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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/P46/009

Note

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

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1. Introduction

On 24 May 2022, the MAH submitted a completed paediatric study for brivaracetam (BRV), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the study N01349 "A Multicenter, Open-Label, Single-Arm Study to Evaluate the Pharmacokinetics, Efficacy, and Safety of Brivaracetam in Neonates with Repeated Electroencephalographic" is part of a clinical development program.

2.2. Information on the pharmaceutical formulation used in the study

Brivaracetam was administered as an intravenous solution. Two study participants were treated with BRV oral solution.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

N01349 A Multicenter, Open-Label, Single-Arm Study to Evaluate the Pharmacokinetics, Efficacy, and Safety of Brivaracetam in Neonates with Repeated Electroencephalographic Seizures

2.3.2. Clinical study

Clinical study N01349 - A Multicenter, Open-Label, Single-Arm Study to Evaluate the Pharmacokinetics, Efficacy, and Safety of Brivaracetam in Neonates with Repeated Electroencephalographic Seizures

Description

N01349 was a Phase 2/3, multicenter, open-label, single-arm study to evaluate the PK, efficacy, and safety of BRV in neonates with repeated electroencephalographic seizures. This study consisted of a 2-step design (step 1=Exploratory Cohort; step 2=Confirmatory Cohort) and was planned to include a descriptive comparison with a historical control group (matched in age and condition) from literature treated with AEDs per standard of care and diagnostic methods.

Since the first study sites of N01349 were activated in Jan 2018, recruitment proved to be a challenge. The Exploratory Cohort was completed on 29 Sep 2020, after almost 3 years of recruitment. Recruitment for the Confirmatory Cohorts was opened on 13 Nov 2020, but no study participants were successfully enrolled in the Confirmatory Cohort after more than a year. The study was stopped 13 months after the Confirmatory Cohort was opened, following agreement with the Pediatric Committee

(EMA Decision P/0003/2022 dated 18 Jan 2022), because it was considered infeasible and no eligible study participants enrolled into this Cohort.

Methods

Study participants

The study included neonates with epilepsy who had seizures that were not adequately controlled with previous antiepileptic drug (AED) treatment. To be eligible to participate in this study, study participants must have been at least 34 weeks of corrected gestational age (CGA). In addition, term neonates up to 27 days of PNA and preterm neonates up to 40 weeks of CGA and 27 days of PNA could have been enrolled. Study participants weighed at least 2.3kg at the time of enrolment.

Treatments

After implementation of Protocol Amendment 6 (dated 28 Oct 2019), study participants enrolled into the Exploratory Cohort received 1 or more of the following AEDs prior to or at the time of enrollment: phenobarbital (PB), midazolam (MDZ), phenytoin (PHT), levetiracetam, or lidocaine for the treatment of ENS (first line, second line, or subsequent treatment; choice of treatment, dose, and dosing frequency were at the discretion of the Investigator) prior to receiving BRV.

For all study participants, subsequently, a 0.5mg/kg BRV intravenous (iv) solution for injection was administered. At the discretion of the Investigator, 3 additional iv BRV doses, up to a total of 4 iv BRV doses (0.5mg/kg bid), could have been administered during the 48-hour Evaluation Period. This treatment, which was the first use of BRV in neonates, was 4-fold less than the highest dose of 4mg/kg/day dosage (2mg/kg bid) that has been used previously in infants $\geq$1 month old.

Objective(s)

The primary objective was to evaluate the pharmacokinetics (PK) of BRV in neonates who had seizures that were not adequately controlled with previous AED treatment, and to identify the optimal BRV dose (Exploratory Cohort) for the treatment of study participants planned to be enrolled into the Confirmatory Cohorts of this study.

The secondary objectives were as follows:

- To evaluate the efficacy of BRV in severe and non-severe seizure burden (defined as total minutes of electroencephalographic neonatal seizures [ENS] per hour) in neonates with seizures that were not adequately controlled with previous AED treatment
- To evaluate the short-term safety and tolerability of BRV in neonates.

However, efficacy was not evaluated since the study was stopped after the Exploratory Cohort due to the lack of enrollment of eligible study participants.

Outcomes/endpoints

Pharmacokinetics

The primary PK variable was the plasma concentration of BRV following the first dose on Day 1.

