (EMEA-000332-PIP01-08-M06). In addition, the CHMP considered that BRV efficacy data would be fundamental for the extrapolation to patients ≥1 month to <2 years of age. Therefore, the extrapolation model has been externally validated using seizure count data from N01263 and N01266. As agreed with the CHMP, UCB has provided further information and discussion regarding the similarities and dissimilarities between BRV and LEV as well as the anticipated impact of the dissimilarities between BRV and LEV. It was further supported that the extrapolation of efficacy would be supported by pharmacokinetic(s) (PK) data from paediatric participants and by relevant safety data from at least 100 paediatric participants treated for at least 1 year.

To support the proposed paediatric indication, the paediatric pool includes clinical safety data from all paediatric study participants in N01263 and N01266 regardless of age or duration of treatment. In addition, support of the extension of the currently approved BRV indications down to 1 month of age will be provided by post-marketing data, literature, and reference to previously submitted adult data from Pool S4 and Pool Monotherapy.

In 2020, the MAH also received scientific advice from the Swedish Medical Products Agency (MPA) (MPA Ref No 4.2.3-2020-056158) regarding the proposed extrapolation strategy.

2.2. Quality aspects

Oral solution

The currently approved formulation, 10 mg/ml oral solution for children from 4 years of age, was initially applied to be used in children from 1 month of age. However, the extension of the indication was revised and the formulation is now intended to be used from 2 years of age. No new formulation has been developed for the lower age group applied.

The oral solution contains the excipients sodium citrate, citric acid anhydrous, methyl parahydroxybenzoate, carmellose sodium, sucralose sorbitol liquid, glycerol, raspberry flavour and purified water.

The solution is filled in amber glass bottles with child resistant closures (polypropylene). The bottle, filled with 300 ml solution, will be provided with a 5 ml and a 10 ml oral dosing syringe and an adaptor, as already approved for children from 4 years of age. In view of the final revised extension of indication to children from 2 years of age, the addition of a 1 ml syringe intended to be used for dosing children from 1 months of age is no longer applied for. This is agreed.

Suitability of the oral formulation for the paediatric population from 2 years of age.

In line with the Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012 Rev.2, the suitability of the proposed formulation in the proposed age group has been satisfactorily addressed considering the safety profile of the excipients for children in the target age groups in relation to exposure.

Suitability of the Container closure system, including dosing devices

The same container closure system as already on the market, an amber glass bottle with a child resistant closure (polypropylene) containing 300 ml of the drug product is intended to be used in all age groups. To justify the bottle size when used for the smallest children, additional in-use stability data supporting an in-use shelf life of 8 months, were provided. This is acceptable.

The already approved package contains a 5 ml and a 10 ml oral syringe which is considered sufficient to cover the recommended doses from 2 years of age.

IV formulation

The currently approved formulation, 10 mg/ml Solution for injection/infusion for children from 4 years of age, is intended also to be used in children from 2 years of age. The excipients of the solution for injection/infusion formulation are sodium chloride, sodium acetate(trihydrate), glacial acetic acid and water for injection.

The solution is filled in type 1 glass vials with an extractable volume of not less than 5 ml. The same vial size 5 ml as already approved is intended to be used for all age groups.

Suitability of the iv formulation for the paediatric population from 2 years of age.

The excipients, as described in table 2.2-1 above, included in the current formulation is commonly used and of no safety concern for the use in children from 2 years of age.

For a child weighing 10 kg the lowest dose to be administered on one occasion is 0.5 ml. When using a 1 ml syringe no issues with regards to accuracy and precision are expected since commonly available syringes of 1 ml syringes with 0.01 increments are to be used for dosing. The lowest volume to be dosed corresponds to 50% of the maximum capacity of the capacity of the 1 ml syringe. *This is acceptable.*

The risk of a 10-fold overdose, by the use of a 5 ml presentation for the youngest children, has been addressed. The conclusion not to develop a smaller presentation for these children is acceptable since it is a temporary replacement from oral administration, handled and administered by highly trained medical professionals in hospital.

2.3. Non-clinical aspects

2.3.1. Introduction

No new clinical data have been submitted in this paediatric extension of indication, which was considered acceptable by the CHMP.

The previously submitted reproductive and developmental toxicity studies, including juvenile toxicity studies, included and reviewed in the Briviact iMAA, are summarised hereafter. The relevant findings are reflected in the Product Information.

An updated environmental risk assessment (ERA) has been provided in this submission

2.3.1. Toxicology

Reproduction toxicity

Prenatal and postnatal development, including maternal function

Rats were dosed orally up to 600 mg/kg, twice daily with 10 hours apart, from gestation day 6 to day 20 of lactation. The F_1 pups were exposed to BRV and to its metabolites irrespective of the dose administered to the mothers indicating that BRV and possibly metabolites were present in the mother's milk. An increased liver weight was noted from 300 mg/kg in the F0 generation. In the F1 generation, at BRV doses of 600

mg/kg, up to 13% lower body weight loss was observed during post-natal day (PND) 10-14 and 14-17 resulting in lower body weight of up to - 5.2% on post-natal day 17 and lower mean body weights during the post-weaning period. In addition, the mean age of attainment of vaginal patency was delayed 2 days compared to controls at 600 mg/kg. The no-observed-adverse-effect level (NOAEL) for F_0 maternal effects, F_0 and F_1 generation reproductive toxicity and F1 generation functional/neurobehavioral development was set to 600 mg/kg, giving a margin to maximum human exposure of 17. The NOAEL for female F_1 generation neonatal/postnatal development is 300 mg/kg due to slightly delayed vaginal patency, and for males the NOAEL was set to 600 mg/kg, giving a margin to maximum human exposure of 6 and 17, respectively.

Studies with offspring (juvenile animals)

Juvenile rats and dogs were evaluated from postnatal day 4-70 and 4-276, 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 behavioural 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 BRV 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 central nervous system (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 area under the curve (AUC) values derived from the main repeat-dose toxicity study, generate a margin to clinically relevant exposure of approximately 5-8.

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.

2.3.2. Ecotoxicity/environmental risk assessment

The MAH has submitted an updated ERA in this application which accounts for the extended paediatric indication, but no new data has been provided. The MAH concludes that the inclusion of children ≥1 month to <4 years of age in the indication is not expected to impact the default F_{PEN} value of 0.01 previously used for the $PEC_{Surface\ Water}$ calculation and consequently the existing $PEC_{Surface\ Water}$ of 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. The PEC/PNEC ratio for microorganisms was below 0.1. The PEC/PNEC ratios for surface water, groundwater and sediments were below 1.

The ERA concludes that the proposed use of BRV is considered unlikely to represent an unacceptable risk to water, sewage treatment plants and sediment. There are therefore no changes to the proposed precautionary measures to be taken for administration, disposal and labelling as described in the existing ERA.

2.3.3. Discussion on non-clinical aspects

The non-clinical aspects of BRV were thoroughly evaluated during the original Marketing Authorisation procedure for Briviact and no new non-clinical studies were submitted in support of the present extension of indication application. This is acceptable since the already assessed juvenile studies cover the relevant age span. In the previously conducted juvenile studies, 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 available non-clinical juvenile toxicity studies have not identified any new or unique risks with regards to the safety of BRV in a juvenile population.

The findings are adequately reflected in the SmPC and the CHMP agreed that no further updates are needed.

2.3.4. Conclusion on the non-clinical aspects

From a non-clinical point of view, the CHMP agreed that there are no objections regarding the proposed extension of the indication.

The CHMP agrees with the ERA conclusions that BRV is unlikely to represent a risk to the environment under the proposed conditions of use and no changes to the precautionary measures described in the existing ERA are needed.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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 extension of indication in children ≥1 month to <4 years of age, consists of 1 completed study (N01263) and 1 ongoing long-term safety study (N01266) (Pool Paediatric Studies), is summarized in **Table 1**. In addition, an IV PK, safety and tolerability study in paediatrics ≥1 month to <16 years of age with epilepsy (EP0065) is included in this application. The final N01263 clinical study report was previously submitted in the first paediatric extension application (EMEA/H/C/003898/II/0010/G).

***Table 1**: Phase 2/3 studies of BRV in paediatric study participants with epilepsy*

Study number	Study description	Number of study participants 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 participants from ≥1mo to <16y old with epilepsy	99	Total: 48/51 ≥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 participants with epilepsy	247	Total: 135/112 ≥1mo to <2y: 12/15[a] ≥2y to <12y: 88/66[a] ≥12y to <17y: 35/31[a]	NA[b]	Ongoing

BRV=brivaracetam; CSR=clinical study report; F=female; LTFU=long-term follow-up; M=male; mo=months; NA=not applicable; y=years

Note: N01266 was initially designed as a LTFU to N01263 (enrolled participants with either partial-onset or generalized seizures), but was amended to allow direct enrollment of participants with POS from ≥4 to <17 years of age with epilepsy. N01266 also serves as the follow-up study for pediatric studies evaluating BRV for the treatment of epilepsy, including N01349 and EP0065.

[a] As of the clinical cutoff of 14 Jan 2020.

[b] There is no defined maximum duration of treatment in this study.

Data sources: N01263 CSR, interim N01266 CSR

The following modelling and simulation studies are included in this application in support of extrapolation:

- CL0187: A population PK (popPK) study in paediatric study participants with POS (previously submitted in the initial paediatric extension application).
- CL0258: An exposure-response modelling study of BRV as adjunctive therapy in paediatric study participants with POS (previously submitted in the initial paediatric extension application).
- CL0428: An extension of CL0258 to paediatric study participants ≥1 month to < 4 years of age

(new information in the current submission, which includes comparisons of the modelling projections on efficacy with the open-label efficacy data collected in N01263 and N01266).

In addition to the modelling and simulation studies, pooled safety data from the following 2 paediatric BRV studies that comprise Pool Paediatric Studies are included in this application:
– N01263: A completed open-label, Phase 2 study of BRV in paediatric participants with epilepsy, including participants with POS.
– N01266: An ongoing open-label long-term study of BRV in paediatric participants with epilepsy, including participants who enrolled from N01263 and at least 100 directly enrolled participants with POS who have at least 1 year of BRV exposure.

Further support of the proposed paediatric indication is provided by updated safety data from 2 adult safety pools included in the initial Marketing Authorization Application (MAA): Pool S4 and Pool Monotherapy. No new study participants were added to these pools since the initial MAA or initial paediatric extension (for patients ≥4 to < 16 years of age) applications were reviewed; however, the clinical cut-off date for the current application provides data for approximately 3 years of additional exposure to BRV compared with the initial paediatric extension application (from 4 years to 16 years of age).

Lastly, post marketing data from paediatric patients (data cut-off date: 14 Jul 2020) including a literature review as well as reference to previously submitted adult data are included

2.4.2. Pharmacokinetics

The pharmacokinetics of BRV was investigated in paediatrics in studies N01263, EP0065 and in the ongoing study N01266.

An oral popPK model was previously developed, using exposure data from study N01263, to describe the PKs of BRV in paediatrics aged ≥1 month to <16 years (Report no. CL0187). The model was assessed in the initial paediatric extension of indication procedure. In this application, the popPK model was further extended to include exposure data from study N01266 (Report no. CL0428 external validation). Based on the paediatric popPK model, different weight-based dosing schemes for oral BRV, that would result in BRV steady state plasma concentrations in the range of adults receiving 200 mg/day (maximum recommended therapeutic dose), were simulated. Population PK/PD analyses for BRV and LEV were performed to support the extrapolation of effect between adults and paediatrics (≥1 month to <4 years). A summary of the PK and PK/PD modelling and simulation studies to support the indication for BRV as adjunctive therapy in the treatment of POS in paediatric patients ≥1 month of age with epilepsy is presented in **Table 2** hereafter.

Table 2: *Summary of LEV and BRV PK and PK/PD modeling and simulation studies supporting paediatric adjunctive therapy*

Study number	High-level objectives[a]	BRV study data included	Total number of study participants [b]
Pediatric studies			
CL0187 (Amended report)	1) To develop a population PK model for BRV in pediatric study participants 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 study participants, to assess the potential change in PK/PD relationship between adult and pediatric participants 2) To use the obtained scaling in LEV PK/PD relationship from adult to pediatric participants to predict the BRV efficacious dose in pediatric participants 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)
N01288[c]	1) To characterize the PK of LEV in pediatric participants, including estimation of the inter- and intra-patient variability in the main PK parameters, using data pooled from 6 clinical studies 2) To assess the linearity of LEV PK on the investigated dose range 3) To identify relevant demographic and/ or physiologic determinants of LEV disposition, including if possible a potential influence of concomitant AEDs in that population 4) To simulate optimal dosing regimens as a function of the relevant covariates	N151 (pediatric Phase 2) N01010 (pediatric Phase 2) N01052 (pediatric Phase 2) N01103 (pediatric Phase 2) N01009 (pediatric Phase 3) N01148 (pediatric Phase 3)	437
CL0428	1) To provide estimated participants LEV exposures in study N01009 2) To extend the existing adult/pediatric population PK/PD model for effects of LEV on seizure counts, and to use the extended model to predict effects of BRV in patients 1 month to <4 years of age	N01263 (pediatric Phase 2a)	96
CL0428 external validation	1) To update the previously developed oral BRV pediatric population PK model by including new oral BRV PK data from study N01266 2) To compare simulations to scale BRV effects into children of 1 month to <4 years of age with observed BRV effects in this age group from studies N01263 and N01266	N01263 (pediatric Phase 2a) N01266 (pediatric long-term follow-up Phase 3)	232

AED=antiepileptic drug; BRV=brivaracetam; LEV=levetiracetam; PK=pharmacokinetic; PK/PD=pharmacokinetic/pharmacodynamics
a Some objectives have been summarized to provide a high-level overview
b The total number of study participants is the number of participants with data included in the PK or PK/PD modelling and simulation study referenced.
c N01288 was not submitted as part of this Common Technical Document.

The proposed BRV dosing recommendations in adults and children, according to the MAH, are summarised in **Table 3**.

Table 3*: Summary of paediatric BRV recommended dosing*

	Adults	Children ≥50kg	Children ≥20 - <50kg	Children ≥10 - <20kg	Children ≥3 - <10kg
Starting dose[a]	50mg/day (or 100mg/day)	50mg/day (or 100mg/day)	1 mg/kg/day (up to 2 mg/kg/day)	1 mg/kg/day (up to 2.5 mg/kg/day)	1.5 mg/kg/day (up to 3 mg/kg/day)
Maximum recommended dose	200mg/day	200mg/day	4mg/kg/day[b]	5mg/kg/day[b]	6mg/kg/day[b]
Therapeutic dose range	50 to 200mg/day	50 to 200mg/day	1 to 4mg/kg/day	1 to 5mg/kg/day	1.5 to 6mg/kg/day

BRV=brivaracetam
[a] Based on physician assessment of need for seizure control.
[b] Maximum recommended doses are based on the pharmacokinetic modeling and simulation studies CL0187 and CL0428 to match the equivalent exposures in adults at the maximum recommended dose of 200mg/day.

Summary of PK and PK/PD modelling of BRV in paediatric patients aged ≥4 years with POS

In the initial paediatric extension of indication variation (for patients ≥4 to < 16 years of age) BRV PK data came from sparse sampling in the Phase 2a study N01263 where study participants had received at least 7 days of treatment. This study was performed in participants aged ≥1 month to <16 years. All PK data were modelled in CL0187, including the data from participants below the age of 4. Covariates investigated to explain interparticipant variability included:

- Demographic and physiological covariates, ie, postconceptional age, sex, (lean) body weight, race, ethnicity, and renal function (estimated glomerular filtration rate)
- Covariates that are specific for treatment of epilepsy, ie, use of the antiepileptic drugs (AEDs) carbamazepine (CBZ), valproate (VPA), phenytoin (PHT), and phenobarbital/Primidone (PB); use of cytochrome P450 (CYP)-inducing AEDs in general; and use of combinations of AEDs
- Covariates that are relevant due to the PK properties of BRV, ie, use of CYP3A4 or CYP2C19 inhibitors

The PK of BRV could be described by a linear 1-compartment model with first order absorption. Allometric scaling factors for CL/F and V/F were fixed to the theoretical values of 0.75 and 1.00, respectively. Lean body mass was used as a metric for body size. The covariates that proved to be relevant and were retained in the final model were use of CBZ, PB, and VPA, and lean body weight. Use of the metabolic inducers PB and CBZ increased CL/F by 40.8% and 47.9%, respectively, while VPA decreased Cl/F by 10.1%.

An exposure-response modelling study (CL0258) of BRV as adjunctive therapy in children with POS, was conducted to support the dosing regimens. CL0258 was based on Phase 3 PK/PD data from adults and children who received 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 was used to assess if and how the PK/PD relationship scales from adults to paediatric subjects. The final objectives of the analysis were to scale the 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 MoA, and to predict the effective dose of BRV in children aged 4 to 16 years. Using the popPK model of CL0187, doses were determined in CL0258 that resulted in the same exposure as therapeutic doses in adults.

Population PK modelling of oral BRV in paediatric patients aged > 1 month

The previously developed BRV paediatric popPK model, based on exposure data from Study N01263, was a one compartment model with first order absorption and an allometrically scaled effect of body size on clearance (CL) and Vc (fixed allometric exponents). In report CL0428, this model included body weight as a metric for body size. Coadministration effects on CL of inducer AEDs were also included. The model was updated by including data from the long-term follow-up (LTFU) study N01266 (Study report CL0428 external validation). The updated model is considered as the final model since it includes more paediatric data.

The analysis was performed using Nonlinear mixed effects modelling (NONMEM, Version 7.4.3) and the first order conditional estimation method with interaction. The study designs for N01263 and N01266 are summarized below.

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 with epilepsy. BRV oral solution was administered at weekly increasing doses of approximately 0.4 mg/kg twice a day (bid), 0.8 mg/kg bid, and 1.6 mg/kg bid for subjects ≥8 years of age and 0.5 mg/kg bid, 1.0 mg/kg bid, and 2.0 mg/kg bid for subjects <8 years of age. The doses did not exceed a maximum of 50, 100 and 200 mg/day, respectively. The overall planned study duration per subject was 8 weeks. Two to three PK samples were taken per visits, with one visit for each of three dosing levels.

N01266 is an ongoing open-label, single-arm, multicenter, long-term study to evaluate safety and efficacy of BRV oral solution and oral tablets used as adjunctive treatment in paediatric participants with epilepsy. N01266 is a LTFU to N01263 and EP0065, which enrolled only subjects with either focal or generalized epilepsy (1 month to < 16 years of age), but also includes direct enrolment of subjects 4 years to <17 years of age who have focal epilepsy. Participants enrolled from other studies continue their treatment. Directly enrolled subjects enter N01266 at the screening visit and then participate in up to 3 weeks of an up-titration period. If a directly enrolled subject demonstrates, acceptable tolerability and seizure control on the same daily dose of BRV (no lower than 1 mg/kg/day) for 7±2 days during the up-titration period, the subject will attend the entry visit and enter the evaluation period on that dose.

The maximum dose is 5 mg/kg/day, not to exceed a dose of 200 mg/day in subjects with body weights > 40 kg. Pharmacokinetic samples are collected at the entry visit, the yearly evaluation visit/final visit, the early discontinuation visit and whenever the subject experiences a serious adverse event (SAE). Data available in the current analysis are from 227 subjects (data cut-off 20 January 2020). Planned total enrolment is approximately 600 subjects.

A summary of categorical and continuous covariates included in the updated PK dataset is provided in **Table 4** and **Table 5**.

***Table 4**: Summary of PCA (post-conceptional age), age, body weight and lean body weight at baseline by age category, for all subjects in the PK analysis data selection of the CL0428 data file.*
Source: Table 6 in Report CL0428 external validation

Variable	*Mean*	*SD*	*Median*	*Min*	*Max*	*N*
PCA (years)						
1 month-<2 years	1.89	0.55	2.00	0.92	2.67	29
2 years-<4 years	3.58	0.49	3.58	2.72	4.42	9
4 years-<18 years	10.61	3.55	10.65	4.83	17.85	194
Overall	9.25	4.49	9.35	0.92	17.85	232
Age (years)						
1 month-<2 years	1.15	0.55	1.25	0.17	1.92	29
2 years-<4 years	2.84	0.46	2.83	2.08	3.67	9
4 years-<18 years	9.86	3.55	9.90	4.08	17.10	194
Overall	8.50	4.49	8.60	0.17	17.10	232
Weight (kg)						
1 month-<2 years	9.3	2.7	9.0	3.9	14.8	29
2 years-<4 years	13.2	2.5	12.9	9.5	18.3	9
4 years-<18 years	36.5	19.8	30.9	9.2	159.8	194
Overall	32.2	20.6	27.1	3.9	159.8	232
LBW (kg)						
1 month-<2 years	8.0	2.4	7.9	3.6	12.7	29
2 years-<4 years	11.2	1.6	11.4	8.8	14.4	9
4 years-<18 years	29.1	11.8	26.5	8.5	69.0	194
Overall	25.7	13.2	24.0	3.6	69.0	232

Baseline is defined as the first value recorded for a subject. PCA: post-conceptional age, LBW: lean body weight.

***Table 5:** AED coadministration and sex distribution at baseline, by age category (N and %), for all subjects in the PK analysis data selection of the CL0428 data file*

Age category	Carbamazepine	Phenytoin	Phenobarbital/Primidone	Valproate	Females
1 month-<2 years	2 (6.9%)	1 (3.4%)	11 (37.9%)	16 (55.2%)	15 (51.7%)
2 years-<4 years	0 (0%)	0 (0%)	1 (11.1%)	4 (44.4%)	4 (44.4%)
4 years-<18 years	69 (35.6%)	23 (11.9%)	12 (6.2%)	95 (49%)	88 (45.4%)
Overall	71 (30.6%)	24 (10.3%)	24 (10.3%)	115 (49.6%)	107 (46.1%)

Baseline is defined as the first value recorded for a subject

A total of 855 concentration records from 232 individuals were included in the updated analysis (**Table 6**). Only concentrations up to up to 180 days after first administration was included, which is in line with the range of seizure count data that were analysed in the external validation of the BRV popPK/PD model (see section 2.4.3. PK/PD modelling). This was also the main reason for data exclusions in study N01266. In study N01266, less than 4% of the observations were considered outliers and were excluded from the analysis. Handling of missing data, data exclusions and outliers in study N01263 were assessed in the previous application ((EMEA/H/C/003898/II/0010/G).

Table 6: *Number of BRV concentration records and subjects (in parentheses) by age category in the full CL0428 data file and the PK analysis dataset with time restricted to less than 180 days*
Source: Table 3 in Report CL0428 external validation

Age category	Full CL0428 data file	PK analysis data selection
1 month-<2 years	220 (29)	195 (29)
2 years-<4 years	127 (9)	63 (9)
4 years-<18 years	1855 (200)	597 (194)
Overall	2202 (238)	855 (232)

Subjects and concentrations classified in N01266 were newly enrolled in study N01266.

The AED coadministration covariates were reassessed. Additionally, the potential association between post-conceptional age (PCA) and CL was assessed using a sigmoid Emax model to investigate potential age-related maturation of BRV CL.

Results

Parameter estimates of the final updated popPK model (run603) are provided in **Table 7**.

Table 7*: Parameter estimates of the final updated PK model (run603).*
Source: Table 10 in Report CL0428 external validation

Parameter	Estimate (95% CI)	IIV	Shrinkage*
CL (L/h)	4.17 (3.94/4.40)	25.9%	24.2%
Vc (L)	71.3 (65.0/77.7)	20.7%	58.6%
ka (1/h)	2.11 (1.46/2.76)	0.0%	100.0%
Allometric scaling CL	0.75 Fixed		
Allometric scaling Vc	1.00 Fixed		
fold-change CL due to PB coadministration	1.39 (1.19/1.62)		
fold-change CL due to CBZ coadministration	1.27 (1.14/1.42)		
Proportional RUV (fraction)	0.307 (0.280/0.334)		8.8%

CL and Vc scaled to a typical body weight value of 70 kg. CL: clearance, Vc: central volume, ka: absorption rate constant, PB: phenobarbital/primidone, CBZ: carbamazepine, RUV: residual unexplained variability, IIV: inter-individual variability.
**Shrinkage calculated using the standard deviation*

PCA was not identified as a covariate. Goodness of fit plots and prediction-corrected visual predictive checks (pcVPCs) are shown in **Figure 1**, **Figure 3** and **Figure 3**.

