24 June 2021
EMA/393940/2021
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Briviact

brivaracetam

Procedure no: EMEA/H/C/003898/P46/008

Note

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

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List of abbreviations

	AE	adverse event
	bid	twice daily
	BP	blood pressure
	BRV	brivaracetam, Briviact®
	CHMP	Committee for Medicinal Products for Human Use
	CSR	clinical study report
	DBP	diastolic blood pressure
	ECG	electrocardiogram
	IIB	initiating iv BRV
	IOB	initiating oral BRV
	IPD	important protocol deviation
	iv	intravenous
	MPA	Medical Products Agency
	OLB	open-label BRV
	PCST	possibly clinically significant treatment-emergent
	PDILI	potential drug-induced liver injury
	PK	pharmacokinetics
	POS	partial-onset seizure(s)
	PT	preferred term
QTcF	QT interval corrected by Fridericia's formula	
	RxB	prescribed BRV
	SAE	serious adverse event
	SBP	systolic blood pressure
	SD	standard deviation
	SS	Safety Set
	SS-iv	Safety Set-intravenous
	TEAE	treatment-emergent adverse event
	VNS	vagus nerve stimulation

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1. Introduction

On 8 April 2021, the MAH submitted a paediatric dossier for study EP0065, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

2. Scientific discussion

2.1. Information on the development program

Briviact® is currently approved for use as adjunctive therapy in the treatment of partial-onset seizures (POS) with or without secondary generalisation in adults, adolescents, and children ≥4 years of age with epilepsy.

UCB submitted a grouped variation application on 01 Feb 2021 to extend the current indication of Briviact in patients ≥1 month to <4 years of age (EMEA/H/C/003898/II/0032/G). EP0065 was not included in Pool Pediatric Studies submitted in the grouped variation application because it included iv BRV in its evaluation while Pool Pediatric Studies included oral treatment only; therefore, the iv data from EP0065 were not included in the previous submission. The iv application for pediatric patients ≥4 to <16 years of age has been formally approved based upon extrapolation from adult data; therefore, the results from EP0065 were not needed in the previous and currently ongoing submissions.

Based on the final data presented in this clinical report and the corresponding clinical study report (CSR), the Applicants concludes that data do not influence the benefit-risk balance of BRV to require any regulatory action on the marketing authorization of BRIVIACT.

CHMP comments

The ongoing variation procedure (EMEA/H/C/003898/II/0032/G) aims at market authorisation for children aged between 1 month and 4 years. EP0065 includes data for children of this age. Extrapolation of efficacy and iv administration, as for children ≥4 years, has been not possible for the youngest children. According to the SmPC section 4.2 of the BRV iv solution, the iv solution is an alternative when oral administration temporarily is not possible. Thus, the use of iv solution assumes an indication of oral use and separate assessment of the pediatric iv data preceding the CHMP decision on the oral indication, is suboptimal. A joint assessment of oral and iv data would enable a full assessment of the totality of data and it is therefore suggested that the MAH submits the report of study EP0065 to be included in the EMEA/H/C/003898/II/0032/G variation procedure. The paediatric iv data can then be assessed in an appropriate context and any possible regulatory action decided upon. Please see also the comment at the end of this report.

2.2. Information on the pharmaceutical formulation used in the study

EP0065 studied iv BRV administered as a 15-minute infusion and bolus (up to 2 minute infusion) in study participants ≥1 month to <16 years of age with epilepsy.

2.3. Clinical aspects

2.3.1. Introduction

Briviact® is currently approved for use as adjunctive therapy in the treatment of partial-onset seizures (POS) with or without secondary generalisation in adults, adolescents, and children ≥4 years of age with epilepsy. A grouped variation application was submitted on 01 Feb 2021 to extend the current indication of Briviact in patients ≥1 month to <4 years of age. This report concerns study EP0065 in which iv administration of BRV was studied in children aged ≥1 month to <16 years.

2.3.2. Clinical study EP0065

Description

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.

Methods

Objective

The primary objective of EP0065 was to evaluate the PK, safety, and tolerability of BRV administered as a 15-minute iv infusion and iv bolus (up to 2 minute infusion) in study participants ≥1 month to <16 years of age with epilepsy.

Study design

It was planned for approximately 50 enrolled study participants to receive iv BRV in 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

The following study participants were eligible for enrollment in EP0065:

- Open-label BRV (OLB) participants: currently receiving oral BRV as participants in a long term, open label study
- Prescribed-BRV (RxB) participants: currently receiving prescribed oral BRV from commercial supply
- Initiating Oral BRV (IOB) participants: not currently receiving BRV; first dose of BRV in EP0065 was oral tablet or solution (Note that, in the Czech Republic, only IOB study participants were enrolled in the study)
- Initiating iv BRV (IIB) participants: not currently receiving BRV; first dose of BRV in EP0065 was by iv infusion

During the Screening Period, OLB and RxB participants continued to receive oral BRV (tablet or oral solution) in accordance with their long term, open label study dosing or prescribed dosing, respectively. The IOB and IIB participants did not receive BRV during the Screening Period.

Eligible OLB, RxB, and IIB participants progressed directly from the Screening Period to the iv PK Period; whereas, IOB participants entered a 2- to 10-day IOB Treatment Period in which they received oral BRV before progressing to the iv PK Period. The initial oral BRV dose in the IOB Treatment Period was 2mg/kg/day.

During the iv PK Period, iv BRV was administered every 12 hours ±2 hours. All study participants received 1 to 2 consecutive doses of BRV; however, based on medical need, study participants may have received up to 10 consecutive doses of iv BRV. Blood sampling for PK analyses (herein referred to as "PK sampling") occurred with the first iv BRV administration and with 1 other iv BRV administration. For OLB, RxB, and IOB participants, the first iv BRV dose was equivalent (mg to mg) to the final dose of oral BRV prior to the first iv dose. For IIB participants, the first iv BRV dose was 1mg/kg, not to exceed 50mg for study participants with body weights ≥50kg. For all study participants, iv BRV doses may have been adjusted at the Investigator's discretion after PK sampling for 2 iv doses; however, no doses may have exceeded the maximum doses indicated below. During the iv PK Period, BRV may only have been administered by iv infusion.

At the completion of the iv PK Period, study participants who planned to continue oral BRV treatment enrolled in a long term, open-label BRV study. Study participants who had received ≥4 doses of BRV and did not plan to continue treatment with BRV after completion of the iv PK Period or who discontinued BRV treatment during the study had a Down Titration Period of up to 4 weeks (28 days) for gradual discontinuation of BRV and a Safety (BRV free) Period of 2 weeks (14 days) after the final dose of BRV. Study participants who had received <4 doses of BRV may have had BRV down titrated at the discretion of the Investigator.

Dose

For IOB and IIB participants, the maximum BRV dose was 4mg/kg/day (2mg/kg twice daily [bid]). For OLB and RxB participants, the maximum BRV dose was 5mg/kg/day (rounded) in recognition of the possibility that some of these study participants may have been using this dose when they entered EP0065. Throughout the study, no study participants may have received a dose greater than BRV 200mg/day. Oral BRV was administered in equally divided doses bid.

The maximum possible study duration was 68 days and the maximum period of BRV administration was 44 days including a minimum of 1 dose of iv BRV.

Study population /Sample size

A total of 50 study participants enrolled in the study and all 50 study participants were included in the Safety Set (SS) and the Safety Set-intravenous (SS-iv) (identical analysis sets). No study participants discontinued due to an AE or discontinued for any other reasons. All 50 study participants completed the study: 26 study participants in the 15-minute infusion group and 24 study participants in the bolus group.

Overall, there were 22 IOB participants who entered and completed the IOB Treatment Period. All 50 study participants entered and completed the iv PK Period and entered and completed the Follow-up Period. Only those study participants who received ≥4 doses of BRV during either the IOB Treatment Period or the iv PK Period and who did not plan to continue treatment with BRV or who discontinued from the study were required to down titrate (and enter the Safety Period). No study participants required down titration; therefore, none entered the Safety Period.

Treatments

Table 1 BRV dosing during the screening, IOB treatment , and iv PK periods

	Study Period				
	Screening (1-10 days)	IOB Treatment (2-10 days)[a]	iv PK (1-6 days)[b]		
Study Participants	**Dose (oral)**	**Dose (oral)**	**First dose (iv)**	**Subsequent dose(s) (iv)**	**Maximum BRV Dose**
OLB	Per Long-Term, Open-Label study	N/A	mg-to-mg equivalent to last oral dose	Equivalent to first iv dose until PK sampling was completed.	5mg/kg/day (rounded) nte. 200mg/day for body weight ≥40kg
RxB	As prescribed	N/A	mg-to-mg equivalent to last oral dose	Equivalent to first iv dose until PK sampling was completed.	5mg/kg/day (rounded) nte. 200mg/day for body weight ≥40kg
IOB[c]	Not receiving BRV	Participants <50kg: 2mg/kg/day Participants ≥50kg: nte. 100mg/day	mg-to-mg equivalent to last oral dose	Equivalent to first iv dose until PK sampling was completed.	4mg/kg/day nte. 200mg/day for body weight ≥50kg
IIB	Not receiving BRV	N/A	Participants <50kg: 1mg/kg Participants ≥50kg: 50mg	Equivalent to first iv dose until PK sampling was completed.	4mg/kg/day nte. 200mg/day for body weight ≥50kg

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

Note: Oral BRV was administered in equally divided doses bid as either tablets or oral solution. Tablets were administered orally and oral solution was administered either orally or by enteric administration (eg, feeding tube) based on study participant need.