Other PK variables were as follows:

- Plasma concentrations of BRV on other occasions
- Plasma concentrations of BRV metabolites ucb-42145 (acid), ucb-100406-1 (hydroxy), and ucb-107092-1 (hydroxyacid)

- Area under the curve (AUC), maximum plasma concentration (Cmax), time to reach Cmax (tmax), elimination half-life (t½), volume of distribution (Vd), and clearance (CL) of BRV
- Plasma concentrations of concomitant AEDs if administered

Safety

The secondary objectives were as follows:

- To evaluate the efficacy of BRV in severe and non-severe seizure burden (defined as total minutes of electroencephalographic neonatal seizures [ENS] per hour) in neonates with seizures that were not adequately controlled with previous AED treatment
- To evaluate the short-term safety and tolerability of BRV in neonates

However, efficacy was not evaluated since the study was stopped after the Exploratory Cohort due to the lack of enrollment of eligible study participants.

Outcomes/endpoints

The secondary safety variable was adverse events (AEs) as reported by the Investigator.

- Other safety variables described below are for both the Exploratory Cohort and Confirmatory Cohorts. Note: Safety variables were collected in the Exploratory Cohort only as no eligible study participants were enrolled into the Confirmatory Cohorts.
- Change from Baseline in vital signs (blood pressure, heart rate, respiratory rate [including apneas], oxygen saturation [pulse oximetry], and body temperature) to 3 hours, 6 hours, 9 hours, 12 hours, 15 hours, 18 hours, 21 hours, 24 hours, 48 hours, 72 hours, and 96 hours
- Change from Baseline in safety laboratory tests to the end of the Evaluation Period
- Change from Baseline in heart rate at 3 hours, 24 hours, 48 hours, and 96 hours after the start of initial BRV treatment
- Change from Baseline in physical and neurological examination 24 hours, 48 hours, 72 hours, and 96 hours after the start of initial BRV treatment (Sarnat scale; for study participants with hypoxic-ischemic encephalopathy [HIE] only)
- Change from Baseline in electroencephalogram parameters (assessment of sedation) to the end of the Evaluation Period (Confirmatory Cohorts only)
- Change from Baseline in severity of HIE to the end of the Evaluation Period (Thompson score; for study participants with HIE only)
- Change from Baseline in neonatal pain, agitation, and sedation scale (N-PASS) score (neonatal pain and agitation measures) to the end of the Evaluation Period
- Change from Baseline in biometric parameters at the Safety Follow-Up Visit: length, body weight, and head circumference (head circumference Baseline measurement was taken within 7 days prior to study drug administration, or at birth for study participants ≤7 days old)
- Withdrawal and rebound phenomena (only applicable for Exploratory Cohort)

Mechanical ventilation:

- Number and percentage of study participants who required mechanical ventilation during the Evaluation Period
- Duration of mechanical ventilation during the Evaluation Period

Neurodevelopmental tests validated for age and language were done after 1 year for study participants who entered the long-term follow-up study in countries where a validated translation of the Bayley Scales of Infant and Toddler Development®, Third Edition (Bayley-III®) score was available.

Efficacy

The planned efficacy endpoints are not listed. Since no patient was included in the Confirmatory Cohort, there were no efficacy data to report.

Sample size

At least 42 evaluable study participants were planned to be enrolled in this study, with at least 6 study participants in the Exploratory Cohort and at least 36 study participants enrolled in 3 successive Confirmatory Cohorts, each consisting of 12 study participants.

This was a multicenter study that enrolled study participants in 4 countries, and 3 investigational sites enrolled 6 eligible participants.

Randomisation and blinding (masking)

Not applicable as the study was single-arm, open-label.

Statistical Methods

Descriptive statistics, such as the number of study participants with available measurement (n), mean, standard deviation (SD), median, minimum value, and maximum value for quantitative variables, and counts and percentages for categorical variables, were provided.

In general, descriptive summaries were used to present study results overall for the Exploratory Cohort. By-participant listings were provided and presented source data and key derived variables for statistical analyses.

Pharmacokinetics

Pharmacokinetics summary tables and listings were produced for the pharmacokinetic per-protocol set (PK-PPS). By-participant listings of the PK parameters and plasma concentrations were provided.

For the Exploratory Cohort, summary tables were provided for the PK parameters; and for plasma concentrations of BRV, ucb-42145, ucb-100406-1, ucb-107092-1, and of concomitant AEDs (PB and PHT). Individual plots of plasma concentrations over time were provided.