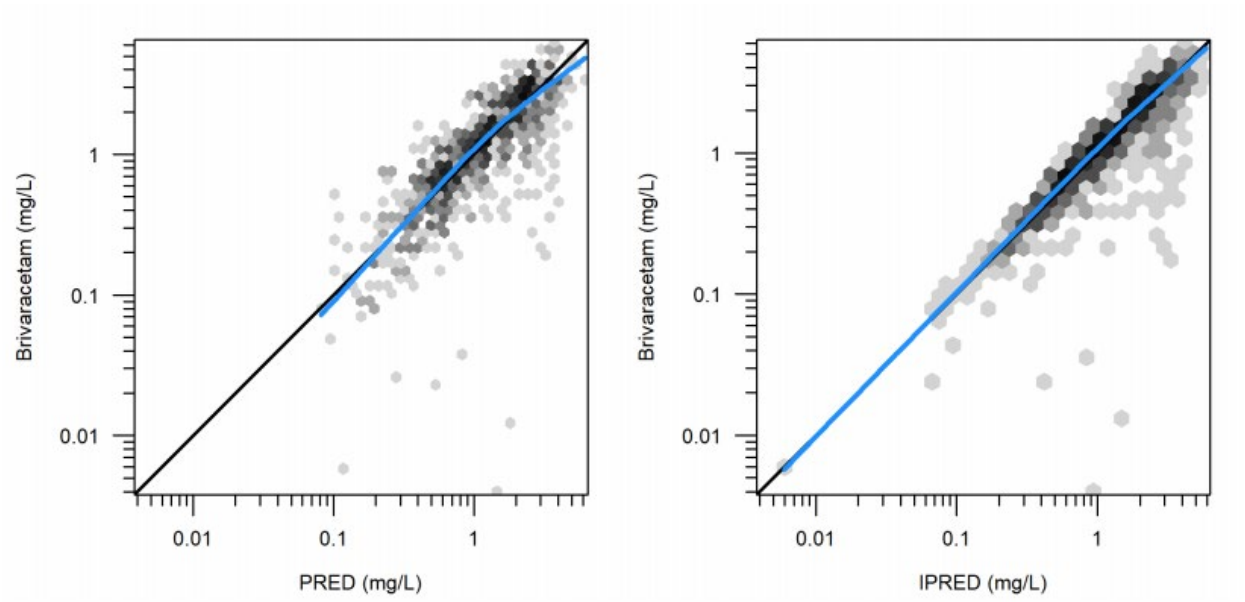


Figure 1: *Brivaracetam goodness of fit plots for the final updated population PK model (run603). The black lines are lines of identity, the blue lines are loess smoothers through the data. PRED: population predictions, IPRED: individual predictions. The darkness of the hexagons corresponds to the data density at that location.*
Source: Figure 7 in Report CL0428 external validation

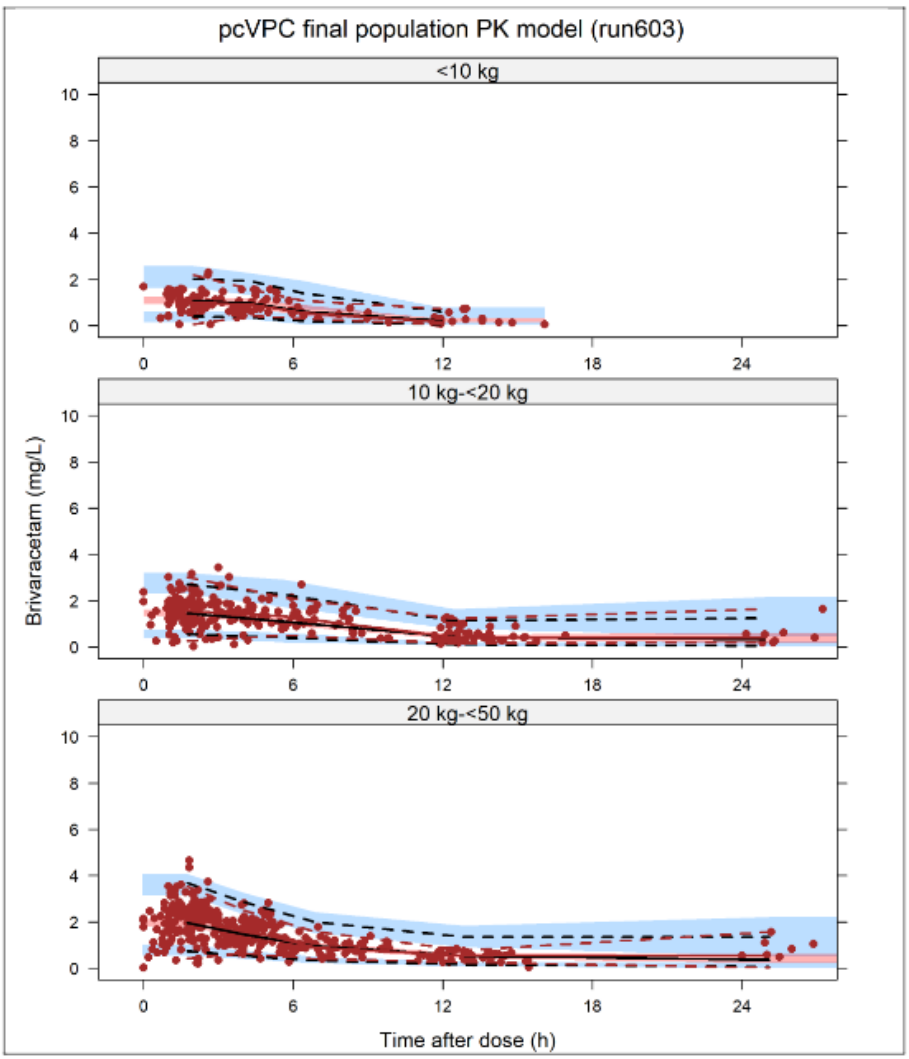


Figure 2: *pcVPC for the final updated population PK model (run603) stratified on weight categories Red lines: observed BRV quantiles (2.5th, 50th, 97.5th), black lines: median of BRV quantiles (2.5th, 50th, 97.5th) across simulated trials, blue and red shaded areas: 95% of the BRV quantiles (2.5th, 50th, 97.5th) across simulated trials, red circles: observations.*

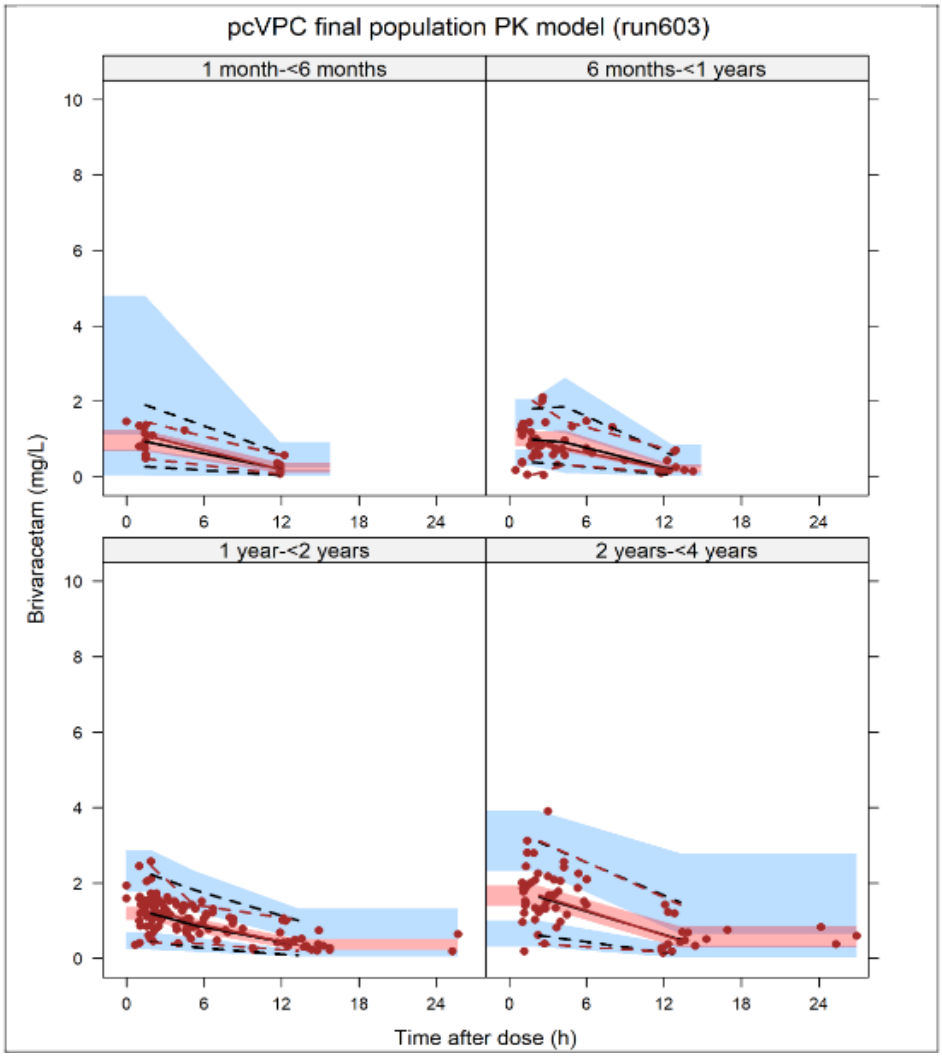


Figure 3: *pcVPC for the final updated population PK model (run603) stratified on age categories Red lines: observed BRV quantiles (2.5th, 50th, 97.5th), black lines: median of BRV quantiles (2.5th, 50th, 97.5th) across simulated trials, blue and red shaded areas: 95% of the BRV quantiles (2.5th, 50th, 97.5th) across simulated trials, red circles: observations.*

IV PK study (EP0065)

EP0065 was a Phase 2, multicenter, open-label study to evaluate the PK, safety, and tolerability of IV BRV administered as a 15-minute iv infusion and an IV bolus (up to 2-minute infusion) in study participants ≥1 month to <16 years of age with epilepsy. Participants received at least 1-2 consecutive doses of BRV (for further information about the study design, see section 2.5.1. Studies EP0065). For IOB (initiating oral BRV) and IIB (initiating IV BRV) participants, the maximum BRV dose was 4 mg/kg/day. For OLB (open-label BRV) and RxB (prescribed-BRV) participants, the maximum BRV dose was 5 mg/kg/day (rounded). No study participants received a dose greater than BRV 200 mg/day. Study drug exposure during the IV PK Period is provided in **Table 8**.

Table 8 *Study drug exposure during the iv PK period (SS-iv)*

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

BRV=brivaracetam; iv=intravenous; max=maximum; min=minimum; PK=pharmacokinetic; SD=standard deviation; SS-iv=Safety Set-intravenous
Note: Percentages were based on the number of study participants in the SS-iv.
Note: Duration of iv BRV exposure in days was calculated as follows: start date and time of the last iv BRV minus the start date and time of the first iv BRV plus 1 day.
Data source: Table 4.1

PK samples were collected at pre-dose, and 15 min and 3 h post-dose following two IV administrations (where the first sampling occasion was following the first IV administration). 45 children (out of 50 children) were included in the pharmacokinetic evaluation (PK-PPS).

The main reason for exclusions were no measurable postdose plasma samples. One subject (in the ≥2 to <6 years age cohort [RxB/bolus group]) was excluded, since the BRV concentrations were above the upper LOQ (20 000 ng/mL) at the 15-minutes and 3-hour postdose timepoints, even after a 100-fold dilution step. These high concentrations were thought to be due to contamination of the sample during blood sampling. One study participant in the ≥1 month to <2 years age cohort (RxB/bolus group) had plasma concentration above the upper LOQ (>20 000 ng/mL) at the 15-minute postdose time point, and the value remained high (7280 ng/mL) at the 3-hour postdose time point. The sample that had a concentration greater than the upper LOQ was considered an outlier and was not included in the summary statistics.

Most of the plasma samples were collected following the first IV dose (Visit 3). A summary of Briviact plasma concentrations at Visit 3 are shown in **Table 9** and **Table 10**, whereas plasma concentrations for the different age cohorts are graphically displayed in **Figure 4**.

Table 9 *Brivaracetam plasma concentration statistics at Visit 3 (iv PK Period)*

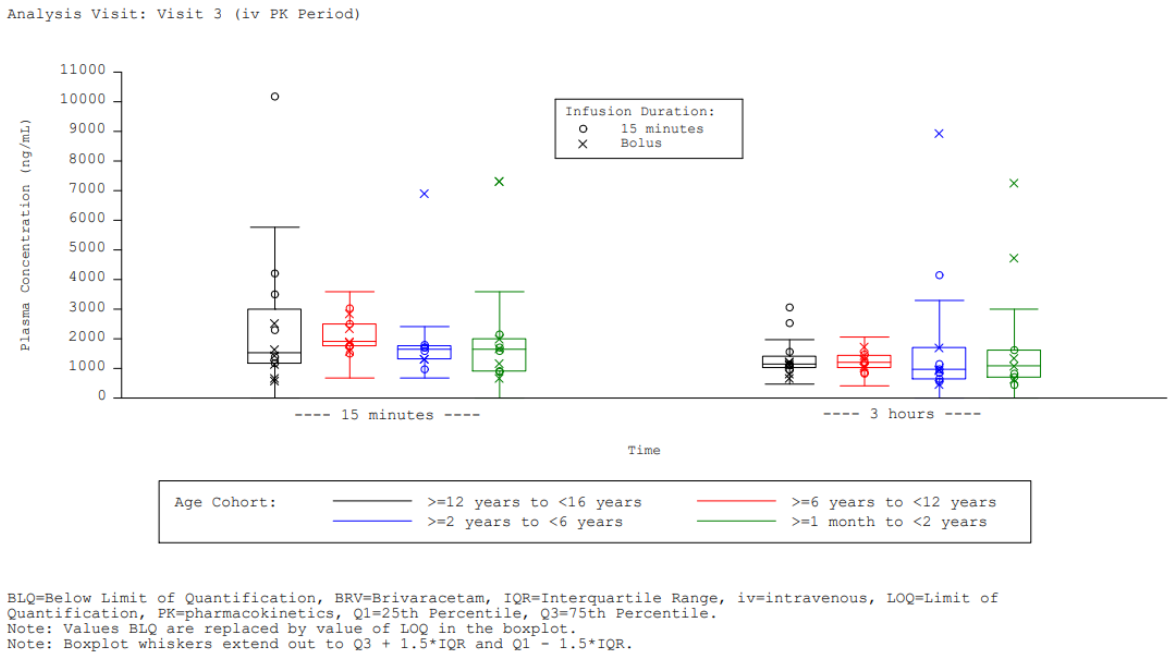
Visit 3 time point	Descriptive statistic	By age cohort				Infusion group	
		≥1 month to <2 years	≥2 to <6 years	≥6 to <12 years	≥12 to <16 years	15-minute infusion	Bolus
Predose (≤1 hour)	n	9	10	10	12	19	22
	GeoMean (ng/mL)	310.6	--	--	149.0	--	120.5
	GeoCV (%)	331.1	--	--	3389.7	--	1222.5
Postdose 15 minutes (±2 minutes)	n	10	8	10	12	21	19
	GeoMean (ng/mL)	1566.6	1774.9	2058.8	1844.6	1903.0	1704.8
	GeoCV (%)	74.7	64.0	25.0	94.5	60.7	74.5
Postdose 3 hours (±15 minutes)	n	9	11	10	12	21	21
	GeoMean (ng/mL)	1341.7	1225.3	1189.5	1260.6	1130.3	1383.9
	GeoCV (%)	116.7	108.8	23.8	44.4	58.8	85.0

BLQ=below the level of quantification; GeoCV=geometric coefficient of variation; GeoMean=geometric mean; iv=intravenous; LOQ=limit of quantification; PK=pharmacokinetic; PK-PPS=Pharmacokinetic Per-Protocol Set
Note: Values BLQ were replaced by the value of LOQ in calculation of CVs. The CVs were only calculated if at least two-thirds of the concentrations were quantified at the respective time point.
Data source: Table 5.1

Table 10 *Brivaracetam plasma concentration statistics at Visit 3 (iv PK Period) by weight group*

Visit 3 time point	Descriptive statistic	Weight group	
		<50kg	≥50kg
Pre-dose (≤1 hour)	n	34	7
	GeoMean (ng/mL)	--	--
	GeoCV (%)	--	--
Postdose 15 minutes (±2 minutes)	n	33	7
	GeoMean (ng/mL)	1939.3	1291.5
	GeoCV (%)	64.6	67.0
Postdose 3 hours (±15 minutes)	n	35	7
	GeoMean (ng/mL)	1253.5	1236.4
	GeoCV (%)	77.4	48.6

BLQ=below the level of quantification; GeoCV=geometric coefficient of variation; GeoMean=geometric mean; iv=intravenous; LOQ=limit of quantification; PK=pharmacokinetic; PK-PPS=Pharmacokinetic Per-Protocol Set
Note: Values BLQ were replaced by the value of LOQ in calculation of CVs. The CVs were only calculated if at least two-thirds of the concentrations were quantified at the respective time point.
Data source: Table 5.2



BLQ=Below Limit of Quantification, BRV=Brivaracetam, IQR=Interquartile Range, iv=intravenous, LOQ=Limit of Quantification, PK=pharmacokinetics, Q1=25th Percentile, Q3=75th Percentile.
Note: Values BLQ are replaced by value of LOQ in the boxplot.
Note: Boxplot whiskers extend out to Q3 + 1.5*IQR and Q1 - 1.5*IQR.

Figure 4 *Plasma concentrations of BRV relative to iv administration of BRV by Age Group*

Absorption

No specific studies have been performed to evaluate the absorption of BRV in paediatrics.

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

BRV is weakly bound to plasma proteins in adults (≤20%) and shows a nearly even distribution between plasma and blood. No relevant change in the low plasma protein binding is expected to occur in paediatric patients.

The volume of distribution of BRV is 0.5 L/kg in adults. Based on the updated paediatric popPK model, the apparent volume distribution of BRV in the paediatric population was estimated to 71.3 L for a total body weight of 70 kg (95% CI: 65.0, 77.7 L).

Metabolism

In paediatrics, the plasma clearance was estimated to 4.17 L/h (normalised to a 70 kg person). This estimate is comparable to that reported with the previous popPK model.

Expression of the amidase enzyme, which represents the main disposition pathway of BRV and accounts for 60% of metabolism, 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 P450 (CYP) 2C19 and accounts for 30% of metabolism, 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 in young children. However, such an effect was not evidenced in the small dataset of paediatric subjects (see section Population PK modelling). None of the 3 metabolites are pharmacologically active. The concentrations of BRV and the 3 metabolites of BRV were determined in all plasma samples collected in paediatric study N01263. The results indicated that the plasma concentrations of the metabolites in paediatric study participants were similar to those observed in healthy adults.

Elimination

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 (t½) 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 (SD) plasma half-life of BRV in children, estimated by simulation in CL0187, ranged from 5.6 hours (1.9 hours) in the group from 0 to < 1 years to 9.1 hours (3.1 hours) in the group from 15 to <16 years of age.

Special populations

Age and gender

The previous paediatric popPK analysis (Report no. CL0187) did not identify a significant effect of gender, or age on BRV CL. Clinical studies in adults with epilepsy showed that gender and race does not have a clinically significant influence on the plasma concentrations of BRV.

Race

The previous paediatric popPK analysis (Report no. CL0187) did not identify a significant effect of race on BRV CL. 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

Body weight was identified as a covariate for both CL and V.

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 23.1 µg.h/mL (normalized to a dose of 1 mg/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 and hepatic impairment

The effects of renal and hepatic impairment were not evaluated in the paediatric studies.

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

In adults with chronic liver disease corresponding to Child-Pugh classes A, B and C, exposure to BRV was increased by 50%, 57% and 59%, respectively, compared with matched healthy controls. A maximum daily dose of BRV 150 mg administered in 2 divided doses is recommended for all stages of hepatic impairment in adults, and a starting dose of BRV 50 mg/day should be considered

Based on these data, a starting dose of BRV 1.5 mg/kg/day for body weight below 10 kg, 1 mg/kg/day for body weight ≥10 to 20 kg, and 1 mg/kg/day for body weight ≥20 to < 50 kg is recommended for paediatric patients aged ≥1 month to 4 years at any stage of hepatic impairment. Based on the maximum dose recommended for adults, similar BRV maximums (4.5 mg/kg/day for body weight ≥3 to <10 kg, 4 mg/kg/day for body weight ≥10 to <20kg and 3mg/kg/day for body weight ≥20 to 50 kg) are recommended for paediatric patients aged ≥1 month to <4 years with any stage of hepatic impairment.

Drug-drug interactions

As in adults, for paediatric patients prescribers should consider increasing the BRV dose in patients starting treatment with rifampicin and decreasing when stopping rifampicin treatment. For paediatric subjects, coadministration with PB and CBZ increased BRV clearance. The estimated increase was 39% (95% CI: 19%/62%) and 27% (95% CI: 14%/42%) for PB and CBZ, respectively. Coadministration with VPA or PHT did not have any significant impact on BRV clearance.

Simulations to establish dosing recommendations for oral administration

Simulations of the proposed dosing schedule for BRV, based on the updated paediatric popPK model, are shown in **Figure 5**. The population estimates from the final adult patient popPK model (Report no. CL0028) were used to derive the target reference range of concentrations for adults receiving 100 mg BRV bid (200 mg/day). The adult popPK model has been assessed in an earlier application. In the simulations, effects of inducer AED coadministration were excluded from both adult and paediatric populations to allow an unbiased comparison. The Nhanes DXA database was used to provide demographic variables (age and body weight) for both adults and children to drive the simulations.

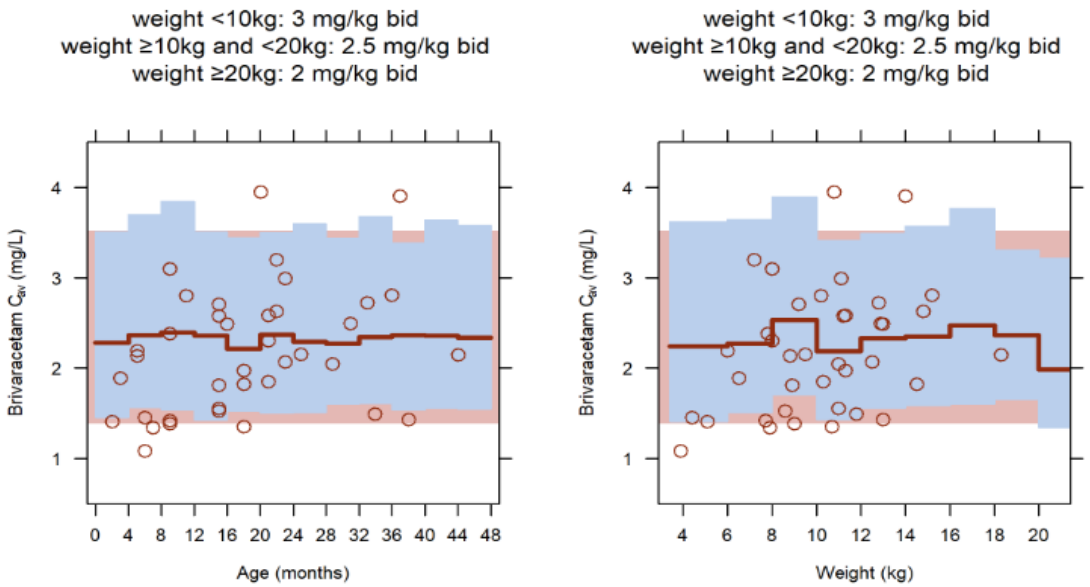
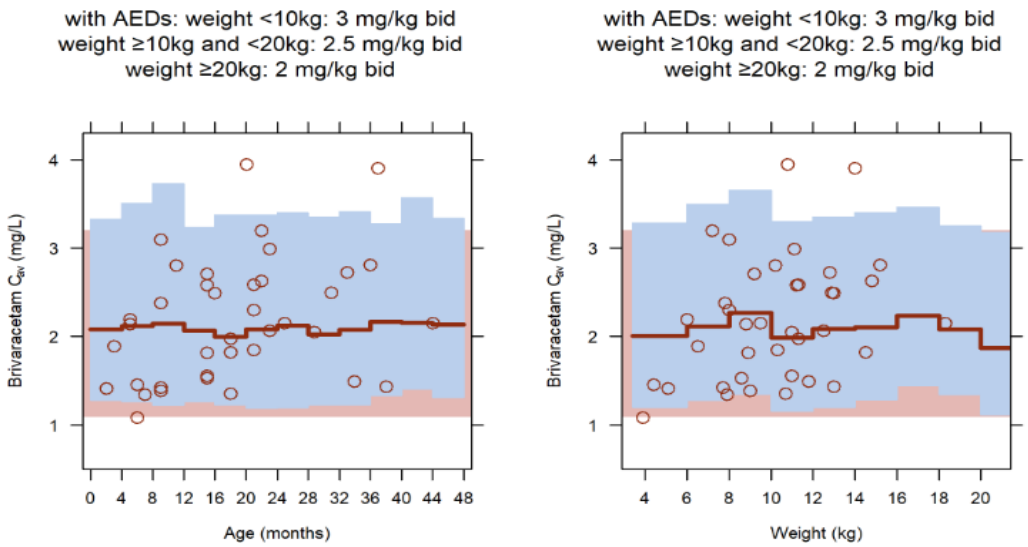


Figure 5: *Simulated brivaracetam C_{av} exposures vs. age (left) and weight (right) at the proposed posology without concomitant administration of AEDs for children 1 month to < 4 years.*

Red line and blue area: median and 90% of simulated BRV Cav values for study participants sampled from the NHANES database and using the original BRV paediatric population PK model (run603, with weight but without applying AED covariate effects). Red circles: individual predicted BRV Cav values for study participants from N01263 and N01266 and using empirical Bayes estimates from the original BRV paediatric population PK model (run603). Pink area: 90% of simulated BRV Cav values for a 100mg bid dose for adults ≥18 years sampled from the NHANES database and using the previously developed BRV adult population PK model (run20, with weight but without applying AED covariate effects).

Simulations were also performed for BRV when co-administered with AEDs (**Figure 6**). PB, PHT and CBZ co-administration was sampled from the adult patient dataset for simulated adult patients, and PB, CBZ and VPA co-administration was sampled from the paediatric dataset restricted to children <4 years for simulated paediatric patients.



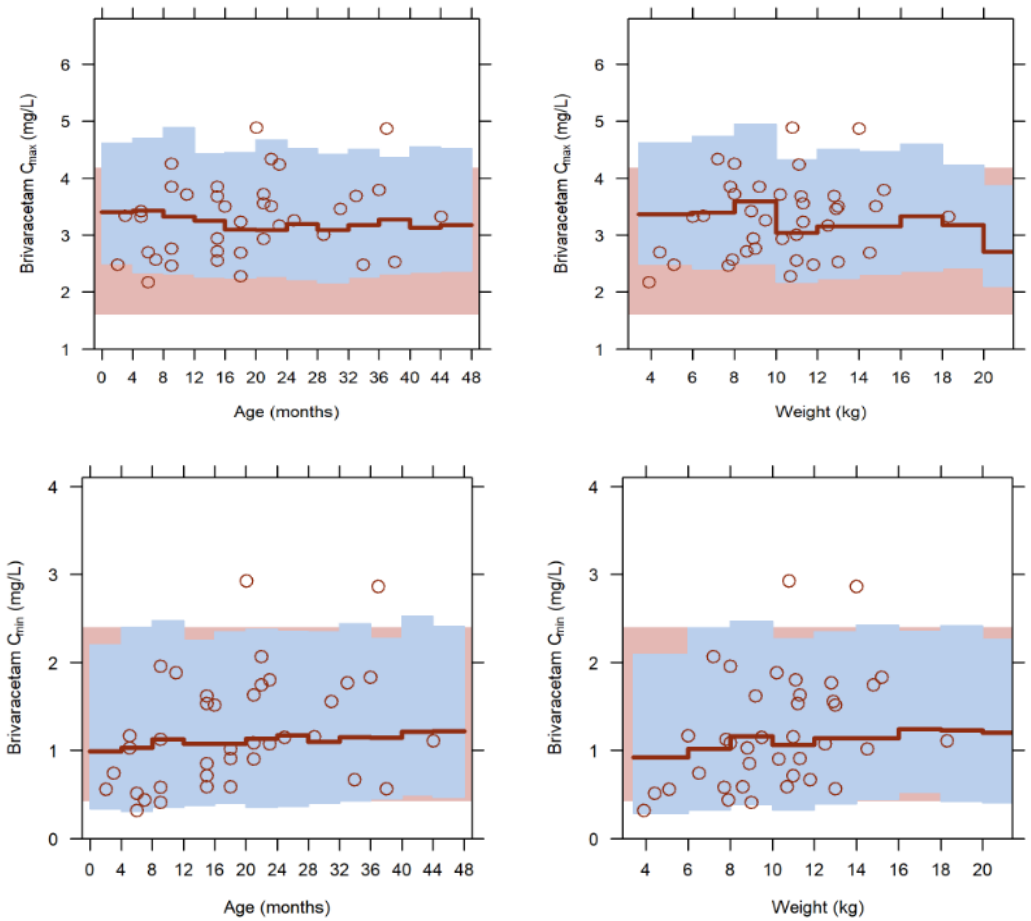


***Figure 6**: Simulated brivaracetam C_{av}, C_{max} and C_{min} vs age and WT at the proposed posology with concomitant AEDs.*

Red line and blue area: median and 90% of simulated BRV C_{av}, C_{max} or C_{min} values for study participants sampled from the NHANES database and using the original BRV paediatric population PK model (run603, with weight and with applying AED covariate effects). Red circles: individual predicted BRV C_{av}, C_{max} or C_{min} values for study participants from N01263 and N01266 and using empirical Bayes estimates from the original BRV paediatric population PK model (run603). Pink area: 90% of simulated BRV C_{av}, C_{max} or C_{min} values for a 100 mg bid dose for adults ≥18 years sampled from the NHANES database and using the previously developed BRV adult population PK model (run20, with weight and with applying AED covariate effects)

2.4.3. PK/PD modelling

Exposure-response modelling was conducted to support the proposed dosing recommendations for BRV as adjunctive therapy in children 1 month to <4 years of age with POS. The modelling was based on Phase 2 and 3 data of LEV and BRV.