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

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

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

[c] Note that only IOB study participants were enrolled in the study in the Czech Republic.

Outcomes/endpoints

The PK variable of EP0065 was the plasma concentration of BRV (parent compound only) before, during, and after iv BRV administration.

The primary safety variables of EP0065 were as follows:

- Adverse events (AEs) throughout the study
- Study participant withdrawals due to AEs

Other safety variables included:

- 12-lead electrocardiogram (ECG) values before, during, and after each iv BRV administration
- Blood pressure (BP), pulse rate, respiratory rate, and temperature values before, during, and after each iv BRV administration
- Clinical laboratory parameters (hematology, chemistry, and endocrinology) pre- and posttreatment
- Urinalysis parameters pre- and posttreatment

Posttreatment parameters were only available for study participants who down titrated and underwent Visit 13 assessments.

Table 2 Schedule of Study Assessments (Screening Period through end of iv PK Period)

Period	Screening	IOB Treatment	iv PK		Unsch[a]
Visit	V1	V2	V3 to V12	TC-1	
Study Day for					
OLB, RxB, IIB study participants	-10 to -1	N/A	1 to 6	2 to 9	N/A
IOB study participants	-20 to -11	-10 to -1			
Clinical chemistry, hematology, and endocrinology	X				
Urinalysis (for study participants for whom sample collection was feasible)	X				
Pregnancy testing (urine; for females of CB potential)	X	X	X[b]		
AEs[h]	X	X	X	X	X
Withdrawal criteria		X	X	X	X
C-SSRS[i]	X	X	X[j]		X[k]
PK sampling			X[g]		
Dispense/collect oral BRV from EP0065 supply		X	X[l]		
Administration of iv BRV			X		
Study Day for					
OLB, RxB, IIB study participants	-10 to -1	N/A	1 to 6	2 to 9	N/A
IOB study participants	-20 to -11	-10 to -1			

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; BRV=brivaracetam; CB=childbearing; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; eCRF=electronic Case Report form; IIB=Initiating iv BRV; IOB=Initiating Oral BRV; iv=intravenous; N/A=not applicable; OLB=Open-label BRV; PK=pharmacokinetic; RxB=Prescribed BRV; TC=Telephone Contact; Unsch=Unscheduled; V=Visit

[a] Additional assessments may have been performed at the Investigator's discretion.
[b] Was to be performed prior to dispensing/administering the initial dose of BRV in this period (for the PK Period, at Visit 3 only).
[c] Complete examinations were to be conducted at Visit 1. Brief physical and neurological examinations were to be conducted at other designated visits. Clinically new or worsened abnormalities must have been reported as AEs.
[d] The Investigator was to use clinical judgment in deciding which study participants were selected for evaluation of Tanner Stage (ie, those study participants who were pubescent).
[e] To be performed prior to the initial dose of BRV (Visit 3) and daily thereafter, ideally after the morning dose.
[f] Body weight determinations were to be made with study participants wearing light clothing and not wearing shoes.
[g] Detailed timings for these assessments were provided in Table 3–4 (15-minute [±3 minutes] infusion) and Table 3–5 (bolus [up to 2-minute infusion]).
[h] Infusion-site related AEs for study participants who returned to/enter a long-term, open-label study should have continued to be recorded in the EP0065 eCRF.
[I] The C-SSRS was assessed only in study participants ≥6 years of age. The C-SSRS versions to be used are specified in Section 4.7.3.
[j] Assessed prior to the administration of iv BRV at Visit 3 and after the final iv dose of BRV each day for Visits 4 to 12, as applicable.
[k] The C-SSRS was assessed only in study participants who attended this visit due to safety reasons.
[l] Collected as needed for IOB study participants who entered the long-term, open-label study. To be dispensed, as needed, for study participants who continued into the Down-Titration Period at the final visit of the PK Period.

Table 3 Schedule for iv PK Period ECGs, vital signs, and PK sampling (15-minute BRV infusion)

	Time relative to initiation of iv BRV infusion							
	Pre-initiation	Post-initiation						
Assessment	≤ 1hr	5min (±1min)	10min (±1min)	15min[a] (±2min)	30min (±5min)	60min (±10min)	2hr (±15min)	3hr (±15min)
12-lead ECG	X	X	X	X	X	X	X	
Vital signs (BP, pulse rate, respiratory rate, temperature)	X	X	X	X	X	X	X[c]	
PK sampling[b]	X			X				X

BP=blood pressure; BRV=brivaracetam; ECG=electrocardiogram; hr=hour(s); min=minute(s); iv=intravenous; PK=pharmacokinetic; PCS=possibly clinically significant

[a] To be conducted at the end of infusion.

[b] Blood samples for PK analyses were collected for the initial BRV infusion and 1 subsequent BRV infusion only. Blood samples were collected after completion of the ECG and the vital sign measurements and from a region of the body not used for iv the BRV administration.

[c] Per Protocol Amendment 1 (19 Jun 2019), only BP was collected at 2 hours post initiation of infusion. Additional vital sign monitoring, specifically BP, was necessary if a low PCS BP value occurred at 2 hours after the start of an infusion.

Table 4 Schedule for iv PK Period ECGs, vital signs, and PK sampling (bolus [up to 2-minute BRV infusion])

	Time relative to initiation of iv BRV administration							
	Pre-initiation	Post-initiation						
Assessment	≤ 1hr	≤ 2min[a]	5min (±1min)	15min (±2min)	30min (±5min)	60min (±10min)	2hr (±15min)	3hr (±15min)
12-lead ECG	X	X	X	X	X	X	X	
Vital signs (BP, pulse rate, respiratory rate, temperature)	X	X	X	X	X	X	X[c]	
PK sampling[b]	X			X				X

BP=blood pressure; BRV=brivaracetam; ECG=electrocardiogram; hr=hour(s); min=minute(s); iv=intravenous; PK=pharmacokinetic; PCS=possibly clinically significant

[a] To be conducted during bolus/infusion, if feasible.

[b] Blood samples for PK analyses were collected for the initial BRV infusion and 1 subsequent BRV infusion only. Blood samples were collected after completion of the ECG and the vital sign measurements and from a region of the body not used for the iv BRV administration.

[c] Per Protocol Amendment 1 (19 Jun 2019), only BP was collected at 2 hours post initiation of infusion. Additional vital sign monitoring, specifically BP, was necessary if a low PCS BP value occurred at 2 hours after the start of an infusion.

Statistical Methods

Tables, figures, and listings (TFLS) are displayed for the defined analysis sets. If the SS and the Safety Set-iv (SS-iv) consisted of the same number of study participants, TFLs were only presented for the SS-iv.

For categorical parameters, the number and percentage of study participants in each category are presented. The denominator for percentages was based on the number of study participants appropriate for the purpose of the analysis. Unless otherwise noted, all percentages were displayed to 1 decimal place. No percentage was displayed for zero counts, and no decimal was presented when the percentage was 100%.

For continuous parameters, descriptive statistics included number of study participants (n), mean, standard deviation (SD), median, minimum, and maximum, unless otherwise stated.

Decimal places for descriptive statistics always applied the following rules unless otherwise stated:

- "n" was an integer

• Mean, SD, geometric mean, and median used 1 additional decimal place compared with the original data

• Coefficient of variation (CV) [%] was presented with 1 decimal place

• Minimum and maximum had the same number of decimal places as the original value; however, the maximum number of decimals displayed did not exceed 4.

All summaries, unless otherwise stated, are presented overall for all study participants, by age cohorts (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), and by infusion duration (15-minute iv infusion and iv bolus [up to 2-minute infusion]). In addition, selected tables are provided by study participant groups (OLB, RxB, and IOB combined, and IIB), or by scheduled assessment time points as defined. Selected summaries were repeated by the country of enrollment (Hungary and Rest of the World).

Results

Recruitment/ Number analysed

Overall, 58 study participants were screened: 50 study participants were enrolled and 8 study participants were screen failures. The most common main reason for screen failure was ineligibility (6 study participants), followed by consent withdrawn by participant (1 study participant; not due to an AE) and consent withdrawn by parent/guardian (1 study participant; not due to an AE). All 50 patients enrolled completed the study.

Baseline data

Table 5 Populations analysed

	Age cohort				
	≥1 month to <2 years	≥2 to <6 years	≥6 to <12 years	≥12 to <16 years	All study participants
Analysis set	N=13 n (%)	N=13 n (%)	N=12 n (%)	N=12 n (%)	N=50 n (%)
SS and SS-iv	13 (100)	13 (100)	12 (100)	12 (100)	50 (100)
15 minutes	7 (53.8)	7 (53.8)	6 (50.0)	6 (50.0)	26 (52.0)
Bolus	6 (46.2)	6 (46.2)	6 (50.0)	6 (50.0)	24 (48.0)
PK-PPS	11 (84.6)	12 (92.3)	10 (83.3)	12 (100)	45 (90.0)
15 minutes	5 (45.5)	7 (58.3)	5 (50.0)	6 (50.0)	23 (51.1)
Bolus	6 (54.5)	5 (41.7)	5 (50.0)	6 (50.0)	22 (48.9)

PK-PPS=Pharmacokinetic Per-Protocol Set; SS=Safety Set; SS-iv=Safety set-intravenous

Note: Percentages were based on the number of study participants in the SS. Percentages for infusion durations were based on the number of study participants in the respective analysis sets.

Table 6 Study participant demographics (SS-iv)

Variable	Descriptive statistic	Age cohort				Infusion duration		All study participants
		≥1 month to <2 years	≥2 to <6 years	≥6 to <12 years	≥12 to <16 years	15-minute infusion	Bolus	
		N=13	N=13	N=12	N=12	N=26	N=24	N=50
Age (years) [a]	n	0	13	12	12	19	18	37
	Mean (SD)	--	3.85 (0.99)	8.33 (1.61)	13.08 (1.16)	7.95 (3.98)	8.67 (4.19)	8.30 (4.04)
	Median	--	4.00	8.00	13.00	8.00	8.00	8.00
	Min, max	--	2.00, 5.00	6.00, 11.00	12.00, 15.00	2.00, 13.00	4.00, 15.00	2.00, 15.00
Age (months) [a]	n	13	0	0	0	7	6	13
	Mean (SD)	11.4 (7.0)	--	--	--	13.3 (6.6)	9.2 (7.5)	11.4 (7.0)
	Median	11.0	--	--	--	12.0	9.0	11.0
	Min, max	2, 22	--	--	--	5, 22	2, 22	2, 22
Participant group								
OLB	n (%)	0	0	0	0	0	0	0
RxB	n (%)	4 (30.8)	2 (15.4)	0	2 (16.7)	2 (7.7)	6 (25.0)	8 (16.0)
IOB	n (%)	6 (46.2)	4 (30.8)	5 (41.7)	7 (58.3)	11 (42.3)	11 (45.8)	22 (44.0)
IIB	n (%)	3 (23.1)	7 (53.8)	7 (58.3)	3 (25.0)	13 (50.0)	7 (29.2)	20 (40.0)
Gender								
Male	n (%)	8 (61.5)	8 (61.5)	4 (33.3)	6 (50.0)	15 (57.7)	11 (45.8)	26 (52.0)
Female	n (%)	5 (38.5)	5 (38.5)	8 (66.7)	6 (50.0)	11 (42.3)	13 (54.2)	24 (48.0)

Participant groups were either naïve to BRV treatment (IIB participants) or non-naïve (OLB, RxB, or IOB participants).

With respect to participant groups, there were no OLB participants in the study and few RxB (non-naïve) participants (8 study participants [16.0%]); proportions of the remaining participants were divided between IIB (naïve to BRV treatment) and IOB (non-naïve) participant groups (20 study participants [40.0%] and 22 study participants [44.0%], respectively). Across the age cohorts, there were fewer IOB participants in the ≥2 to <6 years age cohort (4 study participants [30.8%]) compared with the other age cohorts (ranging from 41.7% to 58.3%).

Table 7 Baseline epileptic characteristics (SS-iv)

Variable	Descriptive statistic	Age cohort				Infusion duration		All study participants
		≥1 month to <2 years	≥2 to <6 years	≥6 to <12 years	≥12 to <16 years	15-minute infusion	Bolus	
		N=13	N=13	N=12	N=12	N=26	N=24	N=50
Duration of epilepsy (years)	n	13	13	12	12	26	24	50
	Mean (SD)	0.68 (0.68)	2.88 (1.48)	5.96 (2.42)	7.91 (4.51)	4.17 (3.91)	4.35 (3.74)	4.25 (3.79)
	Median	0.34	2.25	6.02	8.72	2.32	4.06	3.20
	Min, max	0.04, 1.84	1.01, 4.92	1.64, 9.08	0.03, 14.04	0.04, 12.43	0.03, 14.04	0.03, 14.04
Duration of epilepsy (months)	n	13	13	12	12	26	24	50
	Mean (SD)	8.19 (8.13)	34.56 (17.82)	71.50 (29.00)	94.91 (54.09)	49.99 (46.96)	52.21 (44.90)	51.05 (45.53)
	Median	4.14	27.01	72.25	104.61	27.84	48.71	38.42
	Min, max	0.53, 22.05	12.09, 59.04	19.68, 108.91	0.39, 168.48	0.53, 149.13	0.39, 168.48	0.39, 168.48
Age at time of diagnosis (years) [a]	n	13	13	12	12	26	24	50
	Mean (SD)	0.30 (0.41)	1.63 (1.61)	3.08 (2.82)	5.58 (4.85)	2.34 (2.51)	2.84 (4.22)	2.58 (3.41)
	Median	0.07	0.90	2.35	3.82	1.08	1.15	1.10
	Min, max	-0.05, 1.24	0.00, 4.87	0.14, 9.65	0.64, 13.98	0.00, 9.65	-0.05, 13.98	-0.05, 13.98
Age at time of diagnosis (months)	n	13	13	12	12	26	24	50
	Mean (SD)	3.64 (4.89)	19.62 (19.27)	36.94 (33.78)	66.97 (58.25)	28.12 (30.06)	34.09 (50.62)	30.98 (40.90)
	Median	0.89	10.74	28.17	45.78	12.96	13.75	13.24
	Min, max	-0.56, 14.92	0.00, 58.41	1.71, 115.84	7.66, 167.75	0.00, 115.84	-0.56, 167.75	-0.56, 167.75

Table 8 Summary of concomitant AEDs taken by ≥3% of all study participants (SS-iv)

WHODD Preferred drug name	Age cohort				Infusion duration		All study participants
	≥1 month to <2 years	≥2 to <6 years	≥6 to <12 years	≥12 to <16 years	15-minute infusion	Bolus	
	N=13 n (%)	N=13 n (%)	N=12 n (%)	N=12 n (%)	N=26 n (%)	N=24 n (%)	N=50 n (%)
At least 1 AED	12 (92.3)	12 (92.3)	12 (100)	12 (100)	26 (100)	22 (91.7)	48 (96.0)
Valproic acid	5 (38.5)	3 (23.1)	4 (33.3)	6 (50.0)	10 (38.5)	8 (33.3)	18 (36.0)
Clobazam	1 (7.7)	5 (38.5)	3 (25.0)	5 (41.7)	11 (42.3)	3 (12.5)	14 (28.0)
Carbamazepine	3 (23.1)	3 (23.1)	3 (25.0)	2 (16.7)	5 (19.2)	6 (25.0)	11 (22.0)
Lacosamide	1 (7.7)	3 (23.1)	2 (16.7)	3 (25.0)	4 (15.4)	5 (20.8)	9 (18.0)
Topiramate	3 (23.1)	1 (7.7)	3 (25.0)	2 (16.7)	2 (7.7)	7 (29.2)	9 (18.0)
Lamotrigine	0	4 (30.8)	1 (8.3)	2 (16.7)	5 (19.2)	2 (8.3)	7 (14.0)
Vigabatrin	4 (30.8)	2 (15.4)	1 (8.3)	0	5 (19.2)	2 (8.3)	7 (14.0)
Ethosuximide	0	0	2 (16.7)	3 (25.0)	4 (15.4)	1 (4.2)	5 (10.0)
Zonisamide	0	2 (15.4)	1 (8.3)	2 (16.7)	3 (11.5)	2 (8.3)	5 (10.0)
Phenobarbital	0	4 (30.8)	0	0	2 (7.7)	2 (8.3)	4 (8.0)
Oxcarbazepine	0	0	1 (8.3)	2 (16.7)	0	3 (12.5)	3 (6.0)
Acetazolamide	0	1 (7.7)	0	1 (8.3)	1 (3.8)	1 (4.2)	2 (4.0)
Clonazepam	0	2 (15.4)	0	0	1 (3.8)	1 (4.2)	2 (4.0)
Perampanel	0	0	1 (8.3)	1 (8.3)	0	2 (8.3)	2 (4.0)
Valproate sodium	0	1 (7.7)	1 (8.3)	0	2 (7.7)	0	2 (4.0)

Efficacy results

N/A

Safety results

Exposure

Overall study drug (oral and iv BRV) exposure is summarized for the SS-iv in the table below.

Table 9 Study drug exposure (SS-iv)

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

BRV=brivaracetam; iv=intravenous; max=maximum; min=minimum; SD=standard deviation; SS-iv=Safety Set-intravenous

Note: Summary statistics were calculated using all participants in the SS-iv. In the case when oral and iv BRV were taken on the same day, this day was only counted once in the duration of oral and iv BRV exposure.

Pharmacokinetics

Pharmacokinetic data from EP0065 are included in a PK modeling report. The BRV plasma concentration data reflect a similar pattern of rapid increase in concentrations during the first 15 minutes after iv administration with decreases over the following 3 hours. There were no unexpected differences observed across age cohorts, infusion groups, or weight groups (<50kg vs ≥50kg) (EP0065 CSR Table 5.1 and EP0065 CSR Table 5.2). Similar 15 minute and 3-hour postdose plasma concentrations were also observed in the RxB and IOB (non-naïve) participants compared with the IIB (naïve) participants.