Methods

A popPK/PD model was previously developed to describe the relationship between average concentrations of BRV and daily seizure frequency in adults (Report no. CL0027). In order to support the extrapolation of effect to paediatrics 1 month to <4 year of age, an existing LEV adult/paediatric PK/PD model was extended with data from children aged 1 month to <4 year (Report no. CL0428). The results from the combined LEV adult/paediatric PK/PD model was subsequently used to scale the BRV adult PK/PD model to children of 1 month to < 4 years.

The combined adult/paediatric BRV PK/PD model was also externally validated using observed seizure count data from paediatrics in studies N01263 and N01266. The average daily concentrations from the updated

popPK model used as input in the simulations. The external validation was restricted to records at the baseline, up-titration and evaluation visits. N01266 is a LTFU study, and the duration of treatment of the participants varied considerably. To ensure the comparability of the data with respect to treatment duration for the various studies, the data from N01266 were restricted to a treatment period of up to 180 days.

Patients starting treatment in study EP0065 were excluded from the analysis. This since the study included IV administered BRV data and was not considered relevant for the current analysis. Additionally, no multiple-day recordings of baseline seizure counts were present in the study, which made the calculation of change from baseline in seizure rates problematic for these patients.

The number of subjects and data records in the PK/PD analysis are presented in **Table 11**. In the younger children, <4 year of age, the number of seizures were assessed using two 48-hour continuous video-EEG recordings, in contrast to older children (> 4 years) where daily seizure counts were documented in diaries. EEG data were available in 7 subjects and diary data were available in 22 subjects aged > 1 month to <4 years with POS.

Table 11: *Number of seizure count days and subjects (in parentheses) by age category in the full PK/PD data file, and in the PK/PD analysis data selection.*
Source: Table 7 in Report CL0428 external validation

Age category	*Full CL0428 PK/PD data file*	*PK/PD analysis data selection*
1 month-<2 years	4718 (29)	4571 (29)
2 years-<4 years	1468 (8)	1443 (8)
4 years-<18 years	29249 (171)	28041 (171)
Overall	35435 (208)	34055 (208)

Records are restricted to a maximum of 180 days since first dose

The distribution of individual change from baseline estimates for POS and all seizure types are provided in **Figure 7**.

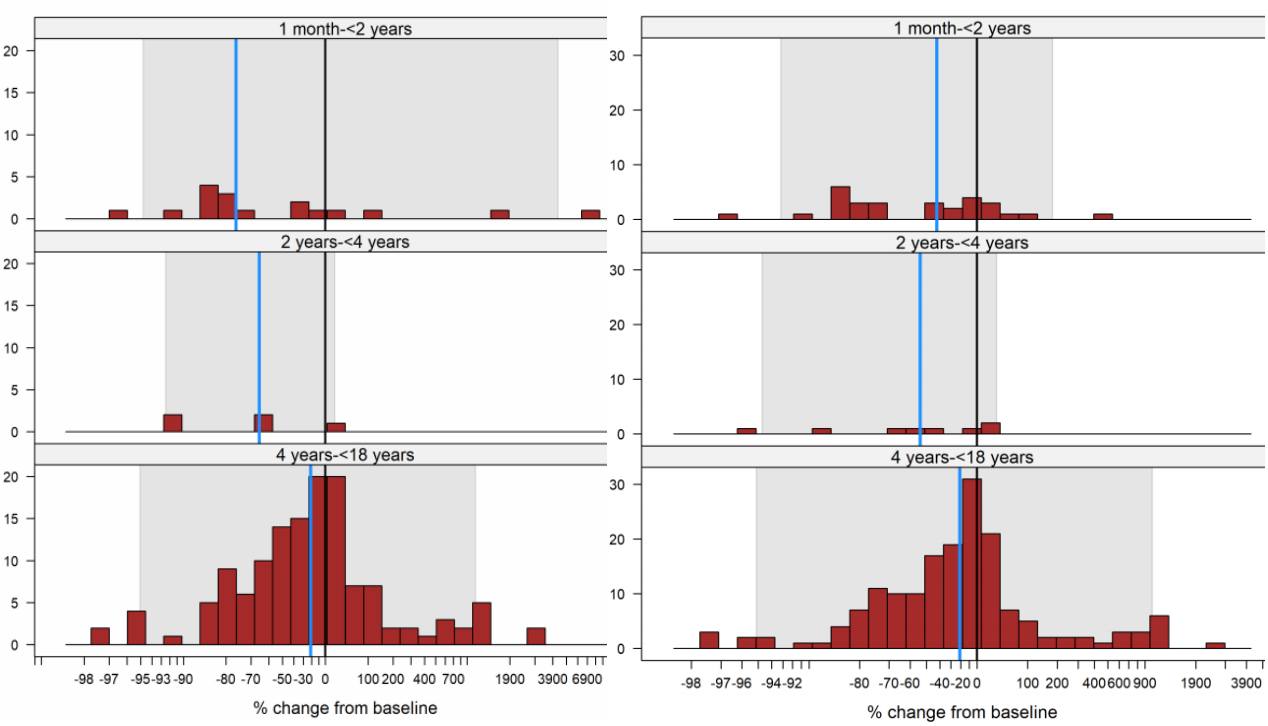


Figure 7: *Distribution of % change from baseline in seizure frequency for paediatric patients with POS (left figure) and all seizures types (right figure), split by age category.*
Source: Figures 15 and 16 in Report CL0428 external validation

Blue line: median change, grey area: 95% of patients.
POS: *Percentage of 50% responders < 2 years: 58.8% (N=10 out of 17), percentage of 50% responders 2-<4 years: 80.0% (N=4 out of 5), percentage of 50% responders ≥4 years: 29.2% (N=40 out of 137).*
All seizure types: *Percentage of 50% responders < 2 years: 48.3% (N=14 out of 29), percentage of 50% responders 2-<4 years: 50.0% (N=4 out of 8), percentage of 50% responders ≥4 years: 29.8% (N=51 out of 171).*

Results

The developed adult/paediatric LEV PK/PD model described seizure frequencies using a negative binomial distribution for the seizure count data and an E_{max} model to describe the relation between change in seizure count and average daily concentrations of LEV. LEV PD data indicated that the lower age group (<4 years) was more severely ill compared to the previous paediatric group (> 4 years), as evidenced by much higher baseline seizure frequencies, with median values of 10.1 seizures/day and 0.75 seizures/day, respectively. The differences in baseline seizure counts between adults and paediatrics were accounted for in this model. A mixture model approach was included to separate a placebo (PBO)–like (i.e. non-responder) and a responder subpopulation. According to the MAH, the analysis showed that in study participants aged ≥1 month to < 4 years the same exposure to LEV as in older study participants resulted in the same clinical efficacy.

The structure of the popPK/PD model for BRV was similar to the model used for LEV. The adult parameter estimates were used from the existing adult BRV popPK/PD model. A LEV scaling factor from adults to paediatrics and adult estimated LEV basal seizure rate values were included in the BRV PK/PD model to take into account the differences in seizure frequency between adults and paediatrics.

In the external validation, the typical baseline seizure count in the BRV PK/PD model was updated to the median baseline seizure count for the 1 month-4 years age group in studies N01263/N01266, and therefore no LEV scaling factor was used. The simulated and observed median percentage change in seizure frequency from baseline are shown in **Figure 8**. Change from baseline was determined by subtracting the logarithm of the average daily seizure count during treatment (over a maximum of 180 days) from the logarithm of the average daily seizure count during baseline, and the result was back-transformed to a percentage change estimate.

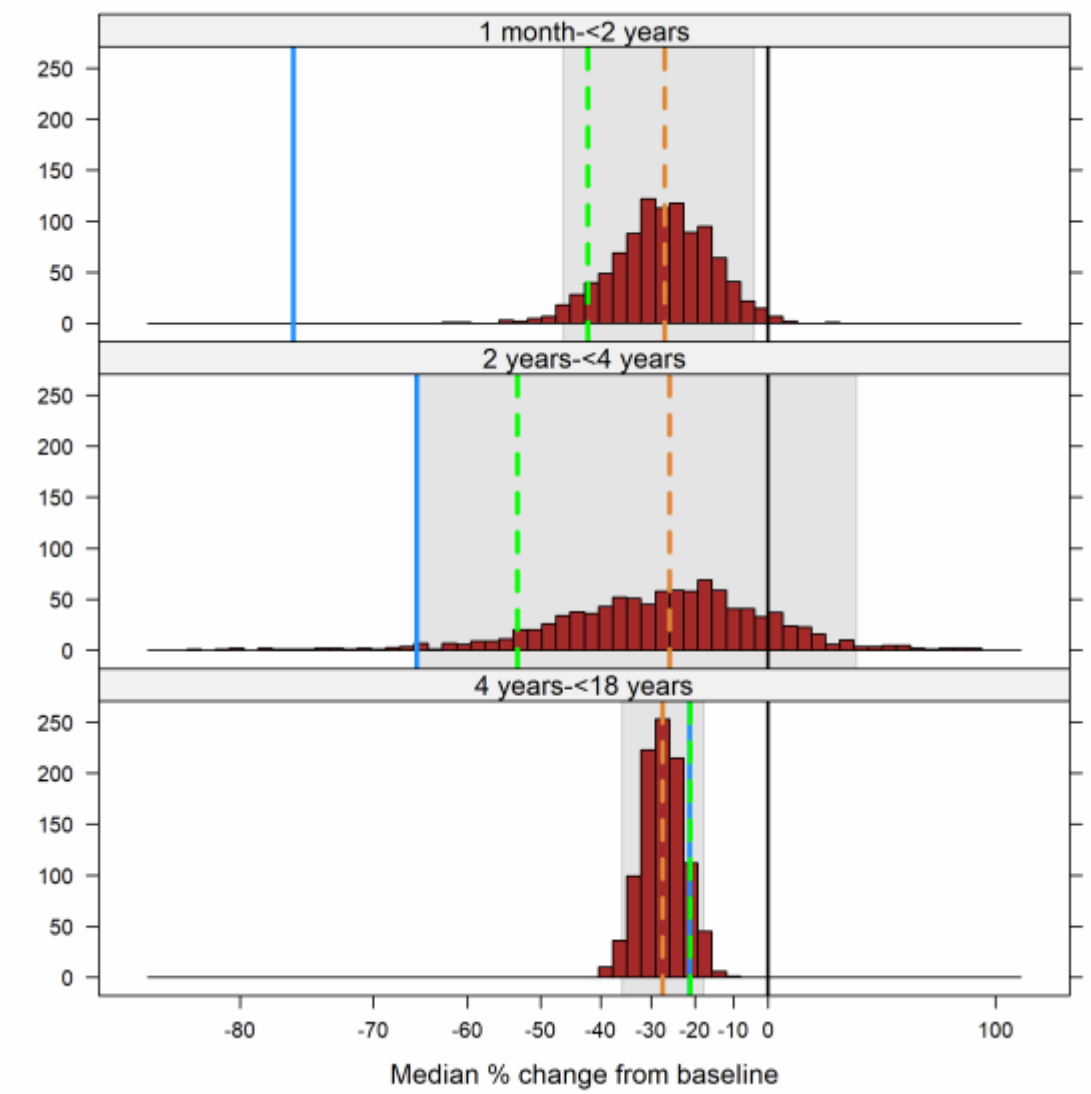


Figure 8: *VPC for median % change in seizure frequency from baseline for all paediatric patients with POS Source: Figures 17 in Report CL0428 external validation*

Blue line: median observed change in POS from baseline
Green dashed line: median observed change in all seizures from baseline
Dotted orange line: median simulated change from baseline across 1000 simulated trials
Grey area: 95% of simulated trial outcomes.

PK and PD simulations for BRV were performed in children for a range of mg/kg doses to predict BRV effect in paediatric subjects.

2.4.4. Discussion on clinical pharmacology

This variation concerns the extension of the current approved indication to include the use of BRV as adjunctive therapy in patients ≥1 month to <4 years of age with POS. The proposed indication covers the use of currently available BRV formulations: film-coated tablets, oral solution and solution for IV injection.

The MAH has performed population PK and PK/PD modelling to support the extrapolation of efficacy between adults and paediatrics (≥1 month to <4 years). There are some limitations in the population PK/PD modelling and therefore it cannot be used to support the extrapolation of efficacy to children ≥1 month to <4 years. Extrapolation of efficacy from adults to children above 2 years of age based on similar exposure may be considered adequate due to the similarity of disease between adults and children in combination

with safety data. The extrapolation of efficacy from adults to paediatric patients ≥1 month to <2 years of age cannot be supported.

The proposed therapeutic dose ranges are 1-4 mg/kg/day (recommended maintenance dose 2 mg/kg/day) for children weighing ≥20 to <50 kg, 1-5 mg/kg/day (recommended maintenance dose 2.5 mg/kg/day) for children weighing ≥10 to <20 kg and 1.5-6 mg/kg/day (recommended maintenance dose 3 mg/kg/day) for children weighing ≥3 to <10 kg. The MAH stated that the proposed dosing regimen results in BRV steady state plasma concentrations in the range of adults (≥16 years of age) receiving BRV 50 to 200 mg/day, based on population PK simulations.

Population PK analysis

PK samples were collected in paediatrics in studies N01263 (included in the initial extension application), EP0065 and in the ongoing LTFU study N01266.

The previous paediatric population PK model was updated with the exposure data in study N01266. The data used in the population PK analysis were restricted to a treatment period of up to 180 days, which was also the main reason for data exclusions. A sensitivity analysis was performed by re-estimating the final updated model with inclusion of concentrations measured after 180 days of dosing. The analysis indicated no greater differences in population PK results between the two models and therefore the exclusion of these observations is acceptable.

Less than 4% of the observations were considered outliers in study N01266 and were excluded from the analysis, which is considered acceptable.

Body weight was included as a covariate on V and CL, using fixed allometric constants. The model could reasonably well describe the BRV PK data in children aged ≥2 month to < 4 years (the youngest child, included in the analysis, was 2 months old). Age related maturation of BRV CL was investigated 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. According to the MAH, this finding could be due to either CL being fully mature at birth, or that the data were insufficient to detect a relationship between CL and PCA.

It is noted that the interindividual variability in k_a is very small, which is unexpected. However, this is not considered to have any greater impact on the results from the PK analysis.

In general, the pcVPC seemed adequate across different weight and age groups and there were no indications of model misspecifications in the goodness of fit plots. The model seem to adequately describe the observed concentration-time profiles.

The previous paediatric population PK model included effects of AED coadministration (PB, CBZ and VPA) on BRV CL. In the updated model, PB and CBZ still induced BRV CL, but VPA coadministration was no longer significant. In accordance with the SmPC recommendations for children ≥4 years and adults, these covariate effects are not considered clinically relevant and therefore no dose adjustments are needed based on coadministration with PB, CBZ, VPA or PHT.

The MAH associated the increased CL in young children with the frequent use of phenobarbital. However, covariate effects based on a small sample size should be interpreted with caution, especially interactions since both substances could be influence by age (maturation) effects not accounted for.

Exposure ranges based on predicted steady state concentrations from individual CL values are considered acceptable due to an adequate population PK model and moderate parameter shrinkage (24%) in individual CL estimates. The eta-shrinkage was high for Vc and Ka, for which reason these parameters cannot be used for individual predictions of exposure.

Population PK/PD analysis

To support the assumption of a similar PK/PD relationship for BRV between the adults and paediatrics, PK/PD modelling of LEV adult/paediatric data was included in this application. LEV and BRV interact with the same target protein (SV2A), and therefore it was assumed that the exposure-response relationship between adults and paediatrics would be similar between these compounds. The LEV analysis indicated that paediatric data could be described using the adult PK/PD parameters, and that the only difference was in the basal seizure frequency. The results from the LEV modelling were used to support the scaling of the existing adult BRV PK/PD model into children.

The BRV adult/paediatric model was externally validated by comparing simulated and observed effect data (seizure counts) in study N01263 and N01266. Although there were limited number of paediatrics, the simulations indicated that the model underestimated the effect on seizures in the younger age groups, especially in children < 4 years of age. For paediatric patients ≥4 years of age, the model could reasonably well describe the effect. Due to the limitations in the external validation, the PK/PD model cannot be used to support this extension. It is noted that the observed effect on seizure counts in the paediatrics included in the BRV PK/PD analysis seems to be different from the effect reported in the clinical studies N01266 and N01263. Due to the limited value of the PK/PD analysis, it has not been assessed in detail.

Simulations to support dose selection

If extrapolation of efficacy from adults to paediatrics ≥1 month of age is considered acceptable, the posology in paediatrics aged ≥ 1 month to <4 years can be supported by a similar exposure in children as compared to adults at therapeutic doses. Since Briviact is indicated for adjunctive therapy in the treatment of POS with or without secondary generalisation, the simulations for BRV with concomitant AEDs are the most relevant for this application.

The simulations indicated higher oral C_{max} values and average concentration over 24h (C_{av}) of BRV at steady state in paediatrics at the maximum proposed doses (3 mg/kg bid for weight<10 kg and 2.5 mg/kg bid for weight ≥10 kg and <20 kg) as compared to adults receiving the maximum recommended flat dose of 100 mg bid. The simulated C_{max} should be interpreted with caution due to the sparse sampling which limits the characterization of the absorption phase. The C_{min} seemed slightly lower in paediatrics aged ≥1 month to <4 years as compared to adults.

The simulations also indicated that if the maximum doses are reduced, there is a higher risk that the children might be underdosed. The highest dose of 3 mg/kg bid (6 mg/kg/day) in children weighing ≥3-<10 kg, which is higher than the maximum dose (5 mg/kg/day) used in study N01266, was also justified from a safety perspective. Based on the limited number of data, the safety profile of BRV in paediatric patients who received oral BRV modal doses >5 mg/kg/day (n=10, most doses close to 5 mg/kg/day) seemed similar to those who received modal doses ≤5mg/kg/day, with predominant TEAEs related to infections and considered as not related. No safety signal was identified. In addition, since the C_{av} is not expected to exceed that in children ≥ 4 years, it is unlikely that there would be a different safety profile. The neurologists are also used to titrate the dose of anti-epileptic drugs to find the lowest dose providing an adequate efficacy and acceptable safety profile.

Regarding the proposed IV posology, the MAH clarified that bioequivalence of the IV and oral formulations of BRV has been discussed in the previously submitted paediatric extension application, where it was concluded that no dose adjustment was needed in adults and in paediatric patients ≥4 years of age when switching between oral and iv dosing.

To support the IV posology, the oral paediatric population PK model was updated by including IV data from the paediatric study EP0065. Only limited information was given about the model. However, the model will not be further assessed since it could not be used to simulate C_{max} (due to the sparse sampling). Regarding C_{av}, it is agreed that comparable C_{av} is expected after administration of the same iv and oral dose, which also seemed to be supported by this model.

A higher IV C_{max} is however expected at similar oral and IV doses. This might be a concern since the oral C_{max} in paediatrics seemed to slightly exceed the adult exposure range at the proposed maximum doses. The maximum IV dose in study EP0065 (4.6 mg/kg/day) was also lower than the proposed maximum IV dose (6 mg/kg/day). As discussed above, a lower maximum dose might result in that more subjects are being underdosed and therefore is not supported. With regards to the expected higher IV C_{max}, the MAH provided treatment-emergent adverse event (TEAE) data from study EP0065, which together with the fact that IV infusions occur only in a hospital setting, where subjects are already closely observed, support that no additional monitoring is needed during IV administration. In addition, there is no risk of cardiac arrythmias or AV block after IV administration of BRV.

2.4.5. Conclusions on clinical pharmacology

The extrapolation of efficacy from adults to paediatric patients ≥1 month to <2 years of age cannot be supported. The proposed posology of BRV in children above 2 years of age is supported by population PK modelling and simulations with the aim to match adult reference exposure levels. It is agreed that the proposed dosing recommendation in paediatric patients match the exposure of the adult patients.

2.5. Clinical efficacy

Background

The MAH sought CHMP scientific advice and received feedback from the CHMP regarding UCB's proposed strategy (EMEA/H/SA/681/11/2020/PA/PED/III) to extrapolate efficacy from data in adults receiving BRV as adjunctive treatment. Efficacy will be extrapolated from data in adults and children receiving adjunctive LEV and efficacy data from adults receiving BRV as adjunctive treatment using the exposure-response modeling study CL0428. In addition, the extrapolation model has been externally validated using seizure count data paediatric patients with POS and generalized seizures collected in studies from N01263 and N01266 to consider all available BRV clinical data in response to the CHMP advice. The MAH has provided further information and discussion regarding the similarities and dissimilarities between the mode of action and age-related responses of BRV and LEV. Because the primary mechanism is similar and LEV did not show any age-related change in response, it is unlikely that BRV would show an age-related change in response for the following reasons:

- BRV's primary MoA is similar to LEV, and LEV did not show any age-related change in response.
- BRV is highly selective for SV2A and does not have another known MoA.

Efficacy extrapolation was considered acceptable by the PDCO in the frame of the PIP request for modification EMEA-000332-PIP01-08-M06 with some caveats that were also raised by the CHMP.

2.5.1. Main studies

Study N01263 (previously submitted and reviewed in the previous paediatric extension of indication, only summarised below)

A phase 2a, open-label, single-arm, multicenter, fixed 3-step up-titration study in participants aged between ≥1 month and <16 years with epilepsy evaluating the PK, safety, and efficacy of BRV

Enrollment was stratified by age group (at least 30 infants and toddlers [28 days to 23 months]; at least 30 paediatric participants [2 to 11 years]; and a maximum of 30 adolescents [12 to <16 years]) to ensure that a substantial number of participants were included in each category.

All participants completed a 1-week Baseline Period, followed by a 3-week Evaluation Period with weekly fixed 3-step up-titration of the BRV dose. Participants may have been eligible for conversion to a LTFU study (N01266) upon completion of at least the lowest dose level (DL) of the Evaluation Period. Participants not choosing the option to enter N01266 or participants discontinuing due to not being able to tolerate the lowest BRV dose or due to other reasons entered a Down-Titration Period of up to 2 weeks followed by a 2-week study drug-free Safety Period and a final Safety Visit.

BRV oral solution was administered at weekly increasing doses of approximately 0.4mg/kg, 0.8mg/kg, and 1.6mg/kg bid for participants ≥8 years of age, and 0.5mg/kg, 1.0mg/kg, and 2.0mg/kg bid for participants <8 years of age.

Primary objectives

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.

Secondary objectives

- To document the short-term safety and tolerability of BRV
- To gain preliminary information on the efficacy of BRV in paediatric subjects with various epileptic syndromes
- To assess compliance to study drug oral solution

Efficacy endpoints:

- For study participants <2 years of age: shift from baseline to the end of the evaluation Period for seizure freedom based on the 24-hour EEG
- For study participants ≥2 years of age: responder rate based on 50% reduction from Baseline to the end of the Evaluation Period for the number of seizure days standardized to a 28-day duration based on the daily record card (DRC) data

Exploratory efficacy variables for seizure data collected on DRC (for study participants greater than or equal to 2 years of age)

- Number of seizure days over the Evaluation Period standardized to a 28-day duration
- Absolute and percentage reduction from Baseline to the end of the Evaluation Period in the number of seizure days standardized to a 28-day duration
- Categorized percentage reduction from Baseline to the end of the Evaluation Period for the number of seizure days standardized to a 28-day duration (<-25%, -25% to <25%, 25% to <50%, 50% to <75%, 75% to <100%, and 100%)
- Seizure freedom rate over the Evaluation Period
- Proportion of seizure-free days over the Evaluation Period

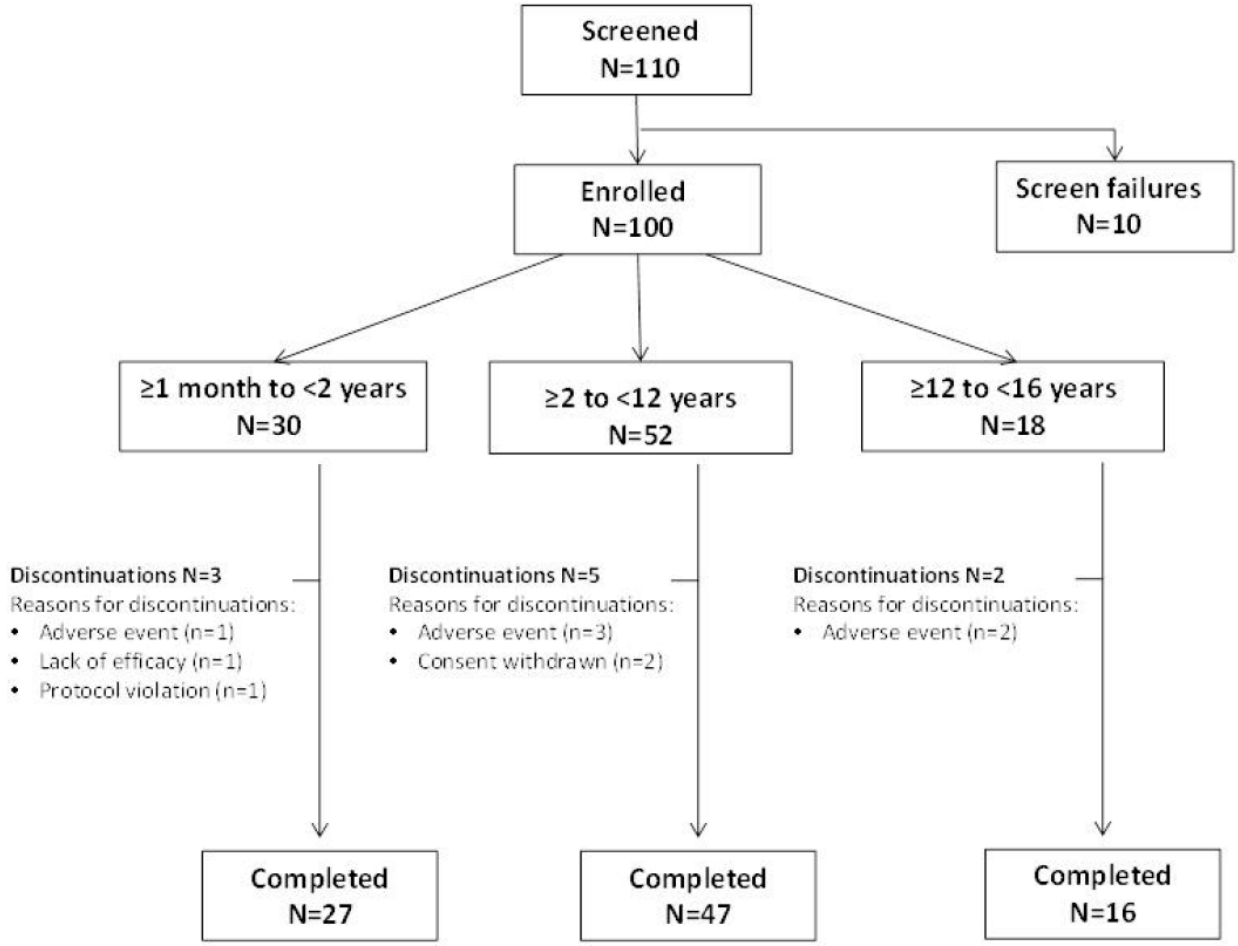
For subjects ≥1 month to <2 years of age, a subject was defined as seizure free based on the 24-hour EEG over the Evaluation Period if the presence of an EEG seizure was recorded as "no" at the V5/EDV assessment.