CHMP comments

PK data should be sufficiently summarised and presented in the submission for the type II variation.

Adverse events

Table 10 Overview of AEs and TEAEs (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
Category	N=13 n (%) [#]	N=13 n (%) [#]	N=12 n (%) [#]	N=12 n (%) [#]	N=26 n (%) [#]	N=24 n (%) [#]	N=50 n (%) [#]
Any AE	2 (15.4) [3]	7 (53.8) [12]	4 (33.3) [5]	3 (25.0) [3]	8 (30.8) [12]	8 (33.3) [11]	16 (32.0) [23]
Any TEAE	2 (15.4) [3]	6 (46.2) [8]	3 (25.0) [4]	3 (25.0) [3]	8 (30.8) [10]	6 (25.0) [8]	14 (28.0) [18]
Serious TEAEs	1 (7.7) [1]	0	0	0	1 (3.8) [10]	0	1 (2.0) [1]
Participant discontinuation due to TEAE	0	0	0	0	0	0	0
Permanent withdrawal of BRV due to TEAE	0	0	0	0	0	0	0
TEAE requiring dose change	0	0	0	0	0	0	0
Drug-related TEAEs	1 (7.7) [1]	5 (38.5) [6]	2 (16.7) [3]	2 (16.7) [2]	6 (23.1) [7]	4 (16.7) [5]	10 (20.0) [12]
Drug-related serious TEAEs	0	0	0	0	0	0	0
Severe TEAEs	1 (7.7) [1]	0	0	0	1 (3.8) [1]	0	1 (2.0) [1]
Deaths	0	0	0	0	0	0	0

The incidence of TEAEs was numerically highest in the ≥2 to <6 years age cohort (6 study participants [46.2%]) compared with the ≥1 month to <2 years (2 study participants [15.4%]), the ≥6 to <12 years (3 study participants [25.0%]), and the ≥12 to <16 years (3 study participants [25.0%]) age cohorts. The incidence of TEAEs considered related to study drug was also numerically highest in the ≥ 2 to <6 years age cohort (5 study participants [38.5%]) compared with the ≥1 month to <2 years (1 study participant [7.7%]) and the ≥6 to <12 years and ≥12 to <16 years (2 study participants [16.7%] each) age cohorts. Interpretation should be made with caution due to the low number of participants in each age group.

There was no obvious difference in the incidences of TEAEs between infusion groups: 8 study participants (30.8%) in the 15-minute infusion group and 6 study participants (25.0%) in the bolus group. The incidence of drug-related TEAEs was similar between infusion groups: 6 study participants (23.1%) in the 15-minute infusion group and 4 study participants (16.7%) in the bolus group.

There was also no difference in the incidence of TEAEs between study participant groups: 7 study participants (35.0%) had TEAEs in the IIB (naïve) group and 7 study participants (23.3%) had TEAEs in the RxB and IOB (non-naïve) group. The incidences of drug related TEAEs were 6 study participants (30.0%) in the IIB (naïve) group and 4 study participants (13.3%) in the RxB and IOB (non-naïve) group.

Table 11 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.

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 in the ≥1 month to <2 years and ≥2 to <6 years age cohorts, respectively). Dizziness was experienced only in the oldest age cohort of ≥12 to <16 years (2 study participants [16.7%]). Pyrexia was experienced only in the ≥2 to <6 years age cohort (2 study participants [15.4%]).

There was no obvious difference in individual TEAEs between infusion durations with the exception of somnolence, which was experienced more frequently in study participants on the 15 minute infusion (3 study participants [11.5%] vs none in the bolus group); however, this result should be interpreted with caution due to the small sample sizes.

There was no obvious difference in individual TEAEs between IIB (naïve) and RxB and IOB (non-naïve) study participants. Dizziness was experienced by 2 study participants, and fatigue, pyrexia, ear infection, pharyngitis, upper respiratory tract infection, aggression, and cough were each experienced by 1 participant in the RxB and IOB (non-naïve) group. Somnolence was experienced by 3 study participants, rash by 2 study participants, and fatigue, pyrexia, insomnia, and pruritus were each experienced by 1 participant in the IIB (naïve) group.

No TEAEs occurred within the first 5 minutes after infusion in either the 15-minute infusion or bolus groups, and no TEAE was experienced by >1 study participant by PT within any given time window.

Within the bolus group, 1 study participant experienced pruritus >5 to ≤15 minutes after infusion start, and 1 study participant experienced rash >12 hours after infusion start. Within the 15-minute infusion group, TEAEs were experienced >5 to ≤15 minutes (somnolence and rash), >15 to ≤60 minutes (somnolence), >60 minutes to ≤12 hours (fatigue, pyrexia, and insomnia), and >12 hours (somnolence) after infusion start.

CHMP comments

TEAEs are similar to what is known from adult patients, pruritus and rash being notifiable exceptions.

Table 12 TEAEs considered drug related by the investigator 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 drug-related TEAE	**1 (7.7)**	**5 (38.5)**	**2 (16.7)**	**2 (16.7)**	**6 (23.1)**	**4 (16.7)**	**10 (20.0)**
General disorders and administration site conditions	**0**	**2 (15.4)**	**1 (8.3)**	**0**	**3 (11.5)**	**0**	**3 (6.0)**
Fatigue	0	1 (7.7)	1 (8.3)	0	2 (7.7)	0	2 (4.0)
Pyrexia	0	1 (7.7)	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)**
Somnolence	1 (7.7)	2 (15.4)	0	0	3 (11.5)	0	3 (6.0)
Dizziness	0	0	0	2 (16.7)	0	2 (8.3)	2 (4.0)
Psychiatric disorders	**0**	**1 (7.7)**	**0**	**0**	**0**	**1 (4.2)**	**1 (2.0)**
Aggression	0	1 (7.7)	0	0	0	1 (4.2)	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)**
Rash	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)

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: n=number of study participants experiencing at least 1 TEAE within the SOC/PT.

Note: Each study participant was counted once within each SOC and PT according to the relationship to study drug for all TEAEs within that SOC or PT. If a study participant experienced a PT related and not related to study drug, then the maximum (related) was taken.

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.

A total of 10 study participants (20.0%) experienced TEAEs considered drug-related by the Investigator. The most common drug-related TEAE was somnolence (3 study participants [6.0%]).

There was no obvious difference across age cohorts; however, drug-related somnolence was experienced only by study participants in the youngest age cohorts (1 study participant in the ≥1 month to <2 years cohort and 2 study participants in the ≥2 to <6 years cohort), and dizziness was experienced only in the oldest age cohort (2 study participants in the ≥12 to <16 years cohort).

The incidences of TEAEs considered drug-related by the Investigator were similar between infusion duration groups: 6 study participants (23.1%) in the 15-minute infusion group and 4 study participants (16.7%) in the bolus group.

CHMP comments

TEAEs considered related to study drug by investigator are similar to what is known from adult patients, the only exception being pruritus and rash. As pointed out by MS1, sample sizes are small and cases few, however considering investigator's relating these TEAEs to study drug, and considering time to onset, these AEs are could be possibly related to BRV and a short amendment to the SmPC section 4.8 should be considered.

MS1 would prefer that when submitting these data to the type II variation procedure, AEs should be presented in age-categories applicable in that procedure, i. e. ≥ 1month - <2 years and ≥ 2 years -<4 years (separated from older children).

Deaths, SEAs, AEs leading to permanent discontinuation of study drug, and TEAS of interest

No deaths occurred in this study. One study participant (4.5%) in the ≥1 month to <2 years age cohort (15-minute infusion group) had a treatment-emergent SAE (cough) that was considered not related to study drug by the Investigator and did not lead to discontinuation. There were no TEAEs that led to study discontinuation.

There were no AEs of special interest reported during the study (no events of autoimmune nephritis, nephritis, nephritis allergic, tubulointerstitial nephritis, tubulointerstitial nephritis and uveitis syndrome, or instances of Hy's Law), but there was one TEAE of interest of aggression was experienced in the ≥2 to <6 years age cohort (bolus group; 25mg); the TEAE was nonserious, moderate, considered related to study drug by the Investigator, and had not resolved; the study participant experienced no other AEs.

Clinical laboratory evaluation

There were no hematology, clinical chemistry, or urinalysis Baseline mean values that were unexpected for pediatric study participants. Due to the fact that there were no study participants who required down titration (Visit 13), there were no shifts in hematology, clinical chemistry, or urinalysis parameters from Baseline to Visit 13 during the study. No study participants had suspected hepatic events or met potential drug-induced liver injury (PDILI) discontinuation criteria.