Efficacy analyses based on DRC or EEG data were performed using the full-analysis set (FAS) population.

Age groups presented

- ≥1 month to <2 years of age
- ≥2 to <12 years of age
- ≥12 to <16 years of age

Figure 9: *Flowchart of subject disposition*



Data sources: Table 1.1, Table 1.2

Table 12: *Baseline epileptic characteristics (SS)*

Characteristic	Descriptive statistic	≥1 month to <2 years N=30	≥2 to <12 years N=51	≥12 to <16 years N=18	All subjects N=99
History of status epilepticus	n (%)	1 (3.3)	4 (7.8)	0	5 (5.1)
Epilepsy duration (years)[a]	n	30	51	18	99
	Mean (SD)	0.65 (0.44)	4.09 (2.67)	7.95 (4.77)	3.75 (3.73)
	Min, Max	0.027, 1.522	00.063, 11.515	0.375, 14.897	0.027, 14.897
Age at time of first seizure (years)	n	30	51	18	99
	Mean (SD)	0.48 (0.43)	2.56 (2.82)	5.83 (4.43)	2.53 (3.29)
	Min, Max	0.003, 1.774	0.003, 10.982	0.003, 12.676	0.003, 12.676
Epileptic seizure profile (type)[b]					
Partial onset seizures (I)	n (%)	18 (60.0)	35 (68.6)	13 (72.2)	66 (66.7)
Simple partial (IA)	n (%)	5 (16.7)	11 (21.6)	2 (11.1)	18 (18.2)
Complex partial (IB)	n (%)	9 (30.0)	27 (52.9)	9 (50.0)	45 (45.5)
Partial evolving to secondary generalized (IC)	n (%)	10 (33.3)	23 (45.1)	6 (33.3)	39 (39.4)
Generalized seizures (II)	n (%)	14 (46.7)	24 (47.1)	9 (50.0)	47 (47.5)
Absence (IIA1)	n (%)	0	3 (5.9)	4 (22.2)	7 (7.1)
Atypical absence (IIA2)	n (%)	0	9 (17.6)	3 (16.7)	12 (12.1)
Myoclonic (IIB)	n (%)	8 (26.7)	9 (17.6)	5 (27.8)	22 (22.2)
Clonic (IIC)	n (%)	1 (3.3)	3 (5.9)	1 (5.6)	5 (5.1)
Tonic (IID)	n (%)	8 (26.7)	8 (15.7)	3 (16.7)	19 (19.2)
Tonic-clonic (IIE)	n (%)	2 (6.7)	11 (21.6)	3 (16.7)	16 (16.2)
Atonic (IIF)	n (%)	0	10 (19.6)	1 (5.6)	11 (11.1)
Unclassifiable (III)	n (%)	3 (10.0)	2 (3.9)	1 (5.6)	6 (6.1)

Max=maximum; Min=minimum; SD=standard deviation; SS=Safety Set
Note: Subjects could have been counted in more than 1 category.
[a] Relative to the date of first diagnosis.
[b] Seizures experienced at any time prior to study entry are summarized.
Data sources: Table 5.1, Table 5.3

Table 13: *Baseline classification of epileptic syndromes (SS)*

Classification	Descriptive statistic	≥1 month to <2 years N=30	≥2 to <12 years N=51	≥12 to <16 years N=18	All subjects N=99
Localization-related	n (%)	15 (50.0)	26 (51.0)	10 (55.6)	51 (51.5)
Idiopathic	n (%)	1 (3.3)	1 (2.0)	0	2 (2.0)
Childhood epilepsy with occipital paroxysms	n (%)	0	1 (2.0)	0	1 (1.0)
Cryptogenic or Symptomatic	n (%)	14 (46.7)	25 (49.0)	10 (55.6)	49 (49.5)
Temporal lobe epilepsy	n (%)	4 (13.3)	18 (35.3)	2 (11.1)	24 (24.2)
Frontal lobe epilepsy	n (%)	9 (30.0)	10 (19.6)	5 (27.8)	24 (24.2)
Occipital lobe epilepsy	n (%)	2 (6.7)	4 (7.8)	1 (5.6)	7 (7.1)
Parietal lobe epilepsy	n (%)	1 (3.3)	3 (5.9)	2 (11.1)	6 (6.1)
Generalized	n (%)	11 (36.7)	21 (41.2)	8 (44.4)	40 (40.4)
Idiopathic	n (%)	1 (3.3)	6 (11.8)	5 (27.8)	12 (12.1)
Childhood absence epilepsy	n (%)	0	2 (3.9)	0	2 (2.0)
Juvenile absence epilepsy	n (%)	0	0	2 (11.1)	2 (2.0)
Juvenile myoclonic epilepsy	n (%)	0	0	1 (5.6)	1 (1.0)
Other generalized idiopathic epilepsies not defined above	n (%)	1 (3.3)	4 (7.8)	3 (16.7)	8 (8.1)
Cryptogenic or Symptomatic	n (%)	7 (23.3)	10 (19.6)	3 (16.7)	20 (20.2)
Infantile spasms[a]	n (%)	5 (16.7)	1 (2.0)	0	6 (6.1)
Lennox-Gastaut syndrome	n (%)	1 (3.3)	6 (11.8)	2 (11.1)	9 (9.1)
Epilepsy with myoclonic-astatic seizures	n (%)	0	1 (2.0)	1 (5.6)	2 (2.0)
Epilepsy with myoclonic absences	n (%)	0	2 (3.9)	0	2 (2.0)

Table 14: *Summary of prior AEDs used by at least 10% of all subjects (SS)*

WHO-DRL Preferred drug name	≥1 month to <2 years N=30 n (%)	≥2 to <12 years N=51 n (%)	≥12 to <16 years N=18 n (%)	All subjects N=99 n (%)
At least 1 prior AED	**25 (83.3)**	**46 (90.2)**	**16 (88.9)**	**87 (87.9)**
Valproic acid	10 (33.3)	28 (54.9)	7 (38.9)	45 (45.5)
Levetiracetam	6 (20.0)	30 (58.8)	7 (38.9)	43 (43.4)
Topiramate	1 (3.3)	22 (43.1)	8 (44.4)	31 (31.3)
Carbamazepine	5 (16.7)	16 (31.4)	3 (16.7)	24 (24.2)
Vigabatrin	10 (33.3)	8 (15.7)	3 (16.7)	21 (21.2)
Lamotrigine	1 (3.3)	15 (29.4)	4 (22.2)	20 (20.2)
Clonazepam	1 (3.3)	13 (25.5)	5 (27.8)	19 (19.2)
Clobazam	1 (3.3)	12 (23.5)	3 (16.7)	16 (16.2)
Phenobarbital	4 (13.3)	10 (19.6)	1 (5.6)	15 (15.2)
Oxcarbazepine	1 (3.3)	9 (17.6)	3 (16.7)	13 (13.1)

AED=antiepileptic drug; SS=Safety Set; WHO-DRL=World Health Organization Drug Reference List
Note: Prior AEDs were AEDs taken at any time prior to study entry and discontinued prior to study entry.
Note: WHO-DRL Version Jun/2012 was used.
Data source: Table 6.3

Table 15: *Summary of concomitant AEDs used by at least 10% of all subjects (SS)*

WHO-DRL Preferred drug name	≥1 month to <2 years N=30 n (%)	≥2 to <12 years N=51 n (%)	≥12 to <16 years N=18 n (%)	All subjects N=99 n (%)
≥1 and ≤3 concomitant AEDs	**30 (100)**	**51 (100)**	**18 (100)**	**99 (100)**
Valproic acid	17 (56.7)	24 (47.1)	10 (55.6)	51 (51.5)
Topiramate	7 (23.3)	18 (35.3)	2 (11.1)	27 (27.3)
Lamotrigine	1 (3.3)	11 (21.6)	5 (27.8)	17 (17.2)
Clobazam	4 (13.3)	8 (15.7)	2 (11.1)	14 (14.1)
Phenobarbital	10 (33.3)	3 (5.9)	1 (5.6)	14 (14.1)
Oxcarbazepine	3 (10.0)	4 (7.8)	6 (33.3)	13 (13.1)

AED=antiepileptic drug; SS=Safety Set; WHO-DRL=World Health Organization Drug Reference List
Note: WHO-DRL Version Jun/2012 was used.
Note: Only AEDs ongoing at the time of study entry were summarized.
Data source: Table 6.6

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, the open-label design of the study, and the short duration of BRV treatment (3 weeks overall; 1 week at each dose). Discussion of seizure type and syndrome analyses was limited based on the small number of subjects available in each subgroup; data for seizure types and syndromes (occurring in at least 3 subjects) are provided in the tables and listings. A minimum baseline seizure count was not required for study entry; therefore, subjects who did not report baseline seizures (n=20) could not be included in any of the percent change analyses.

Efficacy results

Subjects ≥1 month to <2 years of age

Table 16: *Seizure freedom based on 24-hour EEG data overall and by seizure category for subjects greater than or equal to 1 month to less than 2 years of age (FAS)*

	V5/EDV N=26	
	Seizure free n (%)	Not seizure free n (%)
Seizure freedom at Baseline		
Seizure free	9 (34.6)	2 (7.7)
Not seizure free	5 (19.2)	10 (38.5)
Seizure freedom by seizure category at Baseline		
Partial onset seizures		
Seizure free	4 (15.4)	1 (3.8)
Not seizure free	2 (7.7)	5 (19.2)
Primary generalized seizures		
Seizure free	5 (19.2)	1 (3.8)
Not seizure free	3 (11.5)	5 (19.2)

EDV= Early Discontinuation Visit; EEG=electroencephalogram; FAS=Full Analysis Set; V=Visit
Note: Summary only included subjects ≥1 month to <2 years of age. Percentages are based on the number of subjects ≥1 month to <2 years of age with 24-hour EEG data available at Baseline and V5/EDV.
Data sources: Table 8.1, Table 8.1.1.

Seizure status (seizure free/not seizure free) for subjects ≥1 month to <2 years of age, based on 24-hour EEG data, did not change from Baseline to V5/EDV for most subjects overall or by seizure category (POS and primary generalized seizures [PGS]). A total of 5 subjects (19.2%) who were not seizure free at baseline were seizure free based on a 24-hour EEG at V5/EDV. This included 2 subjects (7.7%) with POS and 3 subjects (11.5%) with PGS. Two subjects (7.7%) who were seizure free at baseline were not seizure free at V5/EDV (1 subject [3.8%] each with POS and PGS).

Table 17: *Responder rate during the Evaluation Period based on seizure diary data overall and by age and seizure category (FAS)*

Age group **Responder category**	**n (%)**
All subjects	
Responders, overall (N=80)	17 (21.3)
Responders with partial onset seizures (N=35)	11 (31.4)
Responders with primary generalized seizures (N=45)	6 (13.3)
≥1 month to <2 years	
Responders, overall (N=27)	4 (14.8)
Responders with partial onset seizures (N=12)	3 (25.0)
Responders with primary generalized seizures (N=15)	1 (6.7)
≥2 years to <12 years	
Responders, overall (N=41)	9 (22.0)
Responders with partial onset seizures (N=19)	7 (36.8)
Responders with primary generalized seizures (N=22)	2 (9.1)
≥12 years to <16 years	
Responders, overall (N=12)	4 (33.3)
Responders with partial onset seizures (N=4)	1 (25.0)
Responders with primary generalized seizures (N=8)	3 (37.5)

FAS=Full Analysis Set
Note: Responders were defined as subjects with a 50% or greater reduction in the number of seizure days standardized to a 28-day duration based on the daily record card data.
Note: Subjects with a zero seizure count at Baseline were excluded from the analysis as percent change from Baseline could not be calculated.
Data sources: Table 8.2, Table 8.2.1.

Reduction from Baseline to the end of the Evaluation Period in the number of seizure days

The overall mean (±SD) reduction in the number of seizures days (standardized to a 28-day duration) from the Baseline Period to the Evaluation Period was 1.6 days (±6.5 days). The median reduction in the number of seizure days from the Baseline Period to the Evaluation Period was 0.0 days (Table 8.4.1). The overall mean reduction was similar in subjects with PGS (1.7 days [±4.9 days]) and subjects with POS (1.5 days [±7.8 days]); both groups also had similar median reductions (0.0 days).

The overall mean (±SD) reduction in the number of seizures days (standardized to a 28-day duration) from the Baseline Period to the Evaluation Period was highest in ≥1 month to <2 years group (3.2 days [±8.0 days]), compared with the ≥2 to <12 years group, which had the smallest mean reduction (0.7 days [±5.6 days]), and the ≥12 to <16 years group (1.7 days [±5.7 days]).

The median reduction in the number of seizure days from the Baseline Period to the Evaluation Period was 2.0 days for the ≥1 month to <2 years group compared with 0.0 days for the ≥2 to <12 years and ≥12 to <16 years groups.

The overall median percent reduction in the number of seizures days was 4.8% (range: -533% to 100%;). This was due solely to the reduction observed in subjects with POS (13.6%; range: -533% to 100%), as no median percent reduction was observed in subjects with PGS (0.0%; range: -75% to 100%).

Similar to absolute reductions, the greatest median percent reduction in the number of seizure days was observed in the ≥1 month to <2 years group (13.6% [range: -75% to 100%]), compared with the ≥2 to <12 years group, which had no median percent reduction (0.0% [range: -533% to 100%]), and the ≥12 to <16 years group (9.5% [range: -17% to 100%]).

There were too few subjects in seizure categories to make comparisons across age groups.

Table 18: *Number of Seizure Days by Seizure Category Analysis Set: Full Analysis Set*

Category: Partial onset seizures

	Statistic	>=1 Month to <2 Years N=14 n (%)	>=2 to <12 Years N=25 n (%)	>=12 to <16 Years N=9 n (%)	All Subjects N=48 n (%)
Baseline Period	n	14	25	9	48
	Mean	17.2	11.5	6.7	12.3
	SD	11.0	11.1	11.1	11.4
	Median	19.7	8.0	0.0	8.2
	Min	0	0	0	0
	Max	28	28	28	28
Evaluation Period	n	14	25	9	48
	Mean	13.0	10.4	8.0	10.7
	SD	11.0	12.0	10.7	11.4
	Median	14.6	4.0	2.7	5.0
	Min	0	0	0	0
	Max	28	28	28	28
Absolute Reduction	n	14	25	9	48
	Mean	4.2	1.1	-1.3	1.5
	SD	10.3	7.0	4.0	7.8
	Median	4.0	0.0	0.0	0.0
	Min	-21	-21	-11	-21
	Max	28	15	3	28
Percent Reduction	n	12	19	4	35
	Mean	38.0	-1.6	17.7	14.2
	SD	37.9	138.3	33.7	105.0
	Median	23.7	4.8	1.4	13.6
	Min	0	-533	0	-533
	Max	100	100	68	100

Note: Number of seizure days, based on the Daily Record Card, is standardized to a 28-day duration.
Note: Subjects with a zero seizure count at Baseline were excluded from the analysis as percent change from Baseline could not be calculated.
Reference: Listing 4.1.2 and Listings 6.2, 6.3 and 6.4

Category: Primary generalized seizures

	Statistic	>=1 Month to <2 Years N=16 n (%)	>=2 to <12 Years N=25 n (%)	>=12 to <16 Years N=8 n (%)	All Subjects N=49 n (%)
Baseline Period	n	16	25	8	49
	Mean	22.4	18.8	18.1	19.8
	SD	8.6	10.6	7.2	9.5
	Median	26.0	20.0	17.3	22.4
	Min	0	0	8	0
	Max	28	28	28	28
Evaluation Period	n	16	25	8	49
	Mean	20.1	18.5	12.9	18.1
	SD	8.2	10.6	10.0	9.9
	Median	22.5	24.0	10.0	21.6
	Min	3	0	0	0
	Max	28	28	28	28
Absolute Reduction	n	16	25	8	49
	Mean	2.3	0.3	5.1	1.7
	SD	5.6	3.7	5.5	4.9
	Median	0.6	0.0	4.0	0.0
	Min	-3	-7	-1	-7
	Max	20	11	14	20
Percent Reduction	n	15	22	8	45
	Mean	6.1	5.9	32.2	10.6
	SD	29.9	26.6	39.3	31.2
	Median	4.2	0.0	23.8	0.0
	Min	-75	-40	-17	-75
	Max	71	67	100	100

Note: Number of seizure days, based on the Daily Record Card, is standardized to a 28-day duration.
Note: Subjects with a zero seizure count at Baseline were excluded from the analysis as percent change from Baseline could not be calculated.
Reference: Listing 4.1.2 and Listings 6.2, 6.3 and 6.4

Study N01266 LTFU

N01266 is an ongoing Phase 3, open-label, single-arm, multicenter, LTFU study to evaluate the safety and efficacy of BRV in study participants with epilepsy.

Upon enrollment, eligible LTFU study participants entered the Evaluation Period and continued their BRV treatment in accordance with their individualized dose at the completion of their core study. Directly enrolled study participants were screened and participated in up to 3 weeks of an Up-Titration Period. If a DE study participant demonstrated, 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 study participant attended the Entry Visit (EV) and entered the Evaluation Period on that dose. BRV (tablet and oral solution) was administered bid in 2 equally divided doses. All LTFU study participants must have been able to tolerate the minimum BRV dose specified in the core study to be eligible for entry into the Evaluation Period of N01266. All DE study participants must have been able to tolerate at least 1mg/kg/day during the Up-Titration Period prior to entering the Evaluation Period of N01266.

For all study participants enrolled in N01266, the maximum BRV dose was 5.0mg/kg/day (2.5mg/kg bid), not to exceed a dose of 200mg/day for study participants. Study participants received oral solution or oral tablets, as appropriate. Dose adjustments of BRV and/or concomitant AEDs were allowed at any time based on clinical judgment; however, during the Up-Titration Period, dose adjustments for BRV were made only as specified by the protocol.

During the Evaluation Period, Minimal Evaluation Visits and Full Evaluation Visits were performed alternatively every month during the first 3 months and every 3 months thereafter, with a Yearly Evaluation Visit every 12 months.

The interim N01266 CSR (clinical cutoff date of 14 Jan 2020), which includes safety results only, is provided. Preliminary efficacy data from a clinical cutoff date of 14 Jul 2020 are provided.

Methods

Number of daily epileptic seizures, seizure types, intake of concomitant AEDs, AEs were daily recorded on a DRC.

Endpoints

For study participants ≥2 years of age (based on DRC data):

- Absolute change in 28-days adjusted POS frequency from Baseline to the end of the Evaluation Period (study participants with POS only)
- Percent change in 28-days adjusted POS frequency from Baseline to the end of the Evaluation Period (study participants with POS only)
- 50% responder rate for total seizures (all types)

For study participants <2 years of age (based on EEG data [recorded at least 24 hours]) or study participants with typical absence seizures (based on EEG data):

- Absolute change in average daily frequency (ADF) of POS (study participants with POS only)
- Percent change in ADF of POS (study participants with POS only)
- 50% responder rate for total seizures (all types)

Study population

Table 19: *Study participant demographics by age group (SS)*

Variable	Descriptive Statistic	≥1 month to <2 years N=28	≥2 to <4 years N=14	≥4 to <12 years N=141	≥12 to <17 years N=66	All study participants N=249
Age (years)	n	28	14	141	66	249
	Mean (SD)	1.225 (0.499)	2.779 (0.611)	7.682 (2.386)	13.838 (1.287)	8.312 (4.410)
	Median	1.310	2.825	7.630	13.525	8.370
	Min, max	0.27, 1.95	2.01, 3.91	4.04, 11.90	12.00, 16.95	0.27, 16.95
Gender						
Male	n (%)	13 (46.4)	9 (64.3)	80 (56.7)	34 (51.5)	136 (54.6)
Female	n (%)	15 (53.)	5 (35.7)	61 (43.3)	32 (48.5)	113 (45.4)
Racial group						
White	n (%)	21 (77.8)	12 (92.3)	102 (75.0)	49 (74.2)	184 (76.0)
Black	n (%)	0	0	2 (1.5)	2 (3.0)	4 (1.7)
Other	n (%)	6 (22.2)	1 (7.7)	32 (23.5)	15 (22.7)	54 (22.3)
Missing	n (%)	1	1	5	0	7
Ethnicity						
Hispanic or Latino	n (%)	9 (33.3)	1 (7.1)	37 (27.0)	19 (28.8)	66 (27.0)
Not Hispanic or Latino	n (%)	18 (66.7)	13 (92.9)	100 (73.0)	47 (21.2)	178 (73.0)
Missing	n (%)	1	0	4	0	5
Weight (kg)	n	28	14	141	66	249
	Mean (SD)	9.22 (2.52)	13.07 (2.36)	27.01 (11.18)	53.46 (20.96)	31.23 (20.04)
	Median	8.90	12.60	25.00	49.95	26.70
	Min, max	3.6, 15.2	9.5, 17.9	8.5, 84.2	26.2, 156.5	3.6, 156.5
Height (cm)	n	28	14	141	66	249
	Mean (SD)	73.93 (8.54)	89.87 (8.75)	123.92 (16.52)	157.43 (10.41)	125.27 (28.97)
	Median	72.75	87.05	123.00	157.25	127.50
	Min, max	55.0, 90.0	75.5, 110.0	81.0, 160.0	133.0, 181.0	55.0, 181.0

BMI (kg/m^2)	n	28	14	141	66	249
	Mean (SD)	16.600 (2.461)	16.258 (2.472)	16.917 (3.735)	21.184 (6.399)	17.975 (4.831)
	Median	16.183	16.068	16.321	19.218	16.905
	Min, max	11.90, 23.15	13.02, 20.53	9.07, 35.88	12.02, 49.95	9.07, 49.95
BMI category (kg/m^2)						
<18.5	n (%)	21 (75.0)	11 (78.6)	108 (76.6)	26 (39.4)	166 (66.7)
≥18.5 to <25	n (%)	7 (25.0)	3 (21.4)	29 (20.6)	31 (47.0)	70 (28.1)
≥25 to <30	n (%)	0	0	3 (2.1)	5 (7.6)	8 (3.2)
≥30	n (%)	0	0	1 (0.7)	4 (6.1)	5 (2.0)
Head circumference (cm)	n	27	13	133	62	235
	Mean (SD)	43.67 (3.33)	47.02 (3.16)	51.01 (3.31)	53.86 (3.36)	50.70 (4.47)
	Median	44.50	47.00	51.50	53.75	51.50
	Min, max	35.5, 48.0	40.0, 51.0	40.0, 58.0	43.0, 62.0	35.5, 62.0

BMI=body mass index; DE=directly enrolled; LTFU=long-term follow-up; max=maximum; Min=minimum; ScrV=Screening Visit; SD=standard deviation; SS=Safety Set

Note: Percentages were based on the number of study participants, with available data in each category, in the SS.

Note: Baseline assessments were obtained from the Baseline of previous core studies for LTFU study participants and from the N01266 ScrV for DE study participants.

Data source: N01266 EU Efficacy Supplement Table 3.1

Table: Summary of study participant disposition and discontinuation reasons by cohort (SS)

Disposition	≥1 month to <2 years N=28 n (%)	≥2 to <4 years N=14 n (%)	≥4 to <12 years N=141 n (%)	≥12 to <17 years N=66 n (%)	All study participants N=249 n (%)
Completed study	5 (17.9)	2 (14.3)	32 (22.7)	8 (12.1)	47 (18.9)
Ongoing	9 (32.1)	2 (14.3)	34 (24.1)	19 (28.8)	64 (25.7)
Discontinued	14 (50.0)	10 (71.4)	75 (53.2)	39 (59.1)	138 (55.4)
Primary reason for discontinuation					
Adverse event	4 (14.3)	4 (28.6)	15 (10.6)	8 (12.1)	31 (12.4)
Lack of efficacy	3 (10.7)	4 (28.6)	23 (16.3)	6 (9.1)	36 (14.5)
Protocol violation	0	0	2 (1.4)	0	2 (0.8)
Lost to follow up	0	0	3 (2.1)	3 (4.5)	6 (2.4)
Consent withdrawn	3 (10.7)	1 (7.1)	15 (10.6)	7 (10.6)	26 (10.4)
Other	4 (14.3)	1 (7.1)	11 (7.8)	4 (6.1)	20 (8.0)
Unknown	0	0	6 (4.3)	11 (16.7)	17 (6.8)

eCRF=electronic Case Report Form; SS=Safety Set
Note: Percentages were based on the number of study participants in the SS.
Note: Completed study was defined at study termination visit and assessed on eCRF.
Data sources: N01266 EU Efficacy Supplement Table 1.2.1

Efficacy results

Study participants ≥2 years of age

Table 20: *Absolute and percent change in 28-day adjusted POS seizure frequency during Evaluation Period assessed by DRC (participants ≥2 years of age with POS only) (FAS)*

Time period	Absolute change			Percent change		
	N	Mean (SD)	Median (min, max)	N	Mean (SD)	Median (min, max)
Months 1 to 3	134	-41.47 (628.32)	3.90 (-7075.3, 779.3)	105	16.80 (130.50)	51.65 (-759.3, 100.0)
Months 10 to 12	104	27.08 (82.33)	7.31 (-51.3, 779.0)	80	49.11 (84.35)	64.72 (-576.9, 100.0)
Months 22 to 24	96	34.14 (90.72)	11.62 (-35.0, 779.3)	73	65.17 (51.13)	87.27 (-129.4, 100.0)
Overall Evaluation Period	134	-37.52 (628.27)	7.09 (-7075.3, 715.2)	105	26.45 (123.01)	62.92 (-693.7, 100.0)

DRC=daily record card; FAS=Full Analysis Set; max=maximum; min=minimum; POS=partial-onset seizure(s); SAP=statistical analysis plan; SD=standard deviation
Note: Because percent change cannot be calculated for participants with 0 Baseline ADF, n's for absolute change and percent change may differ and do not necessarily capture the same participants.
Note: Seizure category at Baseline according to N01266 SAP Section 3.10.3.
Note: Change is defined as decrease in 28-day adjusted POS frequency compared with Baseline.
Note: EP0065 participants do not provide appropriate Baseline data and are excluded in the planned analyses.
Data source: N01266 EU Efficacy Supplement Table 7.6.2

Overall, participants ≥2 years of age with POS reported a median (minimum, maximum) absolute change in POS frequency from Baseline over the Evaluation Period of 7.09 (-7075.3, 715.2) per 28-day period and a median (minimum, maximum) percent change in POS frequency of 62.92% (-693.7%, 100.0%) per 28-day period. The median absolute changes from Baseline in 28-day adjusted POS frequency were positive for all 3-monthly intervals, supporting that the number of seizures observed at Baseline from DRC was generally maintained or reduced over the course of N01266.