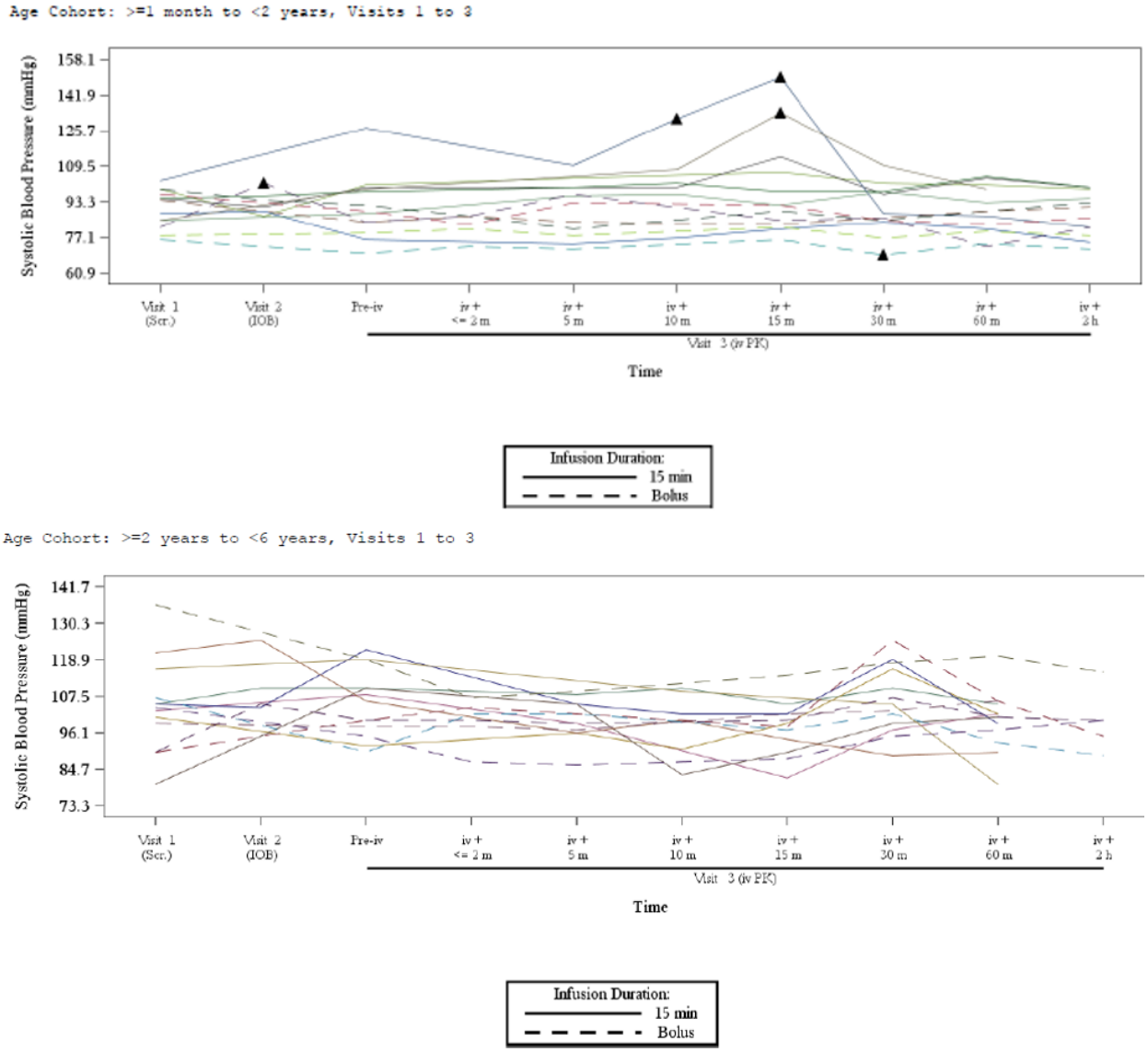
Vital signs

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

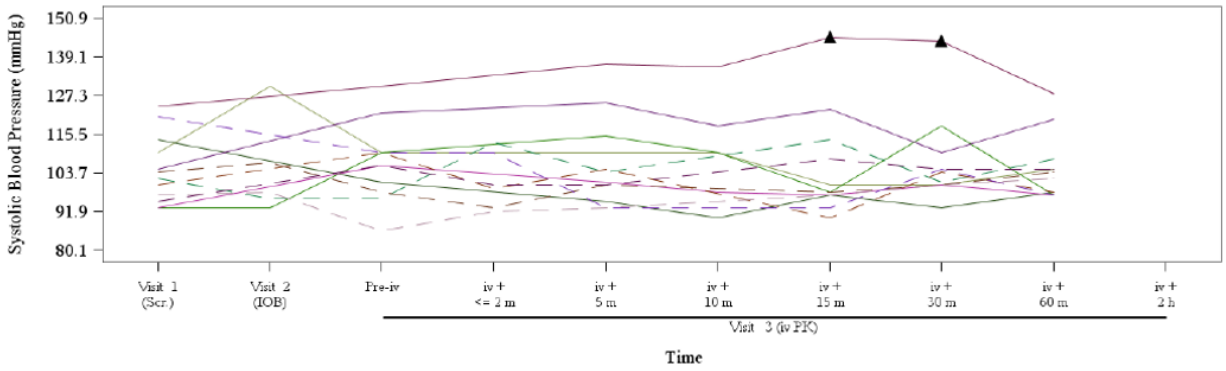
Baseline values for respiratory rate, temperature, and pulse rate were of no clinical concern for this population. The mean changes from Baseline for other vital signs were similar across age cohorts, infusion durations, and study participant groups (RxB and IOB [non naïve] and IIB [naïve]).

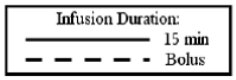
Graphical presentations of SBP and DBP over time are provided for the SS-iv population for Visits 1 to 3 study participant, infusion duration, and age cohort in the figures below.

Figure 1 SBP (mmHg) observed values over time by age cohort (SS-iv)

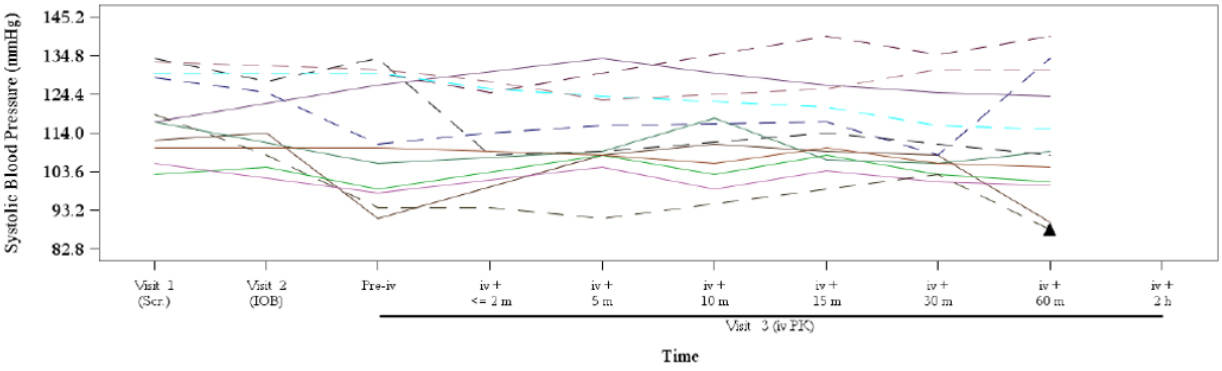


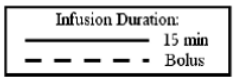
Age Cohort: >=6 years to <12 years, Visits 1 to 3