The large median absolute and percent change values during Months 1 to 3 are attributed to a study participant at study entry who had seizure frequency over the Evaluation Period of 8095.3, resulting in the absolute and percent changes from Baseline of -7075.3 and -693.7%, respectively. The study participant received BRV treatment for 106 days before discontinuing the study due to lack of efficacy.

Table 21: *Summary of responder rate during Evaluation Period by seizure category assessed by DRC (all participants ≥2 years of age) (FAS)*

	POS N=156 N_{sub}=134 n (%)	PGS N=48 N_{sub}=33 n (%)	All participants N=204 N_{sub}=167 n (%)
Responders	61 (48.4)	20 (60.6)	81 (50.9)
Nonresponders	65 (51.6)	13 (39.4)	78 (49.1)
Not evaluable	8	0	8

DRC=daily record card; FAS=Full Analysis Set; PGS=primary generalized seizure; POS=partial-onset seizure(s); SAP=statistical analysis plan

Note: Participants with 0 seizures at Baseline and post Baseline are counted as not evaluable. Percentages for responders and nonresponders are based on evaluable participants only.

Note: Seizure category at Baseline according to N01266 SAP Section 3.10.3.

Note: A responder is defined as a participant with a ≥50% reduction in 28-day adjusted seizure frequency compared with Baseline.

Note: EP0065 participants do not provide appropriate Baseline data and are excluded in the planned analyses.

Note: Nsub refers to participants with appropriate Baseline and post-Baseline DRC data for analysis of responder rate.

Data source: N01266 EU Efficacy Supplement Table 7.7.1

Secondary efficacy variables for study participants <2 years of age (based on EEG data)

Table 22: *Absolute and percent change in POS Average daily frequency during Evaluation Period assessed by EEG (participants <2 years of age with POS only) (FAS)*

Time period	Absolute change			Percent change		
	N	Mean (SD)	Median (min, max)	N	Mean (SD)	Median (min, max)
MEV Month 3	7	2.86 (4.49)	0.00 (0.0, 12.0)	3	97.44 (4.44)	100.00 (92.3, 100.0)
FEV Month 6	7	2.29 (4.86)	0.00 (0.0, 13.0)	2	100.00 (0.00)	100.00 (100.0, 100.0)
Overall Evaluation Period	8	2.56 (4.44)	0.00 (0.0, 12.5)	3	98.72 (2.22)	100.00 (96.2, 100.0)

ADF=average daily frequency; EEG=electroencephalography; FAS=Full Analysis Set; max=maximum; FEV=Full Evaluation Visit; MEV=Minimal Evaluation Visit; min=minimum; POS=partial-onset seizure(s); SAP=statistical analysis plan; SD=standard deviation

Note: Because percent change cannot be calculated for participants with 0 Baseline ADF, n's for absolute change and percent change may differ and do not necessarily capture the same participants.

Note: Seizure category at Baseline according to N01266 SAP Section 3.10.3.

Note: Change was defined as decrease in POS ADF compared with Baseline.

Note: EP0065 and N01349 participants do not provide appropriate Baseline data and are excluded in the planned analyses.

Data source N01266 EU Efficacy Supplement Table 7.1.2.1

Table 23: *Summary of responder rate during Evaluation Period by seizure category assessed by EEG (all participants <2 years of age) (FAS)*

	POS N=40 N_{sub}=8 n (%)	PGS N=46 N_{sub}=6 n (%)	All participants N=86 N_{sub}=14 n (%)
Responders	4 (100)	2 (50.0)	6 (75.0)
Nonresponders	0	2 (50.0)	2 (25.0)
Not evaluable	4	2	6

ADF=average daily frequency; EEG=electroencephalography; FAS=Full Analysis Set; PGS=primary generalized seizure; POS=partial-onset seizure(s); SAP=statistical analysis plan
Note: Participants with 0 seizures at Baseline and post Baseline are counted as not evaluable. Percentages for responders and nonresponders are based on evaluable participants only.
Note: Seizure category at Baseline according to N01266 SAP Section 3.10.3.
Note: A responder is defined as a participant with a ≥50% reduction in ADF compared with Baseline.
Note: EP0065 and N01349 participants do not provide appropriate Baseline data and are excluded in the planned analyses.
Note: Nsub refers to participants with appropriate Baseline and post-Baseline EEG data for analysis of responder rate.
Data source: N01266 EU Efficacy Supplement Table 7.2.1.1

Overall, 6 participants (75.0% of all evaluable participants <2 years of age) were responders during the Evaluation Period (defined as participants with a ≥50% reduction in ADF, based on the EEG data). This included 4 participants with POS (100% of evaluable participants with POS <2 years of age) and 2 participants with PGS (50.0% of evaluable participants with PGS <2 years of age).

Study EP0065 (IV administration)

A Phase 2, multicenter, open-label study to evaluate the PK, safety, and tolerability of iv BRV administered as a 15-minute iv infusion and an ≥ bolus (up to 2-minute infusion) in study participants ≥1 month to <16 years of age with epilepsy.

The following age-based cohorts (approximately 12 study participants/cohort):

- Cohort 1: ≥12 to <16 years
- Cohort 2: ≥6 to <12 years
- Cohort 3: ≥2 to <6 years
- Cohort 4: ≥1 month to <2 years

Eligible for enrollment:

- OLB participants: currently receiving oral BRV as participants in a long-term, open-label study
- RxB participants: currently receiving prescribed oral BRV from commercial supply
- IOB participants: not currently receiving BRV; first dose of BRV in EP0065 was oral tablet or solution
- IIB participants: not currently receiving BRV; first dose of BRV in EP0065 was by IV infusion

Dose limits:

- For OLB and RxB participants: the maximum BRV dose 5mg/kg/day (rounded)

- For IOB and IIB participants: the maximum BRV dose 4mg/kg/day
- No study participant may receive a dose greater than BRV 200mg/day

Eligibility criteria:

Patients with a diagnosis of epilepsy, aged from ≥1 month to <16 years of age, weight ≥3 kg, and being treated with ≥1 AED (including BRV) without a change of dose regimen for at least 7 days prior to Screening.

PK results

The plasma concentrations were generally higher 15 minutes after dosing as compared to 3 hours after dosing. The geometric mean concentrations were 1903 (n=21) and 1705 ng/mL (n=19) 15 minutes after administration of the first IV infusion and IV bolus, respectively. The interindividual variability (geo CV%) was 61 and 75%. For further information, see section 2.4.2 Pharmacokinetics above.

Safety results

Exposure: Overall mean (SD) study drug exposure during the study was 3.98 (3.24) days (ranging from 1 to 13 days).

Adverse events

Table 24: *TEAEs reported for all study participants (SS-iv)*

MedDRA (Version 18.1)	Age cohort				Infusion duration		All study participants
	≥1 month to <2 years	≥2 to <6 years	≥6 to <12 years	≥12 to <16 years	15-minute infusion	Bolus	
SOC	N=13	N=13	N=12	N=12	N=26	N=24	N=50
PT	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any TEAE	**2 (15.4)**	**6 (46.2)**	**3 (25.0)**	**3 (25.0)**	**8 (30.8)**	**6 (25.0)**	**14 (28.0)**
General disorders and administration site conditions	**0**	**3 (23.1)**	**1 (8.3)**	**0**	**3 (11.5)**	**1 (4.2)**	**4 (8.0)**
Fatigue	0	1 (7.7)	1 (8.3)	0	2 (7.7)	0	2 (4.0)
Pyrexia	0	2 (15.4)	0	0	1 (3.8)	1 (4.2)	2 (4.0)
Infections and infestations	**1 (7.7)**	**1 (7.7)**	**0**	**1 (8.3)**	**1 (3.8)**	**2 (8.3)**	**3 (6.0)**
Ear infection	0	1 (7.7)	0	0	0	1 (4.2)	1 (2.0)
Pharyngitis	0	0	0	1 (8.3)	0	1 (4.2)	1 (2.0)
Upper respiratory tract infection	1 (7.7)	0	0	0	1 (3.8)	0	1 (2.0)
Nervous system disorders	**1 (7.7)**	**2 (15.4)**	**0**	**2 (16.7)**	**3 (11.5)**	**2 (8.3)**	**5 (10.0)**
Dizziness	0	0	0	2 (16.7)	0	2 (8.3)	2 (4.0)
Somnolence	1 (7.7)	2 (15.4)	0	0	3 (11.5)	0	3 (6.0)
Psychiatric disorders	**0**	**1 (7.7)**	**1 (8.3)**	**0**	**1 (3.8)**	**1 (4.2)**	**2 (4.0)**
Aggression	0	1 (7.7)	0	0	0	1 (4.2)	1 (2.0)
Insomnia	0	0	1 (8.3)	0	1 (3.8)	0	1 (2.0)

Respiratory, thoracic, and mediastinal disorders	**1 (7.7)**	**0**	**0**	**0**	**1 (3.8)**	**0**	**1 (2.0)**
Cough	1 (7.7)	0	0	0	1 (3.8)	0	1 (2.0)
Skin and subcutaneous tissue disorders	**0**	**1 (7.7)**	**1 (8.3)**	**0**	**1 (3.8)**	**1 (4.2)**	**2 (4.0)**
Pruritus	0	0	1 (8.3)	0	0	1 (4.2)	1 (2.0)
Rash	0	1 (7.7)	1 (8.3)	0	1 (3.8)	1 (4.2)	2 (4.0)

BRV=brivaracetam; MedDRA=Medical Dictionary for Regulatory Activities; OLB=Open-label BRV; PT=preferred term; RxB=Prescribed BRV; SOC=system organ class; SS-iv=Safety Set-intravenous; TEAE=treatment-emergent adverse event
Note: TEAEs were defined as those events which started on or after the first BRV medication taken during the EP0065 study. In study participants who began the study on BRV treatment (OLB and RxB participants), they were assumed to have taken BRV treatment on the first day of Screening.
Note: n=number of study participants experiencing at least 1 TEAE within the SOC/PT.
Note: Percentages were based on the number of study participants in the SS-iv.
Data source: Table 6.2

Overall, the most common TEAE (by preferred term [PT]) was somnolence (3 study participants [6.0%]), followed by fatigue, dizziness, pyrexia, and rash (2 study participants [4.0%], each) (**Table 24**).

All other TEAEs (by PT) were experienced by ≤1 study participant each.

Incidences of TEAEs were generally similar across age groups. Somnolence was experienced in the 2 youngest age cohorts only (1 [7.7%] and 2 [15.4%] study participants, respectively, in the ≥1 month to <2 years and ≥2 to <6 years age cohorts).

Vital signs

Overall, Systolic blood pressure (SBP) and Diastolic blood pressure (DBP) Baseline values were of no clinical concern for this population. Mean BP at each time point fluctuated; however, there was no obvious trend. In some participants, there were somewhat large decreases from Baseline in both SBP and/or DBP at the time points shortly after infusion at Visit 3; however, these decreases were generally short lived. Mean changes from Baseline for SBP and DBP in the 15-minute infusion and bolus infusion groups were generally consistent across age cohorts.

Supportive non-clinical data

The extension of the indication as adjunctive therapy in the treatment of POS with or without secondary generalization in children≥1 month to <4 years of age with epilepsy is based on:

- For patients ≥2 to <4 years: extrapolation of efficacy from data in adults receiving BRV as adjunctive treatment.
- For patients ≥1 month to <2 years: extrapolation of efficacy from data in adults and children receiving adjunctive LEV, and efficacy data from adults receiving BRV as adjunctive treatment.

BRV and LEV mechanisms of action

BRV is a 2-pyrrolidone derivative with a high and selective affinity for SV2A. LEV and BRV are the only 2 marketed AEDs with binding to SV2A, and both possess an ability to modulate neurotransmitter release. Indeed, electrophysiological field recordings in the rat cornu ammonis (CA)1 area of the hippocampus showed that BRV and LEV had similar effects, inducing or augmenting short-term depression under high frequency stimulation and slowing synaptic vesicle recycling (Yang et al, 2015). The comparison between the BRV and LEV mode of action associated to their receptor binding profile is provided in the table below.

Table 25: *BRV and LEV receptor binding profile (in vitro)*

	BRV	LEV
SV2A (pKi)	7.1	6.1
SV2A (IC_{50} µM)	0.08	0.8
Na^+ channel current (IC_{50} value [µM] and max. effect [%])	7 ~65%	No effect up to 1mM
HVA Ca^{2+} channel current (IC_{50} value [µM]) and max. effect [%])	No effect up to 1mM	13.9 ~35%
LVA Ca^{2+} channel current (IC_{50} value [µM])	No effect up to 1mM	No effect up to 100µM
GABA & glycine currents (IC_{50} value [µM])	No effect up to 100µM	No effect up to 100µM
GABA/glycine Zn^{2+} inhibition ([µM])	Inhibition reversed 3 to 100µM	Inhibition reversed 30 to 100µM

BRV=brivaracetam; GABA=gamma aminobutyric acid; HVA=high-voltage activated; IC_{50}=half maximal inhibitory concentration; LEV=levetiracetam; LVA=low-voltage activated; max=maximal; SV2A=synaptic vesicle protein 2A

The affinity of BRV for SV2A binding is approximately 10- to 30-fold higher than of LEV (Gillard et al, 2011). The major difference between BRV and LEV in terms of MoA is the moderate and varying inhibition of fast Na+ current by BRV (half maximal inhibitory concentration [IC50] around 7µM in rat cortical neurons) and the inhibition of high voltage operated calcium currents by LEV (IC50 of 13.9µM in rat neocortical slices with maximal effect around 35% at ≥100 μ M) (Pisani et al, 2004). LEV was also shown to inhibit α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. However, this inhibition seems to lack antiseizure relevance as it occurred only at a high concentration (from 200µM and upwards) and did not confer LEV an ability to inhibit clonic convulsions induced *in vivo* by AMPA (Margineanu and Klitgaard, 2002).

Inhibition of fast Na+ current by BRV was seen in rat cortical neurons. Subsequent patch clamp studies showed weaker (20 to 30%) inhibition of the Na+ current (mouse neuroblastoma cell line, embryonic rat primary cortical neurons), or no effects (entorhinal cortex neurons from sham and pilocarpine mice, adult mouse CA1 pyramidal neurons, rat hippocampal slices). Furthermore, the inhibition in fast Na+ current seen in rat cortical neurons did not translate in modifications of sustained repetitive firing by BRV, suggesting that the magnitude and consistency of the inhibition of fast Na+ currents is likely not sufficient to be of clinical relevance. Therefore, the main MoA of BRV is believed to be through binding of SV2A.

As mentioned above, LEV also partially inhibits high voltage activated (HVA) calcium currents in cortical neurons, with an IC50 of about 17-fold higher than the SV2A IC50. However, in rat brain slices, dose-dependent inhibition of Ca2+ influx and of induced paroxysmal depolarization shifts (PDSs) occurred at higher concentrations (IC50 of 141 and 180µM, respectively with maximal effect at 300µM). This significantly higher IC50 value for LEV inhibition of PDSs and Ca2+ transients in the slice preparation as compared with the value calculated for the inhibition of Ca2+ currents in the isolated cell preparation was not seen with lamotrigine (LTG). The role of this inhibitory effect of LEV on HVA Ca2+ current on the antiepileptic activity of LEV remains unclear. However, due to lack of validation for inhibition of HVA Ca2+ currents to contribute to antiepileptic effects and a major difference in potency between SV2A binding and

inhibition of HVA Ca2+ current, only binding to SV2A is considered to be the main MoA of LEV. This conclusion is further supported by (S)-stereoisomer homologues of LEV showing a rank order of affinity for (3H)-LEV binding site which correlates with their seizure protection (Noyer et al, 1995). Thus, although the detailed molecular events following binding of LEV or BRV to SV2A is unknown, a significant relation between *in vitro* binding affinity for SV2A and *in vivo* suppression of seizure has been established. These findings are further supported by studies with heterozygous SV2A-deficient mice showing a major reduction in the anticonvulsant activity of LEV when brain levels of SV2A were experimentally diminished but not with non-SV2A binding AEDs, like VPA (Kaminski et al, 2009).

Taken together, these mechanistic studies demonstrate that LEV and BRV share SV2A as the primary mechanism for their antiepileptic effects in epilepsy patients.

Of note, the free plasma exposure reached at the maximal approved human dose (MAHD) for BRV and LEV showed a 15- to 20-fold difference in agreement with the reported 10- to 30-fold higher affinity of BRV for binding to SV2A than LEV.

Table 26: *Free plasma exposure to BRV and LEV at the maximal approved human dose*

MAHD	BRV (100mg bid) [a]	LEV (1500mg bid) [b]
AUC (µg.h/mL) free	44	640
C_{max} (µg/mL) free	2.8	57

[a]: $2xAUC_{0-12}$ at the maximum dose of 100mg bid, i.e. 56µg.h/mL (UCB Study Number N01067); corrected for protein binding of 21% in human.

[b]: $2xAUC_{0-12}$ at the maximum dose of 1500mg bid, i.e. 640µg.h/mL (Epileptic patients study; RRLE97J2301 [N143]); almost no protein binding was seen in human plasma.

BRV and LEV *in vivo* data

The comparison between BRV and LEV in animal models of epilepsy in mice and rats are provided in **Table 27**.

Table 27: *BRV and LEV seizure protection*

Models	Seizure protection, ED_{50} value (mg/kg ip)	
	BRV	LEV
Generalized seizures		
Audiogenic seizures (mice)	2.4	30

Pentylenetetrazole (PTZ) sc (mice)	30	Inactive
Maximal electroshock seizures (mice)	113	Inactive
Absence seizures		
Genetic absence epilepsy rats from Strasbourg (GAERS)	MAD: 2.6	MAD: 5.4
Partial Onset Seizures		
6Hz psychomotor seizures, 44mA (mice)	4.4	19.2
Corneal kindling seizures (mice)	1.2	7.3
Amygdala kindling seizures (rats)	44	571

BRV=brivaracetam; ED_{50}=median effective dose; GAERS=genetic absence epilepsy rats from Strasbourg; ip=intraperitoneal; LEV=levetiracetam; MAD=minimal active dose; PTZ=pentylenetetrazole; sc=subcutaneous

The similarity in primary SV2A mechanism of LEV and BRV manifests itself in a similar activity profile in animal models of acute seizures and chronic epilepsy, a profile that differs markedly from AEDs with other mechanisms. Indeed, both LEV and BRV are the only approved AEDs inactive in the 2 classical screening tests, maximal electroshock and pentylenetetrazol seizure tests, at pharmacologically relevant doses, and the only two AEDs to have demonstrated a sustained inhibition of kindling acquisition, even after cessation of treatment.

A similar activity profile was demonstrated for LEV and BRV in various predictive animal models of chronic epilepsy. These have shown that both LEV and BRV provide broad spectrum seizure protection in models of partial, drug-resistant, and primary generalized epilepsy (Matagne et al, 2008a) and in status epilepticus models (Mazarati et al, 2004).

Similar to LEV, BRV provides protection against secondarily generalized motor seizures in corneally kindled mice with a median effective dose (ED50) of 1.2mg/kg intraperitoneal (ip), against clonic convulsions in audiogenic seizure-susceptible mice (ED50 2.4mg/kg ip) (Matagne et al, 2008a), against 6Hz seizures in mice (ED50 4.4mg/kg ip) (Detrait et al, 2008), and against motor seizure and after discharge duration in fully amygdala kindled rats. The latter finding also extends to fully amygdala kindled mice, resistant to phenytoin. In these animals, LEV has previously been demonstrated to possess relative more potent anticonvulsant properties than any other AED, a finding reproduced by BRV (ED50 68.3mg/kg ip) (Matagne et al, 2008b). Finally, BRV and LEV are amongst the very few AEDs that suppress spike-and-wave discharges in genetic absence epilepsy rats from Strasbourg (Matagne et al, 2008a). Furthermore, testing in the kindling paradigm has shown that chronic treatment with both LEV and BRV inhibits kindling acquisition and reveals a sustained effect, even after cessation of treatment, a feature that also differentiates both from the preclinical profile of any other AED (Loscher and Honack, 1993; Matagne et al, 2008a). In all these models, the potency of BRV is higher than LEV, consistent with a higher affinity for SV2A.

Taken together, comparative studies of LEV and BRV in a variety of animal models of acute seizures and chronic, acquired or genetic epilepsy demonstrate that these two AEDs possess a similar activity profile *in vivo* that differs markedly from the profiles of other AEDs. This is supportive for LEV and BRV sharing SV2A a similar mechanism and activity profile in epilepsy patients.

Modelling approach

The modeling approach aimed to determine weight-based dosing regimens for BRV in patients aged ≥1 month to <2 years and ≥2 years to <4 years. For LEV, PK and PD were available for paediatric participants aged 1 month and above and adults that could be used to derive a PK/PD model for LEV showing that the

same exposure to LEV was required in paediatric participants and in adults to achieve the same level of seizure reduction. Since LEV and BRV share a similar mode of action, ie, by interacting with SV2A, it was assumed that also for BRV an equivalent relation between exposure and reduction in seizure count would hold for all ages ≥1 month as was found for LEV. For BRV, PK data were available for paediatric participants aged 1 month and above, but PD data were lacking; and a PK/PD model in adults was available. This knowledge was subsequently used to derive the paediatric BRV doses that would result in the same exposure, and therefore same efficacy, as in adults.

The population PK/PD model for BRV that was used to simulate the effect on seizure count in these 2 age groups was similar to the model used for LEV.

2.5.2. Discussion on clinical efficacy

Study N01263 was a phase 2a, open-label, single-arm, multicenter, fixed 3-step up-titration study in participants aged between ≥1 month and <16 years with epilepsy evaluating the PK, safety, and efficacy of BRV. All participants completed a 1-week Baseline Period, followed by a 3-week Evaluation Period with weekly fixed 3-step up-titration of the BRV dose.

In the paediatric age interval, N=100 patients were enrolled, and 27/30 in the group ≥1 month to <2 years, 47/52 in the group ≥2 to <12 years, and 16/18 in the group ≥12 to <16 years completed the study. The MAH has not presented any separate data on patients ≥2 to <4 years, as would be relevant for this application for extension of Indication.

The baseline epileptic characteristics, where each subject could be counted in more than 1 category, were as follows: ≥1 month to <2 years age group: 60% had POS, 46.7% had generalized seizures and 10% unclassifiable. In the ≥2 years to <12 years age group: 68.6% had POS, 47.1% had generalized seizures and 3.9% unclassifiable. With regards to baseline classification of epileptic syndromes, in the ≥1 month to <2 years age group 5 patients (16.7%) had infantile spasms and 1 patient (3.3%) had Lennox-Gastaut syndrome. In the ≥2 years to <12 years age group 2 (3.9%) had childhood absence epilepsy, 1 (2.0%) had infantile spasms and 6 patients (11.2%) had Lennox-Gastaut syndrome, 1 (2.0%) had epilepsy with myoclonic-astatic seizures and 2 (3.9%) had epilepsy with myoclonic absences.

Currently, BRV only has the indication POS and thus, for this substance it has not been demonstrated whether primary generalized epilepsy syndromes including syndromes with myoclonic seizures may respond differently to the treatment. Accurately classifying seizures in children can be challenging because of the different manifestations of childhood epilepsy: the younger the child, the greater the likelihood of misinterpretation. Thus, in children, it may be hard to differentiate POS from epileptic syndromes which include seizures with partial onset. However, LEV has the same main MoA via SV2A as BRV and LEV has in addition to the POS indication also the indications of primary generalised tonic-clonic seizures and juvenile myoclonic epilepsy. Given the similarities of these two substances, this may indicate that BRV may also display broader treatment effects in various forms of epilepsy. Thus, the potential risk of a less beneficial treatment effect due to misclassification of the epilepsy type in younger children may be foreseen to be low.

According to the eligibility criteria, subjects should be on treatment with ≥1 to ≤3 concomitant AEDs during the study.

Top 3 most frequent concomitant AEDs during the study in the ≥1 month to <2 years age group: VPA 56.7%, PB 33%, topiramate (TPM) 23.3%. In the ≥2 years to <12 years age group: LEV 58.8%, VPA 54.9%, TPM 43.1%.

EEG or video/EEG is recommended in the EMA Epilepsy guidelines as complementary assessment of efficacy of AEDs in children aged 1 month to less than 4 years. (EMA draft epilepsy guideline (2018): "*In younger*

children, from 1 month to less than 4 years, EEG or video/EEG may complete and evidence the clinical manifestation of seizures, in particular subtle clinical seizures can be confirmed when correlated with EEG." EMA Adopted epilepsy guideline (2010): "*In the very young children (i.e. 1 month – less than 4 years), once efficacy has been shown in the older paediatric population, short term assessment of response by using video EEG monitoring may be sufficient*."

In the subgroup of children aged ≥1 month to ≤2 years, of the 26 patients with available 24-h EEG data both at baseline and at the end of the study, the majority had an unchanged seizure status during the study: 10/26 were neither seizure-free at baseline nor evaluation visit whereas 9/26 were seizure-free at both visits, i.e. 19/26 (73% had a unchanged seizure status on EEG. Of the remaining 7 patients, 5 of the 15 patients that were not seizure free at baseline EEG had become seizure-free on EEG at the end of the study, and 2 went from seizure-free to not seizure-free. The proportions were similar in the subgroups of patients with either POS or primary generalized seizures. These data cannot support an effect of BRV as adjunctive therapy in children aged ≥1 month to ≤2 years with epilepsy.

Based on diary data of seizure frequency over the 3-weeks treatment period, 4/27 (14.8%) in the ≥1 month to ≤2 years overall subgroup were 50% responders. In the POS subgroup in this age interval, the responder rate was 3/12 (25%). This was lower than in the older age intervals, where 9/41 (22%) in the overall group ≥2 to <12 years, 7/19 (36.8%) in the POS subgroup of this age interval were 50% responders, and 4/12 (33.3%) in the overall group ≥12 to <16 years, 1/4 in the POS subgroup of this age interval were 50% responders. The low number of treated patients indicates that the data should be interpreted with caution. For comparison, for LEV, the 50% responder rate for paediatric patients aged 1 month to <4 years was 43.6% vs 19.6% for placebo.

For comparison, the extension of approval of LEV to the ≥1 month to <4 year paediatric age group was based on a 5-day placebo-controlled study with a modified intention-to-treat population of N=109 (58 LEV, 51 placebo) using 48-h video-EEG for efficacy evaluation, for which the 50% responder rate for LEV was 43.6% vs 19.6% for placebo.