Age Cohort: >=12 years to <16 years, Visits 1 to 3

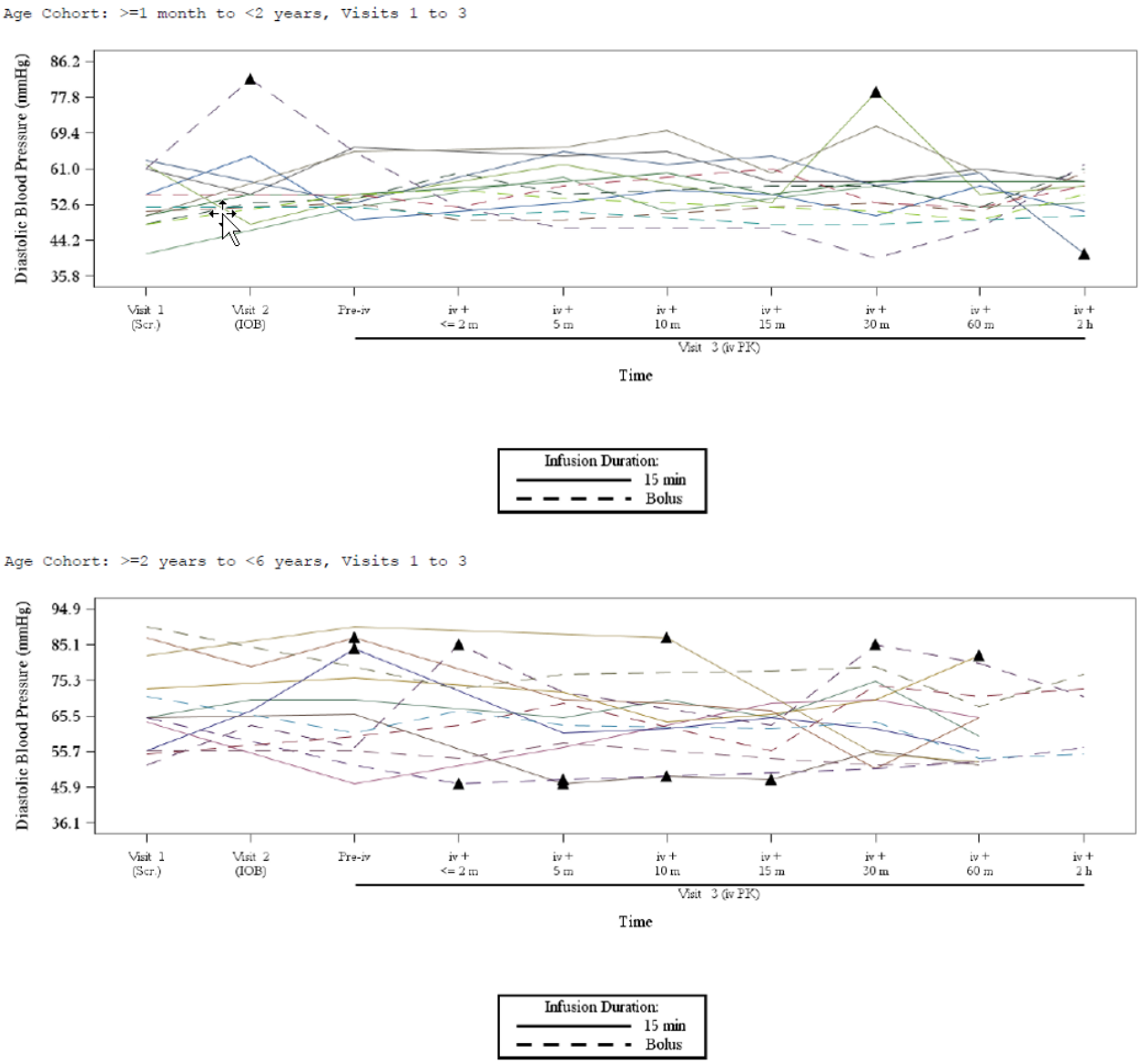


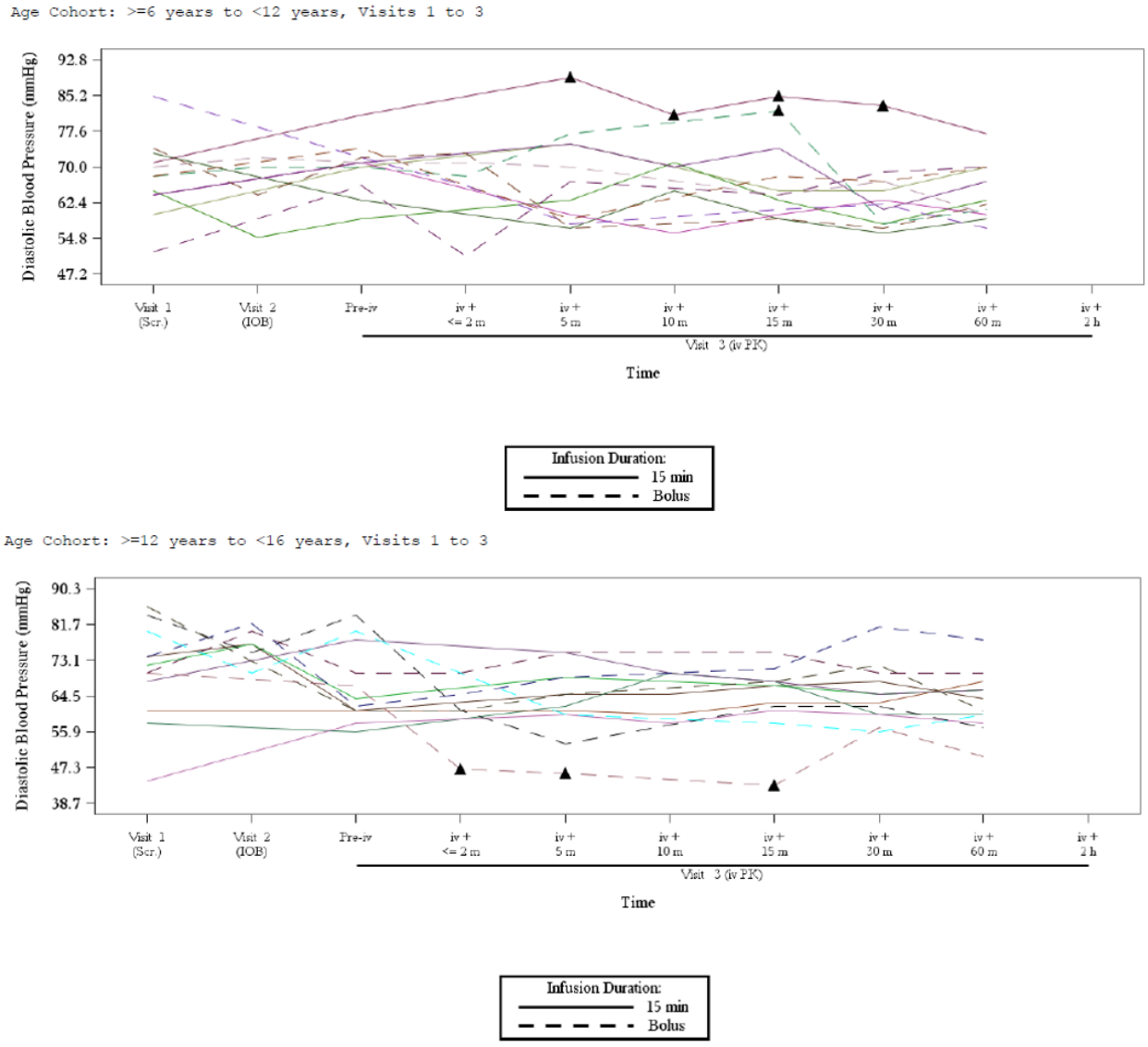


BRV=brivaracetam; IOB=Initiating oral BRV; iv=intravenous; PCST=possibly clinically significant treatment-emergent; PK=pharmacokinetic; Scr=Screening; SBP= systolic blood pressure; SS-iv=Safety Set-intravenous

Note: PCST abnormal values are highlighted using symbols.

Figure 2 DBP (mmHg) observed values over time by age cohort (SS-iv)





BRV=brivaracetam; DBP=diastolic blood pressure; IOB=Initiating oral BRV; iv=intravenous; PCST=possibly clinically significant treatment-emergent; PK=pharmacokinetic; Scr=Screening; SS-iv=Safety Set-intravenous
Note: PCST abnormal values are highlighted using symbols.

Possibly clinically significant treatment-emergent (PCST) vital signs

For Visit 1 (Screening), there were no study participants with PCST values for SBP, DBP, body temperature, or pulse rate; 1 study participant in the ≥1 month to <2 years age cohort had a PCST low respiratory rate at Visit 1. For Visit 2 (IOB Treatment Period), 1 study participant in the ≥1 month to <2 years age cohort had PCST high SBP and DBP values and 1 study participant in the ≥2 to <6 years age cohort had a PCST high respiratory rate.

In general, the incidences of PCST vital sign values were low. Overall, at Visit 3 (iv PK Period), there were 5 study participants with PCST SBP values (3 were high and 2 were low) and 12 study participants with PCST DBP values (8 were high and 4 were low). The most common time points were 5 minutes post-iv start and 15 minutes post-iv start.

At Visit 3, there were 19 study participants with PCST body weight values (4 were high and 15 were low); however, the changes in body weight from Visit 1 (Screening) to Visit 3 (iv PK Period) were minimal. The PCST definition is based on actual weight rather than change in weight. Because weight did not change much over time, the high proportion of participants with weight PCST is caused by the

enrollment of overweight and underweight participants, rather than the study drug. It is expected that some of the participants in this patient population will be underweight because of the high prevalence of low weight in patients with multiple chronic medical conditions, as is the case in this study.

At Visit 3, 6 study participants (12.0%) had PCST pulse rate values and 2 study participants (4.0%) had PCST respiratory rate values; none had PCST temperature values.

The low number of participants who attended Visit 4 and Visit 5 makes it difficult to interpret values at these visits. There was no obvious difference in the incidence of PCST pulse and respiratory rate values at Visit 3.

There were no obvious differences in the incidence of PCST pulse and respiratory rate values between age groups or infusion duration groups.

There were no TEAEs reported that were associated with abnormal vital sign parameters.

CHMP comments

There were no specific patterns seen for any vital sign in any age group or treatment group. There were a few PCST (possibly clinically significant treatment-emergent) AEs but these did not elicit any pattern either. No TEAEs were associated with abnormal vital sign parameters.

Electrocardiogram findings

Table 13 12-lead EDG interpretations for study participants in the 15-minute infusion treatment group at visit 3 (iv PK period) (SS-iv)

Time point ECG interpretation	≥1 month to <2 years N=7 n/Nsub (%)	≥2 to <6 years N=7 n/Nsub (%)	≥6 to <12 years N=6 n/Nsub (%)	≥12 to <16 years N=6 n/Nsub (%)	All study participants N=26 n/Nsub (%)
Visit 1 (Screening)					
Normal	3/7 (42.9)	6/7 (85.7)	5/6 (83.3)	5/6 (83.3)	19/26 (73.1)
Abnormal, not clinically significant	4/7 (57.1)	1/7 (14.3)	1/6 (16.7)	1/6 (16.7)	7/26 (26.9)
Clinically significant	0/7	0/7	0/6	0/6	0/26
Visit 3 (iv PK Period)					
≤1 hour pre-iv start					
Normal	4/7 (57.1)	6/7 (85.7)	6/6 (100)	4/6 (66.7)	20/26 (76.9)
Abnormal, not clinically significant	3/7 (42.9)	1/7 (14.3)	0/6	2/6 (33.3)	6/26 (23.1)
Clinically significant	0/7	0/7	0/6	0/6	0/26
5 minutes post-iv start					
Normal	4/7 (57.1)	6/7 (85.7)	6/6 (100)	5/6 (83.3)	21/26 (80.8)
Abnormal, not clinically significant	3/7 (42.9)	1/7 (14.3)	0/6	1/6 (16.7)	5/26 (19.2)
Clinically significant	0/7	0/7	0/6	0/6	0/26
15 minutes post-iv start					
Normal	3/7 (42.9)	5/7 (71.4)	6/6 (100)	5/6 (83.3)	19/26 (73.1)
Abnormal, not clinically significant	4/7 (57.1)	2/7 (28.6)	0/6	1/6 (16.7)	7/26 (26.9)
Clinically significant	0/7	0/7	0/6	0/6	0/26
30 minutes post-iv start					
Normal	3/7 (42.9)	6/7 (85.7)	6/6 (100)	5/6 (83.3)	20/26 (76.9)
Abnormal, not clinically significant	4/7 (57.1)	1/7 (14.3)	0/6	1/6 (16.7)	6/26 (23.1)
Clinically significant	0/7	0/7	0/6	0/6	0/26
60 minutes post-iv start					
Normal	3/7 (42.9)	6/7 (85.7)	0/6	4/6 (66.7)	19/26 (73.1)
Abnormal, not clinically significant	4/7 (57.1)	1/7 (14.3)	0/6	2/6 (33.3)	7/26 (26.9)
Clinically significant	0/7	0/7	0/6	0/6	0/26

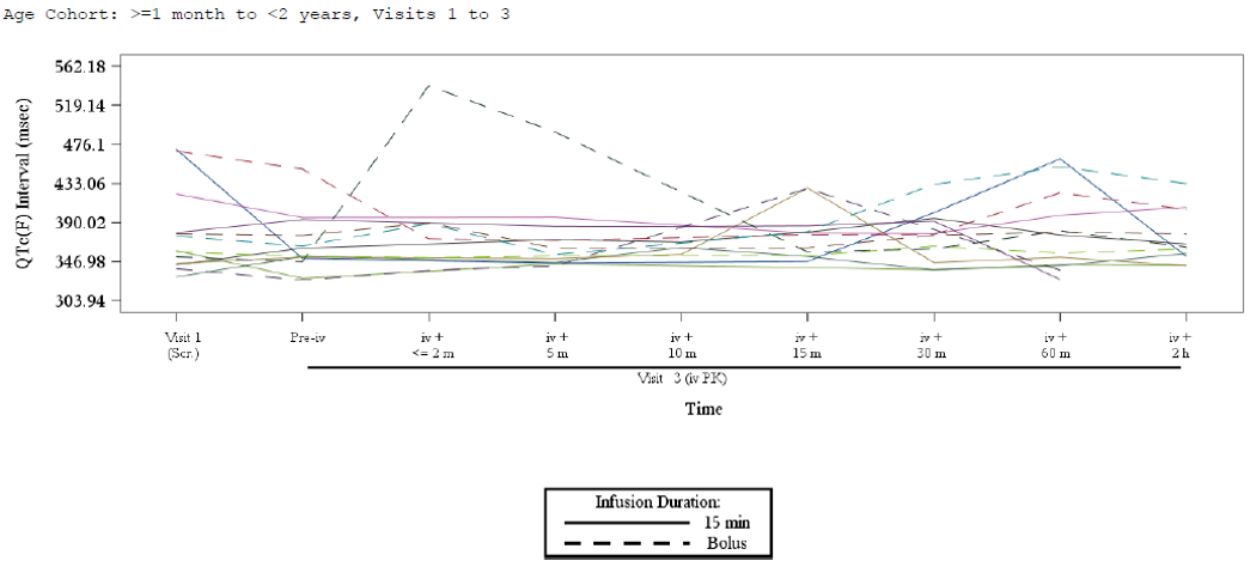
ECG=electrocardiogram; iv=intravenous; PK=pharmacokinetic; SS-iv=Safety Set-intravenous
Note: n=number of study participants with an interpretation at the visit. Nsub=number of study participants with a nonmissing measurement for that variable at the visit/time point. Percentages were based on Nsub.

Table 14 12-lead ECG interpretations for study participants in the bolus treatment group at Visit 3 (iv PK Period) (SS-iv)

Time point ECG interpretation	≥1 month to <2 years N=6 n/Nsub (%)	≥2 to <6 years N=6 n/Nsub (%)	≥6 to <12 years N=6 n/Nsub (%)	≥12 to <16 years N=6 n/Nsub (%)	All study participants N=24 n/Nsub (%)
Visit 1 (Screening)					
Normal	4/6 (66.7)	4/6 (66.7)	5/6 (83.3)	3/6 (50.0)	16/24 (66.7)
Abnormal, not clinically significant	2/6 (33.3)	2/6 (33.3)	1/6 (16.7)	3/6 (50.0)	8/24 (33.3)
Clinically significant	0/6	0/6	0/6	0/6	0/24
Visit 3 (iv PK Period)					
≤1 hour pre-iv start					
Normal	3/6 (50.0)	6/6 (100)	5/6 (83.3)	4/6 (66.7)	18/24 (75.0)
Abnormal, not clinically significant	3/6 (50.0)	0/6	1/6 (16.7)	2/6 (33.3)	6/24 (25.0)
Clinically significant	0/6	0/6	0/6	0/6	0/24
≤2 minutes post-iv start					
Normal	3/6 (50.0)	6/6 (100)	5/6 (83.3)	2/4 (50.0)	16/22 (72.7)
Abnormal, not clinically significant	3/6 (50.0)	0/6	1/6 (16.7)	2/4 (50.0)	6/22 (27.3)
Clinically significant	0/6	0/6	0/6	0/4	0/22
5 minutes post-iv start					
Normal	3/6 (50.0)	6/6 (100)	4/6 (66.7)	3/5 (60.0)	16/23 (69.6)
Abnormal, not clinically significant	3/6 (50.0)	0/6	2/6 (33.3)	2/5 (40.0)	7/23 (30.4)
Clinically significant	0/6	0/6	0/6	0/5	0/23
15 minutes post-iv start					
Normal	2/6 (33.3)	6/6 (100)	5/6 (83.3)	3/6 (50.0)	16/24 (66.7)
Abnormal, not clinically significant	4/6 (66.7)	0/6	1/6 (16.7)	3/6 (50.0)	8/24 (33.3)
Clinically significant	0/6	0/6	0/6	0/6	0/24
30 minutes post-iv start					
Normal	4/6 (66.7)	6/6 (100)	5/6 (83.3)	3/6 (50.0)	18/24 (75.0)
Abnormal, not clinically significant	2/6 (33.3)	0/6	1/6 (16.7)	3/6 (50.0)	6/24 (25.0)
Clinically significant	0/6	0/6	0/6	0/6	0/24
60 minutes post-iv start					
Normal	3/6 (50.0)	6/6 (100)	5/6 (83.3)	3/6 (50.0)	17/24 (70.8)
Abnormal, not clinically significant	3/6 (50.0)	0/6	1/6 (16.7)	3/6 (50.0)	7/24 (29.2)
Clinically significant	0/6	0/6	0/6	0/6	0/24

ECG=electrocardiogram; iv=intravenous; PK=pharmacokinetic; SS-iv=Safety Set-intravenous
Note: Note: n=number of study participants with an interpretation at the visit. Nsub=number of study participants with a nonmissing measurement for that variable at the visit/time point. Percentages were based on Nsub.

Figure 3 QTcF observed values over time by age cohort for Visits 1 to 3 (SS iv)



There were no study participants in any age cohort who had ECG abnormalities considered clinically significant.

CHMP comments

The Applicant claims that there were no clinically significant abnormalities in the ECGs during the study. It is noted however, that one child in the 1 month - 2 years old group had an increase in QTcF from about 350 ms prior to BRV bolus to about 540 ms within 2 minutes after the bolus. At 15 minutes the QTc had returned to about 350 ms.

At the initial MA of Briviact, pre-clinical data were contradictory regarding QTc with one study with no abnormal findings while in another study in anaesthetized male dogs a dose–related decrease in heart rate was seen at i.v. doses from 50 mg/kg. Further, at 150 mg/kg, i.v., increases in QT and QTc intervals, decreases in peak positive and negative rate of rise of left ventricular pressure (dP/dtmax+, dP/dtmax) and a transient reduction in arterial blood pressure and left ventricular systolic pressure were observed. A thorough QT study in healthy subjects was also conducted and no effect of either therapeutic (BRV 150 mg/day) or supra-therapeutic (BRV 800 mg/day) doses on cardiac repolarisation, as measured by QTc prolongation was found.