The study was not primarily designed to capture robust efficacy data in the age intervals ≥1 month to <2 years and ≥2 to <4 years: The study was open-label, single-armed and the evaluation of efficacy was done during a fixed weekly dose titration schedule or after only 1 week at the highest fixed dose level. The dose levels were 1.0, 2.0 and 4.0 mg/kg/day for week 1, 2, and 3, respectively. This is obviously not in line with the recommended dosing strategy for treatment of epilepsy where an individualized dose should be titrated based on a combination of benefit and tolerability. The submitted updated SmPC for the extension proposes a therapeutic dose range of 1-5 mg/kg /day (recommended maintenance dose 2.5 mg/kg/day) for children weighing 10-20 kg and 1.5 to 6 mg/kg/day (recommended maintenance dose 3 mg/kg/day) for children weighing 3-10 kg, indicating that the dose would not be effective during week 1 at least. The number of patients was also low in each subgroup, especially if only paediatric patients with POS should be taken into account.

It is considered that the open study design, the evaluation of seizure frequency through diary data throughout the 3-week titration period, the low number of treated children and low number of evaluable children in each age interval prohibit any robust evaluation of efficacy in the age groups ≥1 month to <2 years and ≥2 to <4 years, which is the remit of this application.

Study N01266 is an ongoing Phase 3, open-label, single-arm, multicenter, LTFU study to evaluate the safety and efficacy of BRV in study participants with epilepsy. In addition to patients having completed study N01263 being offered to roll over to study N01266, additional paediatric patients were enrolled directly into the study. The total number of participants was 249, of which only 28 were aged ≥1 month to <2 years and 14 were aged ≥2 years to <4 years. Thus, the vast majority was 4 years and older. At the time of data cut-off, 14/28 (50%) in the youngest age group and 10/14 (71.4%) from the ≥2 years to <4 years age group had discontinued from the study, In the total study group, 138/249 (55.4%) had

discontinued. For all age groups, adverse events (AEs) and lack of efficacy were equally frequent reasons for discontinuation.

Since this was an open-label long-term safety and efficacy study where the patients were treated with BRV both at baseline and throughout the study, only maintenance of efficacy would be considered an adequate efficacy measure. The MAH puts forward that the majority of participants had either a stable or a reduction in seizure frequency over the study duration, which would show some support for an efficacy of BRV as adjunctive therapy. However, the overall discontinuation rate is 55.4% so far in this still ongoing study, of which 26% of the discontinuations were due to lack of efficacy. Thus, the interpretation of efficacy data in the study participants remaining on study is hampered by many factors.

The 50% responder rate compared to baseline in patients aged ≥2 years to <17 years was 81/167 (50.9%) in the overall group and 61/134 (45.5%) in the POS subgroup of the evaluable patients. The validity of this endpoint may however be questioned, given the design of the study (see discussion above).

For patients ≥1 month to <2 years, based on 24-h EEG data obtained from a total of N=14 patients, only 8 patients contributed with 'evaluable data'. Of these, 4/4 with POS and 2/4 with PGS were 50% responders compared to baseline. The validity of this endpoint may however be questioned, given the design of the study (see discussion above).

The open-label, single arm design of this LTFU study makes the interpretation of any efficacy data very difficult. It is even difficult to claim that the study participants did maintain efficacy on study, since around half of the participants has discontinued from the study at data cut-off, many of them due to lack of efficacy. In addition, the majority of patients were aged 4 years and above and only 28 were aged ≥1 month to <2 years and 14 were aged ≥2 years to <4 years. No conclusions may be drawn for efficacy from this study for these age groups.

Study EP0065 was a phase 2 PK, safety and tolerability study in patients aged ≥1 month to <16 years. The study provided PK and safety data related to the IV administration route.

The MAH has been asked to support the extension of indication from adults to children ≥1 month to <2 years of age, which is partly based on extrapolation of efficacy from data in adults and children receiving adjunctive LEV, on a non-clinical comparison of similarities and dissimilarities between BRV and LEV with regards to mode of action, animal models of epilepsy and free plasma exposure at the maximal approved dose.

The MAH presents data in support of the primary MoA for both BRV and LEV being via binding to SV2A with a reported 10- to 30-fold higher affinity of BRV for binding to SV2A than LEV. This corresponds quite well with the 15-20-fold higher free plasma concentration for BRV than LEV at the maximal approved dose.

Both BRV and LEV have a similar activity profile in animal models of acute seizures and chronic epilepsy, which is quite different from the profile for AEDs with other mechanisms of action. In all the animal models where both have an effect, the potency of BRV is higher than LEV, consistent with a higher affinity for SV2A.

This comparison gives some support to the notion that BRV and LEV are similar in MoA, and above all that a similar difference in potency has been observed through various *in vitro* and *in vivo* tests, supporting the view that the dosing of BRV for children ≥1 month to <2 years of age may use the PK/PD model developed for treatment of paediatric patients with LEV. However, the external validation of the BRV PK/PD model indicated a different PK/PD relationship between adults and children <4 years, and therefore PK/PD modelling cannot be used to support this extension (see 2.4.3. PK/PD modelling and 2.4.4. Discussion on clinical pharmacology).

The MAH was asked to justify the similarity of the pathophysiology of POS epilepsy in children aged ≥1 month to <2 years compared to older children and adults. The MAH refers to data showing that although clinical manifestations of POS may be different between older children and children aged below 2 years,

focal/partial seizures are quite similar in their EEG appearance in the youngest children versus adults, indicating a similar neurophysiological correlate.

2.5.3. While a population PK bridge may support extrapolation down to 2 years of age, the PK/PD model cannot be used to support the extrapolation of efficacy to children below 4 years. Conclusions on the clinical efficacy

Data from the clinical studies N01263 and N01266 do not establish efficacy for age groups ≥1 month to <2 years and ≥2 to <4 years due to the low number of evaluable children in each age interval and aspects relative to study design [open-label, single arm design of this LTFU].

Study EP0065 provided some support that to the notion that BRV and LEV are similar in MoA and therefore that the PK/PD model developed for treatment of paediatric patients with LEV could be used to inform dosing of BRV for children below 4 years. However, the external validation of the BRV PK/PD model indicated a different PK/PD relationship between adults and children <4 years, and therefore PK/PD modelling cannot be used to support this extension of indication.

The absence of robust clinical efficacy results [N01263 and N01266] and support from the PK/PD modelling does not allow to establish the efficacy of BRV in children aged ≥1 month to <2 years, an age range where the pathophysiology of epilepsy is not considered to be sufficiently similar to that of adults to allow for an extrapolation based on only a PK bridge.

However, for children aged ≥2 years to <4 years, it may be considered adequate to base the approval on the similarity of disease between adults and children aged ≥2 years to <4 years in combination with safety data and a PK bridge (similar exposure).

2.6. Clinical safety

Introduction

The Summary of Clinical Safety focuses on the following interpretations:

First, for Pool Paediatric Studies, data from study participants with POS who are <4 years of age (ie, in the ≥1 month to <2 years and ≥2 to <4 years POS groups) are compared with data from the ≥4 to <16 years POS group to determine if there are any differences between age groups. Interpretations are provided collectively for participants ≥1 month to <2 years of age and ≥2 to <4 years of age (ie, for participants ≥1 month to <4 years) for comparison with participants ≥4 to <16 years of age.

Second, for Pool Paediatric Studies, data from all participants with POS (Total POS) are compared with data from All Paediatric Study Participants to determine if there are any differences between paediatric participants with POS and paediatric participants with epilepsy (both POS and non-POS).

The tertiary focus is to compare modal and maximum doses for the Total POS group. The Total POS group was chosen for this comparison as there are too few study participants in each POS summary age group for meaningful interpretations. Where possible, within each group in Pool Paediatric Studies (≥1 month to <2 years, ≥2 to <4 years, ≥4 to <16 years, Total POS, and All Paediatric Study Participants groups), data were compared between gender, race, region, and AED inducer status to identify if there were any data differences associated with these factors.

Finally, data from participants in the Total POS group in Pool Paediatric Studies were compared with data from Pool S4 and Pool Monotherapy to determine if there were any differences between paediatric participants with POS compared with adult participants.

Patient exposure

Table 28: *Overall exposure and duration of exposure to BRV by paediatric summary group (Pool Paediatric Studies)*

	BRV Overall				
	POS summary group				**All Paediatric Study Participants**
	POS 1m to <2y N=15	**POS ≥2 to <4y N=3**	**POS ≥4 to <16y N=168**	**Total POS ≥1m to <17y N=189**	**N=259**
Number of study participants exposed, n (%)	15 (100)	3 (100)	166 (98.8)	187 (98.9)	257 (99.2) [a]
Total participant-years of exposure	46.5	8.6	475.6	535.2	711.1
Duration of exposure, n (%)					
≥1 month	12 (80.0)	3 (100)	159 (94.6)	177 (93.7)	246 (95.0)
≥3 months	11 (73.3)	3 (100)	135 (80.4)	151 (79.9)	209 (80.7)
≥6 months	11 (73.3)	2 (66.7)	125 (74.4)	140 (74.1)	186 (71.8)
≥12 months	9 (60.0)	2 (66.7)	112 (66.7)	125 (66.1)	159 (61.4)
≥18 months	9 (60.0)	2 (66.7)	105 (62.5)	118 (62.4)	144 (55.6)
≥24 months	8 (53.3)	2 (66.7)	97 (57.7)	109 (57.7)	133 (51.4)
≥36 months	7 (46.7)	1 (33.3)	82 (48.8)	90 (47.6)	112 (43.2)
≥48 months	6 (40.0)	1 (33.3)	60 (35.7)	67 (35.4)	87 (33.6)
≥60 months	6 (40.0)	1 (33.3)	40 (23.8)	46 (24.3)	65 (25.1)
≥72 months	5 (33.3)	1 (33.3)	11 (6.5)	17 (9.0)	33 (12.7)
≥84 months	2 (13.3)	0	6 (3.6)	8 (4.2)	20 (7.7)

BRV=brivaracetam; ISS=Integrated Summary of Safety; m=month; POS=partial-onset seizures; y=years
Note: Pool Paediatric Studies consisted of study participants from N01263 and/or N01266.
Note: Total POS included participants with POS ≥1 month to <2 years, ≥2 to <4 years, ≥4 to <16 years, and participants with POS who were 16 years at the time of study entry.
Note: All Paediatric Study Participants included participants in the pool with POS and other seizure types.
[a] Two study participants were excluded from the number of participants exposed, modal daily dose, and durations of exposure due to lack of information.
Data sources: ISS Table 4.1.1A, ISS Table 4.1.1B

Table 29: *Updated BRV Exposure in study N01266 from interim report with cut-off 14 July 2020*

	≥1 month to <2 years N=28	≥2 to <4 years N=14	≥4 to <12 years N=141	≥12 to <17 years N=66	All study participants N=249
Evaluation Period BRV exposure duration (months)					
n	28	14	139	66	247
Mean (SD)	39.33 (36.99)	32.31 (34.50)	39.88 (30.19)	29.30 (22.51)	36.56 (29.67)
Min, max	1.1, 97.3	2.6, 98.4	0.6, 99.3	1.0, 94.2	0.6, 99.3
Overall study BRV exposure duration (months)					
n	28	14	141	66	249
Mean (SD)	39.52 (36.94)	32.57 (34.39)	39.52 (30.20)	29.50 (22.48)	36.47 (29.63)
Min, max	1.3, 97.3	2.8, 98.4	0.2, 99.3	1.2, 94.2	0.2, 99.3
Evaluation Period BRV exposure duration category, n (%)					
Evaluation Period overall	28 (100)	14 (100)	139 (98.6)	66 (100)	247 (99.2)
≤6 months	9 (32.1)	5 (35.7)	37 (26.2)	16 (24.2)	67 (26.9)
>6 to ≤12 months	4 (14.3)	2 (14.3)	4 (2.8)	2 (3.0)	12 (4.8)
>12 to ≤18 months	2 (7.1)	1 (7.1)	13 (9.2)	6 (9.1)	22 (8.8)
>18 to ≤24 months	2 (7.1)	1 (7.1)	3 (2.1)	12 (18.2)	18 (7.2)
>24 to ≤30 months	0	0	7 (5.0)	6 (9.1)	13 (5.2)
>30 to ≤36 months	0	0	2 (1.4)	1 (1.5)	3 (1.2)
>36 months	11 (39.3)	5 (35.7)	73 (51.8)	23 (34.8)	112 (45.0)

BRV=brivaracetam; DE=directly enrolled; max=maximum; Min=minimum; SD=standard deviation; SS=Safety Set

Note: Evaluation Period BRV exposure duration (months) was calculated as the date of the final dose of BRV during the Evaluation Period minus the date of the first dose of BRV in N01266 plus 1 day divided by 30.

Note: Overall study exposure duration (months) including up to Up-Titration Period (DE study participants only), Evaluation Period, and Down-Titration Period (discontinued study participants only) was calculated as the date of the final dose of BRV minus the date of the first dose of BRV in N01266 plus 1 day divided by 30.

Data source: Table 11.1

Table 30: *Disposition and discontinuation reasons by paediatric summary group (Pool Paediatric Studies)*

	BRV Overall				
	POS summary group				**All Paediatric Study Participants[a] N=259 n (%)**
	POS ≥1m to <2y N=15 n (%)	**POS ≥2 to<4y N=3 n (%)**	**POS ≥4 to <16y N=168 n (%)**	**Total POS ≥1m to <17y N=189 n (%)**	
Ongoing study participants [b]	3 (20.0)	1 (33.3)	47 (28.0)	52 (27.5)	75 (29.0)
Completed N01263 and did not enter long-term study	0	0	2 (1.2)	2 (1.1)	4 (1.5)
Discontinued [c]	8 (53.3)	1 (33.3)	90 (53.6)	101 (53.4)	140 (54.1)
Reason for discontinuation					
Adverse event	2 (13.3)	0	19 (11.3)	22 (11.6)	35 (13.5)
Lack of efficacy	2 (13.3)	1 (33.3)	21 (12.5)	25 (13.2)	37 (14.3)
Lost to follow up	0	0	5 (3.0)	5 (2.6)	6 (2.3)
Study participant choice	1 (6.7)	0	18 (10.7)	19 (10.1)	25 (9.7)
Other	3 (20.0)	0	16 (9.5)	19 (10.1)	24 (9.3)
Missing	-	-	11 (6.5)	11 (5.8)	13 (5.0)

BRV=brivaracetam; ISS=Integrated Summary of Safety; m=month; POS=partial-onset seizures; y=years
Note: Study participants with more than 1 reason for discontinuation were summarized for all reported reasons.
Note: Total POS included participants with POS ≥1 month to <2 years, ≥2 to <4 years, ≥4 to <16 years, and participants with POS who were 16 years at the time of study entry.

[a] All Paediatric Study Participants includes paediatric patients with POS as well as other seizure types.
[b] The number of ongoing participants in N01266 at the time of the clinical cutoff (14 Jan 2020).
[c] Included participants who discontinued the study but the reason for discontinuation was not available in the clinical database. Such participants were counted in the Missing category.

Data sources: ISS Table 2.1.1A, ISS Table 2.1.1B

Table 31: *Demographic and Baseline characteristics by paediatric summary group (Pool Paediatric Studies)*

	BRV Overall				
	POS summary group				**All Paediatric Study Participants[a]**
	POS ≥1m to <2y N=15	**POS ≥2 to<4y N=3**	**POS ≥4 to <16y N=168**	**Total POS ≥1m to <17y N=189**	**N=259**
Age (years)					
n	15	3	168	189	259
Mean (SD)	0.6 (0.5)	2.0 (0.0)	9.1 (3.5)	8.4 (4.2)	7.8 (4.5)
Median	1.0	2	9.0	9.0	8.0
Min, max	0, 1	2, 2	4, 15	0, 16	0, 16
Gender, n (%)					
Male	11 (73.3)	3 (100)	92 (54.8)	107 (56.6)	139 (53.7)
Female	4 (26.7)	0	76 (45.2)	82 (43.4)	120 (46.3)
Overall racial group [b], n (%)					
White	11 (73.3)	3 (100)	119 (70.8)	135 (71.4)	196 (75.7)
Black	0	0	5 (3.0)	5 (2.6)	5 (1.9)
Other	4 (26.7)	0	44 (26.2)	49 (25.9)	58 (22.4)
Racial group [c], n (%)					
White	11 (73.3)	3 (100)	119 (70.8)	135 (71.4)	196 (75.7)
Black	0	0	5 (3.0)	5 (2.6)	5 (1.9)
Other/Mixed	4 (26.7)	0	44 (26.2)	49 (25.9)	58 (22.4)
Weight (kg)					
n	15	3	168	189	259
Mean (SD)	9.9 (3.0)	12.5 (0.7)	35.5 (19.0)	33.4 (19.7)	31.1 (20.0)
Median	9.2	12.8	31.8	29.1	26.5
Min, max	5, 15	12, 13	9, 157	5, 157	4, 157
Height (cm)					
n	15	3	168	189	259
Mean (SD)	76.0 (8.6)	82.2 (6.0)	135.1 (20.8)	130.0 (26.5)	124.9 (29.4)
Median	75.5	84.0	136.5	132.0	127.0
Min, max	59, 90	76, 87	86, 181	59, 181	55, 181

	BRV Overall				
	POS summary group				All Paediatric Study Participants[a]
	POS ≥1m to <2y N=15	POS ≥2 to<4y N=3	POS ≥4 to <16y N=168	Total POS ≥1m to <17y N=189	N=259
BMI (kg/m^2)					
n	15	3	168	189	259
Mean (SD)	16.5 (2.4)	18.5 (1.8)	18.3 (5.1)	18.2 (4.9)	17.9 (4.8)
Median	16.5	18.1	17.2	17.2	16.9
Min, max	13, 21	17, 20	9, 50	9, 50	9, 50
Head circumference (cm)					
n	14	2	160	179	244
Mean (SD)	44.4 (3.2)	46.4 (0.9)	52.0 (3.4)	51.4 (4.0)	50.6 (4.5)
Median	44.9	46.4	52.0	52.0	51.3
Min, max	39, 48	46, 47	42, 62	39, 62	36, 62
AED inducer status, n (%)					
Inducer at core study entry	6 (40.0)	2 (66.7)	90 (53.6)	100 (52.9)	115 (44.4)
No inducer at core study entry	9 (60.0)	1 (33.3)	78 (46.4)	89 (47.1)	144 (55.6)
Number of previous AEDs, n (%)					
0 to 1	8 (53.3)	2 (66.7)	58 (34.5)	68 (36.0)	120 (39.4)
2 to 4	7 (46.7)	0	64 (38.1)	73 (38.6)	90 (34.7)
≥5	0	1 (33.3)	46 (27.4)	48 (25.4)	67 (25.9)
Geographic region (FDA classification), n (%)					
North America	4 (26.7)	2 (66.7)	42 (25.0)	49 (25.9)	59 (22.8)
Latin America	6 (40.0)	-	48 (28.6)	55 (29.1)	63 (24.3)
Western Europe	2 (13.3)	-	23 (13.7)	25 (13.2)	42 (16.2)
Eastern Europe	3 (20.0)	1 (33.3)	55 (32.7)	60 (31.7)	95 (36.7)

	BRV Overall				
	POS summary group				All Paediatric Study Participants[a]
	POS ≥1m to <2y N=15	POS ≥2 to<4y N=3	POS ≥4 to <16y N=168	Total POS ≥1m to <17y N=189	N=259
Geographic region (CHMP classification), n (%)					
North America	4 (26.7)	2 (66.7)	42 (25.0)	49 (25.9)	59 (22.8)
Latin America	6 (40.0)	-	48 (28.6)	55 (29.1)	63 (24.3)
Europe (EU member states)	5 (33.3)	1 (33.3)	78 (46.4)	85 (45.0)	137 (52.9)

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

Note: Total POS included participants with POS ≥1 month to <2 years, ≥2 to <4 years, ≥4 to <16 years, and participants with POS who were 16 years at the time of study entry.

[a] All Paediatric Study Participants includes paediatric patients with POS as well as other seizure types.

[b] Overall racial group was based on the racial group recorded on the CRF and was summarized for all ISS long-term study pools (see ISAP Section 4.3.1).

[c] Due to differences in data format across studies, racial group was collected as recorded on the CRF and collapsed for the ISS study pools (see ISAP Section 4.3.1).

Data sources: ISS Table 2.2.1.1A, ISS Table 2.2.1.1B, ISS Table 2.2.1.2A, ISS Table 2.2.1.2B, ISS Table 3.1.1A, ISS Table 3.1.1B

Adverse events

Table 32: *Overview of TEAEs by paediatric summary group (Pool Paediatric Studies)*

	BRV Overall				
	POS summary group				**All Paediatric Study Participants[a] N=259 n (%) [#]**
	POS ≥1m to <2y N=15 n (%) [#]	**POS ≥2 to <4y N=3 n (%) [#]**	**POS ≥4 to <16y N=168 n (%) [#]**	**Total POS ≥1m to <17y N=189 n (%) [#]**	
Any TEAE	14 (93.3) [542]	3 (100) [55]	156 (92.9) [1761]	176 (93.1) [2378]	240 (92.7) [3174]
Discontinuation due to TEAE [b]	2 (13.3) [2]	0	18 (10.7) [27]	21 (11.1) [30]	35 (13.5) [48]
Drug-related TEAE [b]	9 (60.0) [11]	2 (66.7) [2]	63 (37.5) [123]	76 (40.2) [138]	102 (39.4) [197]
Severe TEAE	6 (40.0) [21]	1 (33.3) [2]	20 (11.9) [45]	27 (14.3) [68]	42 (16.2) [88]
Treatment-emergent SAE	7 (46.7) [38]	1 (33.3) [1]	43 (25.6) [101]	52 (27.5) [141]	75 (29.0) [202]
Drug-related treatment-emergent SAE [c]	0	0	3 (1.8) [3]	3 (1.6) [3]	6 (2.3) [6]
Deaths	0	0	2 (1.2)	2 (1.1)	6 (2.3)

BRV=brivaracetam; ISS=Integrated Summary of Safety; m=month; POS=partial-onset seizures; SAE=serious adverse event; TEAE=treatment-emergent adverse event; y=years

Note: n=number of study participants who reported a TEAE for the specified category; #=number of individual TEAEs.

Note: Total POS included participants with POS ≥1 month to <2 years, ≥2 to <4 years, ≥4 to <16 years, study participants with POS who were 16 years at the time of study entry.

[a] All Paediatric Study Participants includes paediatric patients with POS as well as other seizure types.

[b] Discontinuation due to TEAE included cases where study drug was permanently discontinued due to a TEAE.

[c] Relationship to study drug was determined by the Investigator.

Data sources: ISS Table 5.1.1A, ISS Table 5.1.1B

Table 33: *Most frequently reported (⩾2% in any group) common TEAEs by paediatric summary group (Pool Paediatric Studies)*

Primary SOC PT	BRV Overall				
	POS summary group				All Paediatric Study Participants[b]
	POS ≥1m to <2y N=15 n (%)	POS ≥2 to<4y N=3 n (%)	POS ≥4 to <16y N=168 n (%)	Total POS ≥1m to <17y N=189 n (%)	N=259 n (%)
Blood and lymphatic system disorders	**2 (13.3)**	**0**	**5 (3.0)**	**3 (1.6)**	**12 (4.6)**
Anaemia	2 (13.3)	0	1 (0.6)	3 (1.6)	5 (1.9)
Ear and labyrinth disorders	**1 (6.7)**	**1 (33.3)**	**9 (5.4)**	**11 (5.8)**	**15 (5.8)**
Ear pain	0	1 (33.3)	5 (3.0)	6 (3.2)	7 (2.7)
Endocrine disorders	**0**	**0**	**6 (3.6)**	**6 (3.2)**	**7 (2.7)**
Hypothyroidism	0	0	6 (3.6)	6 (3.2)	7 (2.7)
Eye disorders	**3 (20.0)**	**0**	**7 (4.2)**	**10 (5.3)**	**14 (5.4)**
Strabismus	2 (13.3)	0	1 (0.6)	3 (1.6)	3 (1.2)
Gastrointestinal disorders	**9 (60.0)**	**2 (66.7)**	**70 (41.7)**	**83 (43.9)**	**110 (42.5)**
Vomiting	7 (46.7)	2 (66.7)	25 (14.9)	36 (19.0)	53 (20.5)
Diarrhoea	3 (20.0)	0	22 (13.1)	25 (13.2)	37 (14.3)
Abdominal pain upper	1 (6.7)	0	15 (8.9)	17 (9.0)	19 (7.3)
Abdominal pain	4 (26.7)	0	13 (7.7)	17 (9.0)	19 (7.3)
Constipation	3 (20.0)	0	11 (6.5)	14 (7.4)	19 (7.3)
Nausea	4 (26.7)	0	6 (3.6)	10 (5.3)	13 (5.0)
Gastrooesophageal reflux disease	2 (13.3)	1 (33.3)	2 (1.2)	5 (2.6)	9 (3.5)
Toothache	1 (6.7)	0	3 (1.8)	4 (2.1)	8 (3.1)
Abdominal distension	1 (6.7)		1 (0.6)	2 (1.1)	4 (1.5)
Dysphagia	0	1 (33.3)	2 (1.2)	3 (1.6)	4 (1.5)
Dental caries	0	0	4 (2.4)	4 (2.1)	5 (1.9)
General disorders and administration site conditions	**10 (66.7)**	**1 (33.3)**	**50 (29.8)**	**62 (32.8)**	**90 (34.7)**
Pyrexia	10 (66.7)	1 (33.3)	31 (18.5)	42 (22.2)	64 (24.7)
Fatigue	1 (6.7)	0	9 (5.4)	11 (5.8)	18 (6.9)
Asthenia	1 (6.7)	0	3 (1.8)	4 (2.1)	5 (1.9)
Gait disturbance	1 (6.7)	0	1 (0.6)	2 (1.1)	3 (1.2)