According to the EP0065 study protocol, ECG should be performed at 5 and 10 minutes as well. When submitting study data to the type II variation, the Applicant should provide all data (including EGC findings at 5 and 10 minutes) and information necessary for the child described above and discuss the nearly 200 ms increase in QTcF.

2.3.3. Discussion on clinical aspects

Safety conclusions by the Applicant

Given the pediatric population studied, the safety findings of EP0065 were generally consistent with the known safety profile of BRV. No new safety concerns for the pediatric population from ≥1 month to <16 years of age were identified.

- A total of 14 participants (28.0%) experienced TEAEs. Overall, the most common TEAE was somnolence (3 study participants [6.0%]), followed by fatigue, dizziness, pyrexia, and rash (2 study participants [4.0%], 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). Dizziness was experienced only in the oldest age cohort of ≥12 to <16 years (2 study participants [16.7%]). Pyrexia was experienced only in the ≥2 to <6 years age cohort (2 study participants [15.4%]).
  - There was no obvious difference in individual TEAEs between infusion durations with the exception of somnolence, which was experienced more frequently in study participants given the 15-minute infusion (3 study participants [11.5%] vs none in the bolus group); however, this result should be interpreted with caution due to the small sample sizes.
  - There was no obvious difference in individual TEAEs between IIB (naïve) and RxB and IOB (non-naïve) study participants. Dizziness was experienced by 2 study participants and fatigue, pyrexia, ear infection, pharyngitis, upper respiratory tract infection, aggression, and cough were each experienced by 1 participant in the RxB and IOB (non-naïve) group. Somnolence was experienced by 3 study participants, rash by 2 study participants, and fatigue, pyrexia, insomnia, and pruritus were each experienced by 1 participant in the IIB (naïve) group.
- Most study participants experienced TEAEs with a maximum intensity of mild (10 study participants [20.0%]) or moderate (3 study participants [6.0%]). One study participant experienced a TEAE with a maximum intensity of severe (a TEAE of somnolence during the iv PK Period in the ≥1 month to <2 years age cohort). There were no obvious differences with regard to intensity by age group or infusion duration.
- A total of 10 study participants (20.0%) experienced TEAEs considered drug-related by the Investigator. The most common drug-related TEAE was somnolence (experienced by 3 study participants [6.0%]). There was no obvious difference in the incidence of drug-related TEAEs by age cohort or infusion group.
- No deaths occurred in this study.
- One study participant in the ≥1 month to <2 years age cohort (15-minute infusion group) had a serious TEAE of cough during the IOB Treatment Period that was considered to be not related to study drug by the Investigator and did not lead to discontinuation.
- There were no TEAEs leading to study discontinuation.
- One participant experienced a TEAE of interest (a nonserious, moderate event of aggression in the ≥2 to <6 years age cohort considered related to study drug). There were no AEs of special interest reported during the study.
- No study participants required down titration. There were no Baseline mean hematology, clinical chemistry, or urinalysis values that were unexpected for pediatric study participants, and no laboratory PCST or PDILI criteria were met.

- No clinically relevant changes from Baseline were observed for vital signs or 12-lead ECGs.
  - 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 were generally consistent across age cohorts, infusion durations, and study participant groups (RxB and IOB [non-naïve] and IIB [naïve]).
- In general, the incidences of PCST vital sign values were low.
  - Weight was the most frequent PCST vital sign: at Visit 3, there were 19 study participants with PCST body weight values (4 were high and 15 were low); however, the changes in body weight from Visit 1 (Screening) to Visit 3 (iv PK Period) were minimal.
  - At Visit 3, there were 5 study participants with PCST SBP values (3 were high and 2 were low) and 12 study participants with PCST DBP values (8 were high and 4 were low). The most common time points were 5 minutes post-iv start and 15 minutes post-iv start.
  - At Visit 3, 6 study participants (12.0%) had PCST pulse rate values and 2 study participants (4.0%) had PCST respiratory rate values; none had PCST temperature values.
  - There were no obvious differences in the incidence of PCST values incidence between age groups or infusion duration groups.
- The ECG parameters were of no clinical concern for this patient population. For the majority of participants, the ECG parameters remained stable over time.
- No study participants reported positive findings on the Columbia-Suicide Severity Rating Scale or reported suicide attempts.

In general, there were no obvious differences between the groups of participants enrolled in Hungary vs the Rest of the World with regard to overview of AEs, incidence of TEAEs, incidence of TEAEs by maximum relationship, and PCST vital signs and ECGs; however, the incidence of important protocol deviations (IPDs) was greater in the Rest of the World (75.0%) compared to Hungary (36.7%), although most IPDs were related to procedural noncompliance.

CHMP comments

The MAH has submitted the results of study EP0065 in accordance with Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation). EP0065 was designed to evaluate the PK, safety, and tolerability of BRV administered as a 15-minute iv infusion and iv bolus (up to 2-minute infusion) in study participants ≥1 month to <16 years of age with epilepsy. According to the SmPC section 4.2 of the BRV iv solution, the iv solution is an alternative when oral administration temporarily is not possible. Thus, the use of iv solution assumes an indication of oral use. A separate assessment of the paediatric iv data preceding the CHMP decision on the oral indication in children ≥1 month – 4 years of age, is suboptimal. A joint assessment of oral and iv data would enable a full assessment of the totality of data and it is therefore suggested that the MAH submits the report of study EP0065 to be included in the ongoing EMEA/H/C/003898/II/0032/G variation procedure, aiming at market authorisation for children aged between 1 month and 4 years. The paediatric iv data can then be assessed in an appropriate context.

TEAEs considered related to study drug by investigator are similar to what is known from adult patients, the only exception being pruritus and rash. As pointed out by MS1, sample sizes are small

and cases few, however considering investigator's relating these TEAEs to study drug, and considering time to onset, these AEs are could be possibly related to BRV and a short amendment to the SmPC section 4.8 should be considered.

MS1 would prefer that when submitting these data to the type II variation procedure, AEs should be presented in age-categories applicable in that procedure, i. e. ≥ 1month - <2 years and ≥ 2 years -<4 years (separated from older children).

One child in the youngest age group had an increase in QTcF from about 350 ms prior to BRV bolus to about 540 ms within 2 minutes after the bolus. At 15 minutes the QTc had returned to about 350 ms. At the initial MA of Briviact one preclinical study found prolonged QT and QTc intervals at high doses (150 mg/kg) of BRV. A thorough QT study in healthy subjects was also conducted and no effect of either therapeutic (BRV 150 mg/day) or supra-therapeutic (BRV 800 mg/day) doses on cardiac repolarisation, as measured by QTc prolongation was found. As the QTc change in the child was large, the Applicant should provide all data and information necessary (including the results of the ECGs performed at 5 and 10 minutes) for this paediatric case and discuss the nearly 200 ms increase in QTcF, when submitting the study report to the type II variation.

3. Rapporteur's overall conclusion and recommendation

The MAH has submitted the results of study EP0065 in accordance with Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation). EP0065 was designed to evaluate the PK, safety, and tolerability of BRV administered as a 15-minute iv infusion and iv bolus (up to 2-minute infusion) in study participants ≥1 month to <16 years of age with epilepsy. According to the SmPC section 4.2 of the BRV iv solution, the iv solution is an alternative when oral administration temporarily is not possible. Thus, the use of iv solution assumes an indication of oral use. A separate assessment of the pediatric iv data preceding the CHMP decision on the oral indication, is suboptimal. A joint assessment of oral and iv data would enable a full assessment of the totality of data and it is therefore suggested that the MAH submits the report of study EP0065 to be included in the ongoing EMEA/H/C/003898/II/0032/G variation procedure, aiming at market authorisation for children aged between 1 month and 4 years. The pediatric iv data can then be assessed in an appropriate context.

The MAH concludes that the study results do not require any regulatory action. However, two TEAEs, rash and pruritus, were found in EP0065 and could be possibly related to study drug. These are not included in the present SmPC of Briviact. There is also a concern regarding a QTcF prolongation in a child ≥ 1 month – 2 years of age during the first 15 minutes after BRV iv bolus. These issues, as well as pharmacokinetic and clinical data, need to be assessed and decided upon in a variation procedure in which data from the paediatric studies of per oral use of BRV are available, preferably the ongoing EMEA/H/C/003898/II/0032/G.

☒ Fulfilled:

In view of the available data regarding iv infusion and iv bolus of brivaracetam in study participants ≥1 month to <16 years of age with epilepsy, the MAH should preferably submit the results of the study EP0065 within the ongoing variation procedure EMEA/H/C/003898/II/0032/G, or either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided without any delay and ***no later than 60 days after the receipt*** of these conclusions.

4. Additional clarification requested

Based on the data submitted, the MAH should not address any questions as part of this procedure but should submit results from study EP0065 to the ongoing variation procedure EMEA/H/C/003898/II/0032/G.