Primary SOC PT	BRV Overall				
	POS summary group				All Paediatric Study Participants[b] N=259 n (%)
	POS ≥1m to <2y N=15 n (%)	POS ≥2 to<4y N=3 n (%)	POS ≥4 to <16y N=168 n (%)	Total POS ≥1m to <17y N=189 n (%)	
Immune system disorders	**1 (6.7)**	**0**	**5 (3.0)**	**6 (3.2)**	**9 (3.5)**
Hypersensitivity	1 (6.7)	0	3 (1.8)	4 (2.1)	4 (1.5)
Infections and infestations	**12 (80.0)**	**2 (66.7)**	**111 (66.1)**	**127 (62.7)**	**178 (68.7)**
Nasopharyngitis	6 (40.0)	1 (33.3)	41 (24.4)	49 (25.9)	68 (26.3)
Pharyngitis	4 (26.7)	0	39 (23.2)	43 (22.8)	54 (20.8)
Upper respiratory tract infection	5 (33.3)	2 (66.7)	17 (10.1)	24 (12.7)	40 (15.4)
Pharyngotonsillitis	3 (20.0)	0	27 (16.1)	30 (15.9)	36 (13.9)
Gastroenteritis	5 (33.3)	0	16 (9.5)	21 (11.1)	32 (12.4)
Bronchitis	5 (33.3)	0	14 (8.3)	19 (10.1)	26 (10.0)
Influenza	5 (33.3)	0	13 (7.7)	18 (9.5)	26 (10.0)
Rhinitis	3 (20.0)	1 (33.3)	14 (8.3)	18 (9.5)	24 (9.3)
Pneumonia	0	0	9 (5.4)	9 (4.8)	21 (8.1)
Ear infection	3 (20.0)	0	9 (5.4)	13 (6.9)	19 (7.3)
Tonsillitis	1 (6.7)	0	9 (5.4)	10 (5.3)	16 (6.2)
Urinary tract infection	1 (6.7)	1 (33.3)	7 (4.2)	9 (4.8)	16 (6.2)
Otitis media	4 (26.7)	1 (33.3)	4 (2.4)	9 (4.8)	15 (5.8)
Viral infection	3 (20.0)	1 (33.3)	7 (4.2)	11 (5.8)	15 (5.8)
Conjunctivitis	4 (26.7)	0	5 (3.0)	9 (4.8)	13 (5.0)
Pharyngitis streptococcal	2 (13.3)	0	8 (4.8)	10 (5.3)	12 (4.6)
Varicella	2 (13.3)	0	8 (4.8)	10 (5.3)	12 (4.6)
Sinusitis	2 (13.3)	0	7 (4.2)	9 (4.8)	11 (4.2)
Respiratory tract infection	2 (13.3)	0	4 (2.4)	6 (3.2)	10 (3.9)
Laryngitis	2 (13.3)	0	3 (1.8)	5 (2.6)	9 (3.5)
Viral pharyngitis	2 (13.3)	0	4 (2.4)	6 (3.2)	8 (3.1)

Primary SOC PT	BRV Overall				
	POS summary group				All Paediatric Study Participants[b]
	POS ≥1m to <2y N=15 n (%)	POS ≥2 to<4y N=3 n (%)	POS ≥4 to <16y N=168 n (%)	Total POS ≥1m to <17y N=189 n (%)	N=259 n (%)
Otitis media acute	2 (13.3)	0	2 (1.2)	4 (2.1)	7 (2.7)
Pharyngitis bacterial	1 (6.7)	0	3 (1.8)	4 (2.1)	6 (2.3)
Oral candidiasis	2 (13.3)	0	0	2 (1.1)	3 (1.2)
Lice infestation	1 (6.7)	0	2 (1.2)	3 (1.6)	4 (1.5)
Viral rhinitis	1 (6.7)	0	1 (0.6)	2 (1.1)	3 (1.2)
Viral upper respiratory tract infection	1 (6.7)	0	1 (0.6)	2 (1.1)	4 (1.5)
Acute sinusitis	0	1 (33.3)	2 (1.2)	3 (1.6)	4 (1.5)
Gastroenteritis viral	0	1 (33.3)	3 (1.8)	4 (2.1)	5 (1.9)
Injury, poisoning, and procedural complications	**3 (20.0)**	**0**	**49 (29.2)**	**53 (28.0)**	**67 (25.9)**
Fall	1 (6.7)	0	11 (6.5)	12 (6.3)	17 (6.6)
Contusion	0	0	5 (3.0)	5 (2.6)	10 (3.9)
Laceration	0	0	7 (4.2)	7 (3.7)	10 (3.9)
Head injury	1 (6.7)	0	4 (2.4)	5 (2.6)	8 (3.1)
Arthropod bite	0	0	5 (3.0)	5 (2.6)	5 (1.9)
Joint injury	0	0	5 (3.0)	5 (2.6)	5 (1.9)
Arthropod sting	0	0	4 (2.4)	4 (2.1)	4 (1.5)
Ligament sprain	1 (6.7)	0	1 (0.6)	2 (1.1)	4 (1.5)
Face injury	1 (6.7)	0	2 (1.2)	3 (1.6)	3 (1.2)
Investigations	**5 (33.3)**	**1 (33.3)**	**27 (16.1)**	**33 (17.5)**	**44 (17.0)**
Weight decreased	1 (6.7)	0	10 (6.0)	11 (5.8)	15 (5.8)
GGT increased	0	0	5 (3.0)	5 (2.6)	7 (2.7)
Blood bicarbonate decreased	1 (6.7)	0	2 (1.2)	3 (1.6)	5 (1.9)
Blood triglycerides increased	1 (6.7)	0	4 (2.4)	5 (2.6)	5 (1.9)
Creatinine renal clearance decreased	2 (13.3)	1 (33.3)	2 (1.2)	5 (2.6)	5 (1.9)

Primary SOC PT	BRV Overall				
	POS summary group				All Paediatric Study Participants[b] N=259 n (%)
	POS ≥1m to <2y N=15 n (%)	POS ≥2 to<4y N=3 n (%)	POS ≥4 to <16y N=168 n (%)	Total POS ≥1m to <17y N=189 n (%)	
Metabolism and nutrition disorders	**7 (46.7)**	**2 (66.7)**	**26 (15.5)**	**36 (19.0)**	**51 (19.7)**
Decreased appetite	5 (33.3)	1 (33.3)	16 (9.5)	23 (12.2)	34 (13.1)
Dehydration	3 (20.0)	1 (33.3)	0	4 (2.1)	7 (2.7)
Metabolic acidosis	2 (13.3)	0	1 (0.6)	3 (1.6)	4 (1.5)
Musculoskeletal and connective tissue disorders	**3 (20.0)**	**0**	**21 (12.5)**	**24 (12.7)**	**30 (11.6)**
Arthralgia	1 (6.7)	0	6 (3.6)	7 (3.7)	7 (2.7)
Pain in extremity	0	0	5 (3.0)	5 (2.6)	7 (2.7)
Muscular weakness	1 (6.7)	0	3 (1.8)	4 (2.1)	5 (1.9)
Scoliosis	1 (6.7)	0	1 (0.6)	2 (1.1)	3 (1.2)
Nervous system disorders	**11 (73.3)**	**2 (66.7)**	**91 (54.2)**	**106 (56.1)**	**140 (54.1)**
Seizure	6 (40.0)	1 (33.3)	33 (19.6)	42 (22.2)	56 (21.6)
Headache	0	0	31 (18.5)	32 (16.9)	41 (15.8)
Somnolence	3 (20.0)	0	21 (12.5)	24 (12.7)	32 (12.4)
Dizziness	0	0	14 (8.3)	15 (7.9)	16 (6.2)
Psychomotor hyperactivity	0	0	9 (5.4)	9 (4.8)	9 (3.5)
Status epilepticus	1 (6.7)	0	7 (4.2)	8 (4.2)	8 (3.1)
Complex partial seizures	2 (13.3)	0	4 (2.4)	6 (3.2)	7 (2.7)
Simple partial seizures	0	0	7 (4.2)	7 (3.7)	7 (2.7)
Epilepsy	1 (6.7)	0	3 (1.8)	4 (2.1)	6 (2.3)
Change in seizure presentation	0	0	5 (3.0)	5 (2.6)	5 (1.9)
Partial seizures with secondary generalization	0	1 (33.3)	4 (2.4)	5 (2.6)	5 (1.9)
Syncope	0	0	4 (2.4)	4 (2.1)	5 (1.9)
Generalize tonic-clonic seizure	1 (6.7)	0	0	1 (0.5)	4 (1.5)
Ataxia	1 (6.7)	1 (33.3)	1 (0.6)	3 (1.6)	3 (1.2)
Muscle spasticity	3 (20.0)	0	0	3 (1.6)	3 (1.2)

Primary SOC PT	BRV Overall				
	POS summary group				All Paediatric Study Participants[b]
	POS ≥1m to <2y N=15 n (%)	POS ≥2 to<4y N=3 n (%)	POS ≥4 to <16y N=168 n (%)	Total POS ≥1m to <17y N=189 n (%)	N=259 n (%)
Psychiatric disorders	**8 (53.3)**	**1 (33.3)**	**64 (38.1)**	**75 (39.7)**	**96 (37.1)**
Irritability	4 (26.7)	0	17 (10.1)	21 (11.1)	27 (10.4)
Aggression	0	1 (33.3)	10 (6.0)	11 (5.8)	19 (7.3)
Insomnia	2 (13.3)	0	10 (6.0)	12 (6.3)	16 (6.2)
Suicidal ideation	0	0	8 (4.8)	9 (4.8)	10 (3.9)
Attention deficit/hyperactivity disorder	1 (6.7)	0	6 (3.6)	7 (3.7)	8 (3.1)
Abnormal behaviour	1 (6.7)	0	4 (2.4)	6 (3.2)	7 (2.7)
Anxiety	1 (6.7)	0	6 (3.6)	7 (3.7)	7 (2.7)
Depression	0	0	4 (2.4)	4 (2.1)	5 (1.9)
Sleep disorder	0	0	5 (3.0)	5 (2.6)	5 (1.9)
Confusional state	0	0	4 (2.4)	4 (2.1)	4 (1.5)
Mood swings	2 (13.3)	0	1 (0.6)	3 (1.6)	3 (1.2)
Renal and urinary disorders	**4 (26.7)**	**1 (33.3)**	**15 (8.9)**	**20 (10.6)**	**24 (9.3)**
Enuresis	1 (6.7)	0	5 (3.0)	6 (3.2)	6 (2.3)
Reproductive system and breast disorders	**1(6.7)**	**0**	**11 (6.5)**	**12 (6.3)**	**12 (4.6)**
Dysmenorrhoea	0	0	6 (3.6)	6 (3.2)	6 (2.3)
Respiratory, thoracic, and mediastinal disorders	**10 (66.7)**	**2 (66.7)**	**49 (29.2)**	**61 (32.3)**	**78 (30.1)**
Cough	5 (33.3)	0	21 (12.5)	26 (13.8)	29 (11.2)
Oropharyngeal pain	0	1 (33.3)	9 (5.4)	10 (5.3)	14 (5.4)
Epistaxis	2 (13.3)	0	6 (3.6)	8 (4.2)	11 (4.2)
Rhinitis allergic	2 (13.3)	0	7 (4.2)	9 (4.8)	10 (3.9)
Asthma	3 (20.0)	0	1 (0.6)	5 (2.6)	6 (2.3)
Nasal congestion	2 (13.3)	0	3 (1.8)	5 (2.6)	6 (2.3)
Rhinorrhoea	3 (20.0)	0	3 (1.8)	6 (3.2)	6 (2.3)
Adenoidal hypertrophy	2 (13.3)	0	1 (0.6)	3 (1.6)	4 (1.5)
Asthmatic crisis	2 (13.3)	0	1 (0.6)	3 (1.6)	4 (1.5)
Bronchospasm	3 (20.0)	0	1 (0.6)	4 (2.1)	4 (1.5)

Primary SOC PT	BRV Overall				
	POS summary group				All Paediatric Study Participants[b] N=259 n (%)
	POS ≥1m to <2y N=15 n (%)	POS ≥2 to<4y N=3 n (%)	POS ≥4 to <16y N=168 n (%)	Total POS ≥1m to <17y N=189 n (%)	
Skin and subcutaneous tissue disorders	**5 (33.3)**	**2 (66.7)**	**28 (16.7)**	**35 (18.5)**	**42 (16.2)**
Rash	2 (13.3)	0	9 (5.4)	11 (5.8)	12 (4.6)
Dermatitis allergic	0	0	4 (2.4)	4 (2.1)	4 (1.5)
Dermatitis contact	1 (6.7)	1 (33.3)	2 (1.2)	4 (2.1)	4 (1.5)
Dermatitis diaper	1 (6.7)	0	1 (0.6)	2 (1.1)	4 (1.5)
Ingrowing nail	0	1 (33.3)	2 (1.2)	3 (1.6)	3 (1.2)

BRV=brivaracetam; GGT=gamma-glutamyltransferase; ISS=Integrated Summary of Safety; m=month; 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 18.1.

Note: Total POS included participants with POS ≥1 month to <2 years, ≥2 to<4 years, ≥4 to <16 years, and participants with POS who were 16 years at the time of study entry.

[b] All Paediatric Study Participants included paediatric participants with POS and other seizure types.

Data sources: ISS Table 5.3.1A, ISS Table 5.3.1B

The TEAE incidence was similar for participants with POS aged <4 years and ≥4 to <16 years except for the TEAEs described here. Participants <4 years of age had a higher incidence of pyrexia and decreased appetite. Participants aged <4 years also had a higher incidence of some TEAEs in the System Organ Class (SOCs) of Infections and infestations and Gastrointestinal disorders, which were as normally observed in this age group; however, similar proportions of participants aged <4 years and ≥4 to <16 years reported the particular PTs within these SOCs. In addition, hypothyroidism was reported by 6 participants who were ≥4 to <16 years of age but no participants who were <4 years of age.

Serious adverse event/deaths/other significant events

Deaths

In Pool Paediatric Studies, a total of 6 study participants had TEAEs with fatal outcome during the BRV clinical development program as of the data lock point of 14 Jan 2020; 2 of these participants had POS. Three participant deaths were reviewed with the initial MAA and 1 participant death was reviewed with the initial paediatric extension application (paediatric indication ≥4 to <16 years in POS). An additional 2 participants have experienced TEAEs with fatal outcomes since the initial paediatric extension application was reviewed:

- A study participant with a history of dysphagia and gastroesophageal reflux disease, while concomitantly taking clobazam, LTG, VPA and vigabatrin experienced fatal pneumonia aspiration after approximately 5.9 months of exposure to BRV. An autopsy was not performed. The Investigator assessed the event as not related to study drug.

- A study participant with a history of asthma, hypoxia, respiratory failure, while concomitantly taking lacosamide and vigabatrin experienced fatal apnoea after approximately 6 years of exposure to BRV. An autopsy was not performed. The Investigator assessed the event as not related to study drug.

In Pool S4, a total of 40 participants had TEAEs with fatal outcome during the BRV clinical development program; 35 participant deaths were reviewed with the initial MAA, and 5 participant deaths were reviewed with the initial paediatric extension application. There have been no additional deaths since the initial paediatric extension application.

In Pool Monotherapy, 1 participant had a TEAE with fatal outcome (sudden unexplained death in epilepsy [SUDEP]) during the BRV clinical development program as of the clinical cut-off date of 14 Jan 2020; this participant death was reviewed with the initial MAA. There were no TEAEs with fatal outcome reported in Pool Monotherapy since the initial MAA was reviewed.

No trend has been identified in the causes of death presented by the participants who received BRV. The events observed in the development program could be expected in a program involving participants with epilepsy.

SAEs

In general, the incidence of treatment-emergent SAEs was as expected in this study population. In the ≥1 month to <2 years age group, seizure (3 participants [20.0%]) and pyrexia (2 participants [13.3%]) were the most frequently reported SAEs. In the ≥2 to <4 years age group, 1 participant (33.3%) reported an SAE of spina bifida. In the ≥4 to <16 years age group, the most frequently reported SAEs were seizure (13 participants [7.7%]), status epilepticus (7 participants [4.2%]), pneumonia (5 participants [3.0%]), and epilepsy (3 participants [1.8%]). There were no obvious differences in treatment-emergent SAEs observed between study participants <4 years of age and ≥4 to <16 years of age.

In the Total POS group, 52 participants (27.5%) reported treatment-emergent SAEs. The most frequently reported SAEs were seizure (17 participants [9.0%]), status epilepticus (8 participants [4.2%]), pneumonia (5 participants [2.6%]), epilepsy (4 participants [2.1%]), and pyrexia (3 participants [1.6%]). No other SAEs were reported in more than 2 participants. There were no differences in the incidence of treatment-emergent SAEs across modal doses. The treatment-emergent SAE profile was similar for All Paediatric Study Participants compared with the Total POS group.

The incidence of treatment-emergent SAEs in the adult analysis pools (Pool Monotherapy [20.0%] and Pool S4 [22.6%]) was similar to the incidence in the Total POS group in Pool Paediatric Studies.

TEAEs of special interest

Growth, neurocognitive development, sexual maturation

In the ≥1 month to <2 years POS group in Pool Paediatric Studies, TEAEs of interest for the paediatric population were reported most frequently in the neurodevelopment category (3 participants [20.0%]) and in the endocrine function or sexual maturation category (2 participants [13.3%]). All other TEAEs of interest categories were reported by no more than 1 study participant. In the endocrine function or sexual maturation category, 1 study participant each (6.7%) had a treatment-emergent SAE of cryptorchidism and hypoglycaemia.

In the ≥2 to <4 years POS group in Pool Paediatric Studies, there were no TEAEs potentially related to neurodevelopment or cognitive impairment; 1 participant (33.3%) reported a TEAE of hair growth abnormal in the endocrine function or sexual maturation category. This event was not serious and did not result in the participant's discontinuation of study drug.

In the ≥4 to <16 years POS group in Pool Paediatric Studies, TEAEs of interest for the paediatric population were reported most frequently in the following categories: cognitive impairment (15 participants [8.9%]), neurodevelopment (13 participants [7.7%]), endocrine function or sexual maturation (12 participants [7.1%]), and anxiety (11 participants [6.5%]). All other TEAEs of interest categories were reported by <5% of study participants. No TEAEs were reported in the category of growth. In the neurodevelopment category, 2 participants (1.2%) discontinued study drug due to TEAEs of psychomotor hyperactivity and in the depression category 1 participant each (0.6% each) discontinued study drug due to TEAEs of depression and depressed mood. In the depression category, 1 participant (0.6%) had a treatment-emergent SAE of depression. No other TEAEs were treatment-emergent SAEs or resulted in discontinuation of study drug.

Study participants <4 years of age had greater incidence of TEAEs of interest in the categories of endocrine function or sexual maturation and neurodevelopment compared with participants ≥4 to <16 years of age. There were no other differences between age groups observed.

In the Total POS group in Pool Paediatric Studies, TEAEs of interest for the paediatric population were reported most frequently in the following categories: neurodevelopment and cognitive impairment (16 participants each [8.5%]), endocrine function or sexual maturation (15 participants [7.9%]), and anxiety (12 participants [6.3%]). All other TEAEs of interest categories were reported by <5% of study participants. The profile of TEAEs potentially associated with growth, endocrine function/sexual maturation, neurodevelopment, cognitive impairment, anxiety, and depression were similar in All Study Participants in Pool Paediatric Studies and the Total POS group.

Hepatotoxicity

In the ≥1 month to <2 years POS group in Pool Paediatric Studies, a TEAE potentially associated with hepatotoxicity of hepatic enzyme increased was reported in 1 study participant (6.7%). The TEAE of hepatic enzyme increased was not serious, and considered not related to BRV by the investigator, but resulted in permanent discontinuation of the participant's study drug.

No participant ≥2 to <4 years of age reported a TEAE potentially associated with hepatotoxicity.

Suicidality

As expected, no AEs related to suicidality were reported in the ≥1 month to <4 years age group.

TEAEs that met criteria to add as ADR in paediatric participants

Based on evaluation of TEAEs in participants ≥1 month to <16 years with POS, the following TEAEs met the criteria to add as adverse drug reactions (ADRs) in the paediatric population.

Decreased appetite

Within the ≥1 month to <16 year POS group in Pool Paediatric Studies, the incidence of decreased appetite was higher (22 of 186 participants [11.8%]), compared with the adult population (4.3% in Pool S4). One event of decreased appetite was serious and 2 events led to permanent discontinuation of study drug. The TEAE of decreased appetite was considered related to BRV by the Investigator in 8 of the 16 participants. In 14 participants, the TEAE of decreased appetite started during Months 1 to 3 of BRV treatment. In 1 participant, the event resolved after BRV dose reduction.

Given the characterization of decreased appetite in the paediatric population, including the incidence of events considered related by the Investigator (about 50% of participants), the time course, and the positive dechallenge result, it is thought to be at least possibly causally related to the administration of BRV. Therefore, this term is recommended for addition to the product information for paediatric participants.

Psychomotor hyperactivity

Psychomotor hyperactivity was reported in 9 study participants, representing a higher incidence in participants ≥1 month to <16 years with POS in Pool Paediatric Studies (4.8%) compared with adult Pool S4 (0.3%). No events were serious and all were mild or moderate in intensity. All events but one started within the 3 first weeks of treatment. Two events led to the permanent discontinuation of BRV. The events in 5 participants were considered related to BRV by the Investigator and, in 2 cases, the event resolved after BRV withdrawal. Given the characterization of psychomotor hyperactivity in the paediatric population, including the incidence of events considered related by the Investigator (>50% of participants), the time course, and the positive dechallenge result, it is thought to be at least possibly causally related to the administration of BRV. Psychomotor activity, which is already listed as an ADR in the US PI, also applies to the paediatric population ≥1 month to <4 years of age.

As expected when comparing paediatric and adult populations, behavioral disorders, infection-related disorders, gastrointestinal disorders, and respiratory disorders were reported more frequently in paediatric study participants with POS compared with the established BRV safety profile in adults. The incidences were highest during the first 3 months of treatment. The majority of the events were mild or moderate in intensity, were nonserious, and did not lead to discontinuation of study drug. As these are uncontrolled data, definitive causality cannot be concluded; however, as with adults, prescribers should be made aware of these symptoms.

Laboratory findings

Overall, there were no clinically meaningful mean changes from Baseline over time in haematology and clinical chemistry values and no clinically meaningful observations in qualitative urinalysis parameters in All Paediatric Study Participants and Total POS in Pool Paediatric Studies.

Vital signs

Overall, there were no clinically meaningful mean changes from Baseline over time to the Last Value in BRV Overall for any vital sign parameter in All Paediatric Study Participants in Pool Paediatric Studies.

Post marketing experience

From 14 Jan 2016 to 14 Jan 2020

During the reporting interval from 14 Jan 2016 to 14 Jan 2020, a total of 614 safety case reports of post-marketing BRV use in patients from 1 month to <16 years of age were identified worldwide in the UCB Global Safety database. Of these 614 case reports, 22 cases were reported in patients from 1 month to <2 years, 54 cases were reported with age group 2 years to <4 years, and 538 cases were reported with age group 4 years to <16 years. The majority of cases pertaining to off-label use did not present a clinical event associated with the current age-related off-label usage. Due to the nature of spontaneous reporting, there are some recognized limitations to the search strategies used, mainly due to the lack of reported information.

A comprehensive review of the fatal cases (including potential SUDEP), AEs of interest relevant to BRV in paediatric population (suicidality-related events, behaviour disorders, blood dyscrasias, potential worsening of seizure, potential abuse, DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) syndrome, SCARs (Severe cutaneous adverse reaction), hepatotoxicity-related events, renal injury, psychosis, depression, anxiety, fall and injuries, potential effects on growth, cognition, endocrine, sexual maturation and neurodevelopment, and malignancies), and other medically important events (lack of efficacy and pregnancy) did not show concerns specific to the use of BRV in patients from 1 month to <16 years of age compared with the known safety profile of BRV in adults. No particular pattern was identified in specific syndromes with epilepsy.

As per the Company Core Data Sheet that was approved by the 14 Jan 2020 clinical cut-off (dated 22 Oct 2019), from the pooled open-label safety and PK studies in adjunctive therapy, 149 children with POS in the age range of 4 to <16 years have received BRV, of whom 116 have been treated for ≥6 months, 104 for ≥12 months, 58 for ≥24 months, and 20 for ≥36 months. The safety profile of BRV observed in children was consistent with the safety profile observed in adults.

No new safety concerns were identified in publications on the use of BRV in the paediatric population.

In conclusion, the post-marketing BRV analysis in patients from 1 month to <16 years of age did not identify new safety concerns or paediatric specific risks.

From 15 Jan 2020 to 14 Jul 2020

During the reporting interval from 15 Jan 2020 to 14 Jul 2020, a total of 59 safety case reports of post-marketing BRV use in patients from 1 month to <16 years of age were identified worldwide in the UCB Global Safety database. Of these 59 case reports, 2 cases were reported in patients from 1 month to <2 years, 3 cases were reported with age group 2 years to <4 years, and 54 cases were reported with age group 4 years to <16 years. The majority of cases pertaining to off-label use did not present a clinical event associated with the current age-related off-label usage. Due to the nature of spontaneous reporting, there are some recognized limitations to the search strategies used, mainly due to the lack of reported information.

A comprehensive review of the fatal cases (including potential SUDEP), AEs of interest relevant to BRV in paediatric population (suicidality-related events, behaviour disorders, blood dyscrasias, potential worsening of seizure, potential abuse, DRESS syndrome, SCARs, hepatotoxicity-related events, renal injury, psychosis, depression, anxiety, fall and injuries, potential effects on growth, cognition, endocrine, sexual maturation and neurodevelopment, and malignancies), and other medically important events (lack of efficacy and pregnancy) did not show safety concerns specific to the use of BRV in patients from 1 month to <16 years of age.

In addition, 27 cases that were relevant to the use of BRV as monotherapy and with the use of BRV iv in the paediatric population from 1 month to <16 years of age were evaluated. Based on review of these cases, no specific safety concerns were identified.

As per the newly updated Company Core Data Sheet (dated 07 Sep 2020), from the pooled open-label safety and pharmacokinetic studies in adjunctive therapy, 186 children with POS in the age range of 1 month to <16 years of age have received BRV, of whom 138 have been treated for ≥6 months, 123 for ≥ 12 months, 107 for ≥24 months, and 90 for ≥36 months. The safety profile of BRV observed in children was consistent with the safety profile observed in adults.

No new safety concerns were identified in publications regarding the use of BRV in the paediatric population.

In conclusion, the post-marketing BRV analysis in patients 1 month to <16 years of age did not identify new safety concerns or paediatric-specific risks during the reporting period.

2.6.1. Discussion on clinical safety

For safety, it has been agreed at scientific advice that the safety profile in children aged ≥1 month to <4 years should be compared to the safety in the older paediatric age group of ≥4 to <16 years and that the safety database in paediatric patients should include at least 100 children exposed for at least 12 months.

In the POS subgroup, 125 paediatric patients were exposed for at least 12 months, of which N=9 belonged to the 1 month to <2 years, N=2 to the ≥2 to<4 years, and N=112 to the ≥4 to <16 years age group, respectively.

The MAH has provided a safety update based on a cut-off date 14 July 2020 of long-term study N01266. From this interim report of study N01266, N=28 infants aged 1 month to <2 years have been exposed to BRV with a mean exposure of 39 months and N=14 children aged ≥2 to <4 years were exposed for a mean duration of 32 months. In total, 15 infants aged 1 month to <2 years and 7 children aged ≥2 to <4 years were exposed for at least 12 months.

Considering the safety data available for participants ≥1 month to < 2 years of age, there are 34 participants who were enrolled in the ≥1 month to < 2 years age group from the Pool Paediatric Studies. Of those 34 participants, 20 participants aged up to the ≥2 to <4 years age group. 17 out of the 20 participants were exposed to BRV for more than 1 year. The data show that the safety profile of BRV in this age group is similar to the safety profile of BRV in the paediatric population of 4 years to < 16 years of age. No safety signal was identified. The safety database is still limited for the youngest age groups but is considered sufficient.

The children <4 years generally had a higher SAE rate than the older children. For most primary system organ classes, the AE rates were numerically higher in the youngest age groups (i.e. < 4 years), but this should be interpreted with caution due to the low numbers in the youngest age groups. Thus, it may be concluded that the TEAE incidence was similar for participants with POS aged <4 years and ≥4 to <16 years except for patients <4 years of age having a higher incidence of pyrexia and decreased appetite. Participants aged <4 years also had a higher incidence of some TEAEs in the SOCs of Infections and infestations and Gastrointestinal disorders, which were as normally observed in this age group. The MAH concludes that the safety profile in children ≥1 month to <4 years was similar to the one in the older age groups. No changes have been proposed to the SmPC section 4.8 ADR table. This is agreed.

The rate of discontinuations due to TEAE was 13.5% in the overall paediatric group, and 13.3% in the youngest age group of patients < 2 years of age.

6 deaths occurred in the overall study population, 2 of these participants had POS. 1 patient died from aspiration pneumonia after 5.9 months on treatment with BRV in conjunction with 4 other AEDs.

With regards to TEAEs of special interest in the paediatric population; including growth, cognition, sexual maturation, no TEAEs within this category led to any new safety concerns for this age group.

At the time of approval of the ≥4 to <16 years age group, it was concluded that insufficient data was available on paediatric-specific safety concerns as the potential effects on growth, cognition and sexual maturation. The data provided in this application do not shed sufficient light on these issues. Thus, it is considered adequate that the 'long-term effects on growth, endocrine function or sexual maturation, neurodevelopment, cognitive and psychomotor development in paediatric patients' are included in the RMP Safety Concerns as 'Missing information'.

2.6.2. Conclusions on clinical safety

The safety was similar in the age group <4 years of age compared to older paediatric age groups with no new safety findings in this age group. The total paediatric safety database appears adequate, although it is acknowledged that the number of exposed children in the two youngest age groups was very restricted in number.

2.6.3. 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.

2.7. Risk management plan

The MAH submitted an updated RMP with this application.

The PRAC considered that the risk management plan version 8.1 is acceptable.

The CHMP agreed with the PRAC position and endorsed the Risk Management Plan version 8.1 with the following content:

Safety concerns

Table 34: *Summary of safety concerns*

Important Identified Risks	Suicidality (class label for anticonvulsant products)
Important Potential Risks	None
Missing Information	Data during pregnancy and lactation
	Long term effects on growth, endocrine function or sexual maturation, neurodevelopment, cognitive and psychomotor development in pediatric patients

Pharmacovigilance plan

Table 35: *Ongoing and planned additional pharmacovigilance activities*

Study status	**Summary of objective**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorization				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities that are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Participation in and sponsorship of European and International Registry of Antiepileptic Drugs in Pregnancy 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 Periodic Safety Update Reports (PSURs)
Participation in and sponsorship of North American Antiepileptic Drug 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

Table 36: *Summary table of pharmacovigilance activities and risk minimization activities*

Safety concern	Risk minimization measures	Pharmacovigilance activities
Suicidality (class label for anticonvulsant products)	Routine risk minimization measures: Available by prescription only Section 4.4, Special Warnings and Precautions for Use, of the Summary of Product Characteristics (SmPC; class wording) and Section 4.8, Undesirable Effects, of the SmPC Packaging Additional risk minimization measures: None	Routine pharmacovigilance (PV) activities beyond adverse reactions reporting and signal detection: The Columbia-Suicide Severity Rating Scale used in all clinical studies (in subjects aged <6 years, the symptoms and signs of depression are recorded) Additional PV activity: None
Data during pregnancy and lactation	Routine risk minimization measures: Available by prescription only Section 4.6, Fertility, Pregnancy and Lactation of the SmPC Additional risk minimization measures: None	Routine PV activities beyond adverse reactions reporting and signal detection: None Additional PV activities: Participation in and sponsorship of European and International Registry of Antiepileptic Drugs in Pregnancy and North American Antiepileptic Drug Pregnancy Registry. Activities include provision of requested data from UCB to the registries and regular review of interim outputs from the registries.
Long-term effects on growth, endocrine function or sexual maturation, neurodevelopment, and cognitive and psychomotor development in pediatric patients	Routine risk minimization measures: Available by prescription only Additional risk minimization measures: None	Routine PV activities beyond adverse reactions reporting and signal detection: None Additional PV activity: None

PV=pharmacovigilance; SmPC=summary of product characteristics

2.8. Update of the Product information

As a consequence of this extension of indication variation, sections 2, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.3 and 6.5 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to implement editorial updates, which were reviewed and accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative of United Kingdom (Northern Ireland).

Please refer to Attachment 1 which includes all proposed changes to the Product Information.

2.8.1. User consultation

The MAH 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.

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 have also been found acceptable.

2.9. Additional Expert Consultation

During the assessment procedure, the CHMP convened an ad hoc expert group (AHEG) in order to discuss a number of questions including the extrapolation of efficacy data in POS from the adults to the younger (1 month-2 year) paediatric population, the extrapolation of efficacy in isolated POS to POS with coexisting seizure types and the relevance of LEV data for conclusion on brivaracetam efficacy in the younger paediatric population.

The details of the questions and the summary of the expert group discussion is detailed hereafter:

GENERAL

1. **Is it possible to extrapolate efficacy data in partial onset seizures (POS) from adults to children aged ≥1 month to <2 years based on similar drug exposure only, considering the immaturity of the developing brain, potentially different pathophysiology, and different clinical presentation (POS together with other seizure types) in this age group?**

Whether efficacy can be established based solely on extrapolation (without data from trial) was not considered a straightforward question and the opinion of the experts was clearly split.

- Some experts agreed that extrapolation is possible for this age group based on the arguments presented by the Applicant. Some experts acknowledged that presentation of the seizure is not a relevant aspect related to efficacy. Additionally, it was noted that both drugs are anti-seizures and not anti-epileptogenic drugs and, in this regard, pathophysiology of seizures is considered to be similar in children from 1 month to 2 years and in children from 2 to 4 years. An expert noted that one exception could be West syndrome. Another expert commented that waiting for a perfect study may delay the access for the drug and that extrapolation could be a pragmatic approach provided we are reassured on the safety profile.
- Other experts agreed that extrapolation is possible but based on scientific theoretical grounds that are considered of a rather low scientific level by these experts. Therefore, they must be considered only as supportive arguments in addition to data from trials, which are definitely needed. One expert noted that, paradoxically, extrapolation could be easier for situations without studies (e.g. Brivaracetam) than for situations for which we have studies showing negative results (Lacosamide). Another expert did not believe that extrapolation was possible because even if the physiopathological manifestations are considered to be similar, impact on the brain may be different, due to a different brain developmental status. For this expert, this argument is also applicable for refusing extrapolation from 2-4 years, an argument shared to some extend also by another member. A couple of experts noted that posology (exposure drug) could be a relevant aspect because PK profile could be different in small children which may impact safety (e.g. metabolism may be slower exposing children to higher doses). It was clarified by the Rapporteurs to the experts that this aspect has been considered in the assessment and that extrapolation is considered under comparable exposure levels.

The two patients´ representatives were convinced that pathophysiology could be similar but still they have concerns specially regarding to the impact on neurodevelopmental status, and thus still consider that well-designed clinical trials are needed. One of the patient's representatives was also concerned about the lack of effect in contrast with potential risk of adverse events, especially on children with severe epileptic syndromes.

2. **Can efficacy in isolated POS be extrapolated to efficacy in POS with coexisting seizure types, which is an epileptic syndrome more often present in the younger age group?**

Similarly, experts were split as there were some experts who would not agree on extrapolation approach as a sole strategy to get confirmatory evidence on efficacy. Taken this into consideration, experts also express the following views:
While there is a risk of aggregation of other seizures with certain drugs, overall experts do not think that the existence of other seizure does modifies the response of brivaracetam or lacosamide on seizures. However, it was noted that when there are global and focal seizures in children aged 1 month to 2 years, it is possible that these patients, most likely without a diagnosis, suffer from an epileptic encephalopathy and likely a refractory epilepsy. As per regards of refractory epilepsy, it was noted that except for the auto-

limitated seizures, young children may become refractory quite soon and several changes in the medication is needed. The prevalence of refractory epilepsy is about the same in both groups (up to 30% as reported by one of the patients representative). Therefore, it was agreed that the need for new drugs is the same in the two age groups.
A couple of experts noted that currently prescription is not based on precision medicine (specific to the syndrome) and therefore, the risk of prescribing an ineffective drug already sin the clinical practice and having another drug could be helpful for the management of seizures in these patients.

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3. **For levetiracetam, data from a placebo-controlled trial in pediatric subjects with refractory POS, aged 1 month to < 4 years, supported the granting of a corresponding treatment indication. Taking into consideration that the MOA of levetiracetam and brivaracetam may not be completely identical, does the SAG consider these data relevant for any conclusions on brivaracetam efficacy in children aged ≥1 month to <2 years, given the pharmacological dissimilarity between brivaracetam and levetiracetam?**

Overall and based on the discussion already provided for Q1 and Q2, it may be possible to use levetiracetam data to extrapolate on brivaracetam, as proof of efficacy exists for a similar drug. However, there were some specific concerns:

- One expert thought efficacy could be extrapolated because the MOA is essentially the same, but the expert expressed concerns regarding safety, in particular relevant to the impact on cognition by brivaracetam.
- Another expert noted that this is not a straightforward question because clinical data is more relevant that MOA and the clinical data of brivaracetam was insufficient to provide evidence on efficacy. This expert believes that extrapolation should be better based on data on the same drug in a different age group (brivaracetam) but not on a similar one (levetiracetam).
- Finally, another expert noted that study populations were different.

The two patients' representatives expressed also concerns regarding this strategy, based on personal experience with both drugs.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Partial-onset epilepsies, associated with a local cerebral lesion, are the most frequent, representing approximately 60% of cases. Generalized epilepsies represent approximately 30% of cases. In the remaining 10% of seizures, the classification is uncertain (Noe, 2011; Hauser et al, 1993). Based on the ILAE, revised seizure classification terminology (Fisher et al, 2017), the term "focal seizures" should replace "partial seizures" when describing seizure onset. These terms are synonymous and describe seizures that originate at some point within networks limited to 1 hemisphere of the brain.

Among paediatric populations, there are significant differences in the manifestations, etiology, prognosis, therapeutic response, and impact of epileptic seizures. The etiology of partial epilepsies may be idiopathic (presumably related to genetic factors), symptomatic (identifiable previous brain injury or encephalopathy), or cryptogenic (no identifiable brain lesion or abnormality). Partial-onset seizures have been classified on the basis of whether or not awareness is impaired during the attack and whether or not progression to generalized convulsions occurs:

- Simple partial seizures (when awareness is not impaired).
- Complex partial seizures (when awareness is impaired).

- Partial seizures evolving to secondarily generalized (tonic-clonic or tonic or clonic) seizures.

The clinical presentation of POS may be subjective, objective, or both; convulsive or nonconvulsive; brief or prolonged; inconspicuous or dramatic and bizarre. The subjective and/or objective symptoms observed in POS depend on the functional organization at the site of ictal origin and/or sites of propagation. Thus, symptoms may be motor, sensory, mental, emotional, cognitive, or linguistic (alone or in various combinations).

EEG or video/EEG is recommended in the EMA Epilepsy guidelines as complementary assessment of efficacy of AEDs in children aged 1 month to less than 4 years. (EMA draft epilepsy guideline (2018): "*In younger children, from 1 month to less than 4 years, EEG or video/EEG may complete and evidence the clinical manifestation of seizures, in particular subtle clinical seizures can be confirmed when correlated with EEG*." EMA Adopted epilepsy guideline (2010): "*In the very young children (i.e. 1 month – less than 4 years), once efficacy has been shown in the older paediatric population, short term assessment of response by using video EEG monitoring may be sufficient*."

3.1.2. Available therapies and unmet medical need

Most patients with epilepsy require appropriate pharmacological therapy (Glauser et al, 2006; Perucca, 1996; Abou-Khalil, 2019). The newer AEDs differ from older agents in several important ways, including MoA, spectrum of activity, and PK (Abou-Khalil, 2019).

Pharmacological treatment of epilepsy usually starts with an AED on monotherapy. If seizures are not adequately controlled or there are intolerable adverse drug effects with the initial monotherapy, a second or third different AED on monotherapy can be used. Alternatively, adjunctive therapy can be explored. In adjunctive therapy, it is recommended to use drugs with different mechanisms of action. Despite availability of many approved AEDs, more than 30% of patients have inadequate seizure control on currently available AEDs or experience significant adverse drug effects (Beghi et al, 2015). Therefore, a need remains for AEDs with improved efficacy and tolerability (Sander, 1998; Institute of Medicine, 2012).

LEV is the first-in-class AED with the main MoA through binding to the SV2A. BRV shares the same main MoA via binding to SV2A and is relatively similar molecularly. LEV is approved for adjunctive treatment of POS from 1 months to 4 years of age. For LEV, a placebo-controlled study of 5 days duration in 109 evaluable paediatric patients aged from 1 month to ≤4 years with a primary endpoint using 48 h video-EEG.

3.1.3. Main clinical studies

3.2. Favourable effects

In 2018, an extrapolation of efficacy based on PK/PD data was approved for children ≥4 years to <16 years. The current extension of indication is based on the possibility to further extrapolate efficacy from adults and adolescents aged from 16 years down to infants aged ≥ 1 month to <4 years. To support this extrapolation exercise, data from the main study N01263 and its long-term follow-up study N01266 has been provided.

Population PK and PK/PD modelling, based on seizure count data for BRV and LEV, was performed to support the extrapolation of efficacy between adults and the paediatrics (≥1 month to < 4 years). The PK/PD modelling indicated a similar exposure-response relationship in adults and children for LEV. Therefore, a similar relationship was assumed for BRV. In the external validation of the combined adult/paediatric BRV PK/PD model, the model did not seem to describe the effect on seizure counts in

patients ≥1 month to <4 years in study N01263 and N01266. Due to the limitations in the external validation, the PK/PD model cannot be used to support this extension. It is noted that the observed effect on seizure counts included in the PK/PD analysis seems to be different from the effect reported in the clinical studies N01266 and N01263. The popPK simulations were performed to support the proposed posology based on a similar exposure between adults and the paediatrics.

Study N01263: A phase 2a, open-label, single-arm, multicenter, fixed 3-step up-titration study in participants aged between ≥1 month and <16 years with epilepsy evaluating the PK, safety, and efficacy of BRV. All participants completed a 1-week Baseline Period, followed by a 3-week Evaluation Period with weekly fixed 3-step up-titration of the BRV dose. BRV oral solution was administered at weekly increasing doses of approximately 0.5mg/kg, 1.0mg/kg, and 2.0mg/kg bid for participants <8 years of age.

In the subgroup of children aged ≥1 month to <2 years, of the 26 patients with available 24-h EEG data both at baseline and at the end of the study, the majority had an unchanged seizure status during the study: 10/26 were neither seizure-free at baseline nor evaluation visit whereas 9/26 were seizure-free at both visits, i.e. 19/26 (73%) had a unchanged seizure status on EEG. Of the remaining 7 patients, 5 of the 15 patients that were not seizure free at baseline EEG had become seizure-free on EEG at the end of the study, and 2 went from seizure-free to not seizure-free. The proportions were similar in the subgroups of patients with either POS or primary generalized seizures. These data cannot support an effect of BRV as adjunctive therapy in children aged ≥1 month to <2 years with epilepsy.

Based on diary data of seizure frequency over the 3-weeks treatment period, 4/27 (14.8%) in the ≥1 month to <2 years overall subgroup were 50% responders. In the POS subgroup in this age interval, the responder rate was 3/12 (25%). This was lower than in the older age intervals, where 9/41 (22%) in the overall group ≥2 to <12 years, 7/19 (36.8%) in the POS subgroup of this age interval were 50% responders, and 4/12 (33.3%) in the overall group ≥12 to <16 years, 1/4 in the POS subgroup of this age interval were 50% responders. The low number of treated patients indicates that the data should be interpreted with caution. For comparison, for LEV, the 50% responder rate for paediatric patients aged 1 month to <4 years was 43.6% vs 19.6% for placebo.

Study N01266 is an ongoing Phase 3, open-label, single-arm, multicenter, LTFU study to evaluate the safety and efficacy of BRV in study participants with epilepsy. In addition to patients having completed study N01263 being offered to roll over to study N01266, additional paediatric patients were enrolled directly into the study. The total number of participants was 249, of which only 28 were aged ≥1 month to <2 years and 14 were aged ≥2 years to <4 years.

The 50% responder rate compared to baseline in patients aged ≥2 years to <17 years was 81/167 (50.9%) in the overall group and 61/134 (45.5%) in the POS subgroup of the evaluable patients.

For patients ≥1 month to <2 years, based on 24-h EEG data obtained from a total of N=14 patients, only 8 patients contributed with 'evaluable data'. Of these, 4/4 with POS and 2/4 with PGS were 50% responders compared to baseline.

In addition, a non-clinical comparison of BRV and LEV had previously been recommended and was provided by the MAH. The MAH presents data in support of the primary MoA for both BRV and LEV being via binding to SV2A with a reported 10- to 30-fold higher affinity of BRV for binding to SV2A than LEV. This corresponds quite well with the 15-20-fold higher free plasma concentration for BRV than LEV at the maximal approved dose.

Both BRV and LEV have a similar activity profile in animal models of acute seizures and chronic epilepsy, which is quite different from the profile for AEDs with other mechanisms of action. In all the animal models where both have an effect, the potency of BRV is higher than LEV, consistent with a higher affinity for SV2A.

3.3. Uncertainties and limitations about favourable effects

No randomised controlled trial focusing on clinical efficacy in the paediatric population has been provided in the current application. Both studies N01263 and N01266 are single arm trials that do not allow for the isolation of the effects of BRV. Therefore, the efficacy of BRV is extrapolated from the adult population to those between 2-4 years old, based on presumed similar pathophysiology and PK/PD. This, however, gives rise to some uncertainty about the precise metrics of efficacy. Extrapolation of efficacy in adjunctive therapy of POS as established in adults is proposed by the MAH, with support of clinical pharmacology data. Similar exposure as in adults and dose recommendations are supported with population PK modelling and simulation. However, the AHEG did not consider that the pathophysiology in patients below two years of age is sufficiently similar to that of adults, to allow for an extrapolation based on only a PK bridge (similar exposure).

It is not entirely clear that the MoA of LEV and BRV are fully similar (efficacy exclusively mediated through SV2A). Further, there was limitations, and consequent uncertainty, regarding the external validation of the BRV the PK/PD model and therefore PK/PD modelling cannot be used to support the extrapolation of efficacy from adults to children below 4 years of age.

With regards to differences in disease between children younger than 2 years of age and adults, it is unclear whether efficacy in isolated POS, as more commonly seen in adults, may be extrapolated to efficacy in POS with coexisting seizure types, which is an epileptic syndrome more often present in the younger age group.

3.4. Unfavourable effects

For safety, it has been agreed at scientific advice that the safety profile in children aged ≥1 month to <4 years should be compared to the safety in the older paediatric age group of ≥4 to <16 years and that the safety database in the total paediatric patient population should include at least 100 children exposed for at least 12 months.

In the POS subgroup, 125 paediatric patients were exposed for at least 12 months, of which N=9 belonged to the 1 month to <2 years, N=2 to the ≥2 to<4 years, and N=112 to the ≥4 to <16 years age group, respectively. There are very few children below the age of 4 years. In the POS subgroup, 125 paediatric patients were exposed for at least 12 months, of which N=9 belonged to the 1 month to <2 years, N=2 to the ≥2 to<4 years, and N=112 to the ≥4 to <16 years age group, respectively. Thus, the total paediatric safety database appears adequate, although the number of exposed children in the two youngest age groups was very restricted in number.

The MAH has provided a safety update based on a cut-off date 14 July 2020 of long-term study N01266. From this interim report of study N01266, N=28 infants aged 1 month to <2 years have been exposed to BRV with a mean exposure of 39 months and N=14 children aged ≥2 to <4 years were exposed for a mean duration of 32 months. In total, 15 infants aged 1 month to <2 years and 7 children aged ≥2 to <4 years were exposed for at least 12 months. Considering the safety data available for participants ≥1 month to < 2 years of age, there are 34 participants who were enrolled in the ≥1 month to < 2 years age group from the Pool Paediatric Studies. Of those 34 participants, 20 participants aged up to the ≥2 to <4 years age group. 17 out of the 20 participants were exposed to BRV for more than 1 year. The data show that the safety profile of BRV in this age group is similar to the safety profile of BRV in the paediatric population of 4 years to < 16 years of age. No safety signal was identified. The safety database is still limited for the youngest age groups but is considered sufficient.

The children <4 years generally had a higher SAE rate than the older children. The TEAE incidence was similar for participants with POS aged <4 years and ≥4 to <16 years except for patients <4 years of age having a higher incidence of pyrexia and decreased appetite. Participants aged <4 years also had a higher

incidence of some TEAEs in the SOCs of Infections and infestations and Gastrointestinal disorders, which were as normally observed in this age group.

With regards to TEAEs of special interest in the paediatric population; including growth, cognition, sexual maturation, no TEAEs within this category led to any new safety concerns for this age group.

The safety profile in the age group <4 years of age was consistent with that of older paediatric age groups with no new safety findings in the age group of <4 years of age.

3.5. 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 safety database, particularly in the very young, is relatively small, and inferences of safety rely to a certain extent on extrapolation from adults.

In the previous extension of indication down to 4 years and above (EMEA/H/C/003898/II/0010/G), it was concluded that insufficient long-term data on the possible effects on growth, neurocognitive development and sexual maturation was available. The study data from the current application did not shed sufficient light on these remaining uncertainties. Thus, it is considered adequate that the RMP Summary of safety concerns includes 'Long-term effects on growth, endocrine function or sexual maturation, neurodevelopment, cognitive and psychomotor development in paediatric patients' as missing information.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

In the current extension of indication procedure, the MAH seeks an extension of indication for the adjunctive treatment of partial onset seizures in children ≥1 month to <4 years of age, based on extrapolation of safety and efficacy from studies in patients 16 years and older, given similar exposure from the proposed dosing regimen. Weight-based paediatric dosing regimens are proposed using population PK modelling and simulations.

Extrapolation of efficacy from adults to children above 2 years of age based on similar exposure is considered acceptable based on similarity of disease, in accordance with prior CHMP SA to the MAH and based on available scientific understanding. The extrapolation of efficacy from adult to paediatrics ≥1 month to <2 years of age is not supported, due to limitations in the PK/PD model, and uncertainties about the similarity of pathophysiology given the lack of maturation of the nervous system.

The CHMP convened an AHEG on the 7th of October to discuss whether an extension of indication for those below 2 years of age could be based on these arguments. The AHEG was split in their views regarding whether an extrapolation of efficacy may be based on similar drug exposure only and there were views that efficacy data from a well-designed study was needed for this age group as well.

The CHMP is not sufficiently certain about the possibility to extrapolate efficacy for BRV from efficacy data on LEV. Regarding this, the AHEG was also split, and among other views it was noted that the similarity of MoA is not sufficient but clinical data is needed and that extrapolation should better be based on data on the same active substance (i.e. BRV) from a different age group than on data from a similar active substance (LEV) in the same age group.

In summary, the discussion held by the AHEG did not provide clear support the extrapolation of efficacy based similar drug exposure only, neither on efficacy results from a compound with similar MoA. Therefore, there was not sufficient strength and consistency of arguments for an extrapolation, to impact the CHMP position that extrapolation of efficacy from adults is permissible down to 2 years, whereas substantial uncertainties about this procedure exists for those that are younger.

The paediatric safety profile of BRV evaluated in the long-term follow-up open-label, single-arm study N01266 as adjunctive treatment was consistent with previously established safety profile in adult and adolescent patients with partial onset seizures from 16 years. The total paediatric safety database is in line with what has previously been recommended by the CHMP for a paediatric indication, although the number of exposed children in the two youngest age groups is limited. Overall, however, the safety profile is acceptable in the context, provided that efficacy is deemed to be established.

3.6.2. Balance of benefits and risks

The CHMP agrees that the extrapolated benefit of Briviact as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in children from 2 years to 4 years of age is considered established and outweigh the risks.

It is also agreed that the extrapolation of efficacy to children aged ≥1 month to <2 years has not been established. Therefore, the CHMP cannot recommend an extension of the Briviact indication to this younger paediatric population.

3.7. Conclusions

The overall B/R of Briviact for the extension of indication in children from 2 years of age 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**
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 and IIIB
B.II.f.1.b.2	B.II.f.1.b.2 - Stability of FP - Extension of the shelf life of the finished product - After first opening (supported by real time data)	Type IB	I, IIIA and IIIB

- Extension of indication to include patients from 2 years to 4 years of age for the treatment, as adjunctive therapy, of partial onset seizures with or without secondary generalisation. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The RMP version 8.1 has also been agreed.

- Extension of the shelf life after the first opening of Briviact Oral Solution (supported by real time data) (B.II.f.1.b.2 QUALITY CHANGES - FINISHED PRODUCT - Stability - Change in the shelf-life or storage

conditions of the finished product - Extension of the shelf life of the finished product). As a consequence, section 6.3 of the SmPC (oral solution) is updated.

Furthermore, the PI is brought in line with the latest QRD template version 10.2 and the MAH took the opportunity to implement minor editorial updates.

The Labelling and Package Leaflet are updated in accordance.

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annex(es) I, IIIA and IIIB and to the Risk Management Plan are recommended.

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

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Briviact-H-C-003898-0032G'.

Attachments

1. SmPC, Labelling and Package Leaflet (changes highlighted) as adopted by the CHMP on 27 January 2022.

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by 11 February 2022. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies/european-medicines-agency-guidance-document-identification-commercially-confidential-information_en.pdf

   In addition, should you consider that the CHMP assessment report contains personal data, please provide the EMA Procedure Assistant your proposal for deletion of these data in "track changes" and with detailed justification by <No date in SIAMED>. We would like to remind you that, according to Article 4(1) of Regulation (EU) 2016/679 (General Data Protection Regulation, "GDPR") 'personal data' means any information, relating to an identified or identifiable natural person (the 'data subject'). An identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.

   It is important to clarify that pseudonymised data are also considered personal data. According to Article 4(5) of GDPR pseudonymisation means that personal data is processed in a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information (e.g. key-coded data).

   Accordingly, the name and the patient identification number are two examples of personal data which may relate to an identified or identifiable natural person. The definitions also encompass for instance: office e-mail address or phone number of a company, data concerning health, e.g. information in medical records, clinical reports or case narratives which relates to an identifiable individual."

2. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.

3. If the approved RMP is using Rev. 2 of the 'Guidance on the format of the RMP in the EU' and the RMP 'Part VI: Summary of the risk management plan' has been updated in the procedure, the MAH is reminded to provide to the EMA Procedure Assistant by Eudralink a PDF version of the 'Part VI: Summary of the risk management plan' as a standalone document, within 14 calendar days of the receipt of the CHMP Opinion. The PDF should contain only text and tables and be free of metadata, headers and footers.