Brivaracetam doses and concentration measurements in participants in the Exploratory Cohort were analyzed to determine the PK parameters. Pharmacokinetic parameters were estimated using Bayesian feedback: Individual-specific parameters were determined using the participant's dosing history and BRV concentration assessments, where prior information on the typical population parameters in children (<16 years of age) and their inter-individual variability was taken into account. The prior information was provided by a model (Run412 in PopPK report CL0187) that described BRV PK following oral administration using a one-compartment first order absorption model with allometric scaling of clearance and central volume to body weight using fixed allometric constants of three-fourths and 1, respectively.

Safety

All safety analyses were presented for the safety set (SS). Descriptive summaries were presented.

Results

Recruitment

Nine study participants were enrolled into the study; 3 participants failed screening due to ineligibility. The remaining 6 eligible study participants were enrolled into the Exploratory Cohort of the study at 3 investigational sites. Six study participants (100%) entered the Evaluation Period and were treated with BRV. Four study participants (66.7%) completed the Evaluation Period, entered the Safety Follow-Up Period, and completed the study. Two study participants (33.3%) entered the BRV Extension Period and rolled over to the long-term follow-up study.

Baseline data

Summaries of participant demographics are presented in Table 1.

Table 1 Study participant demographics

Variable	Exploratory Cohort N=6
Postnatal age (days), n	6
Mean (SD)	2.5 (2.1)
Median (min, max)	1.5 (1, 6)
Corrected gestational age (weeks), n	6
Mean (SD)	39.0 (1.9)
Median (min, max)	39.0 (36, 41)
Gestational age <37 weeks, n (%)	1 (16.7)
Gestational age ≥37 weeks, n (%)	5 (83.3)
Gender	
Male, n (%)	[redacted]
Female, n (%)	[redacted]
Weight at Baseline (g), n	6
Mean (SD)	3255.0 (684.8)
Median (min, max)	3110.0 (2550, 4300)
Length at Baseline (cm), n	5
Mean (SD)	52.20 (4.96)
Median (min, max)	52.50 (45.0, 57.0)
Head circumference at Baseline (cm), n	6
Mean (SD)	34.62 (2.49)
Median (min, max)	34.50 (31.0, 38.5)
Racial group, n (%)	
White	6 (100)
Country, n (%)	
[redacted]	1 (16.7)
[redacted]	2 (33.3)
[redacted]	3 (50.0)

BRV=brivaracetam; max=maximum; min=minimum; n=number of study participants; SD=standard deviation; SS=Safety Set
Note: Postnatal age was the number of days between the date of signed informed consent and the date of birth.
Note: Gestational age was the number of weeks between corrected gestational age and postnatal age.
Note: Baseline was defined as the latest assessment prior to the first dose of BRV infusion.
Data source: Table 3.1.1

The mean PNA and CGA at the time of enrollment were 2.5 days and 39.0 weeks, respectively (Table 1). There was a higher percentage of female participants compared with male participants.The mean weight and length at Baseline were 3255.0g and 52.20cm, respectively. All 6 study participants

(100%) were White and were enrolled in Country A (1 participant [16.7%], Country B (2 participants [33.3%]), and Country C (3 participants [50.0%]).

A summary of Baseline characteristics is provided in Table 2.

Table 2 Baseline characteristics

Variable	Exploratory Cohort N=6
Apgar score (1 minute)	
n	6
Mean (SD)	5.2 (4.6)
Median (min, max)	5.5 (0, 10)
Apgar score (5 minutes)	
n	6
Mean (SD)	7.0 (2.9)
Median (min, max)	8.0 (3, 10)
HIE status, n (%)	
Suffered from HIE	3 (50.0)
Did not suffer from HIE	3 (50.0)

BRV=brivaracetam; HIE=hypoxic-ischemic encephalopathy; max=maximum; min=minimum; n=number of study participants; SD=standard deviation; SS=Safety Set
Note: Baseline was defined as the latest assessment prior to the first dose of BRV infusion.
Data source: Table 3.1.1

The mean (SD) Apgar scores at 1 minute and 5 minutes were 5.2 (4.6) and 7.0 (2.9), respectively (Table 2). Increases in mean Apgar score over time indicated that the study participants were evolving well. Among the 6 study participants, 3 participants (50.0%) suffered from HIE.

Number analysed

A summary of disposition of analysis sets is provided in Table 3.

Table 3 Disposition of analysis sets

Analysis set	Exploratory Cohort N=6 n (%)
SS	6 (100)
FAS	NA
PK-PPS	6 (100)

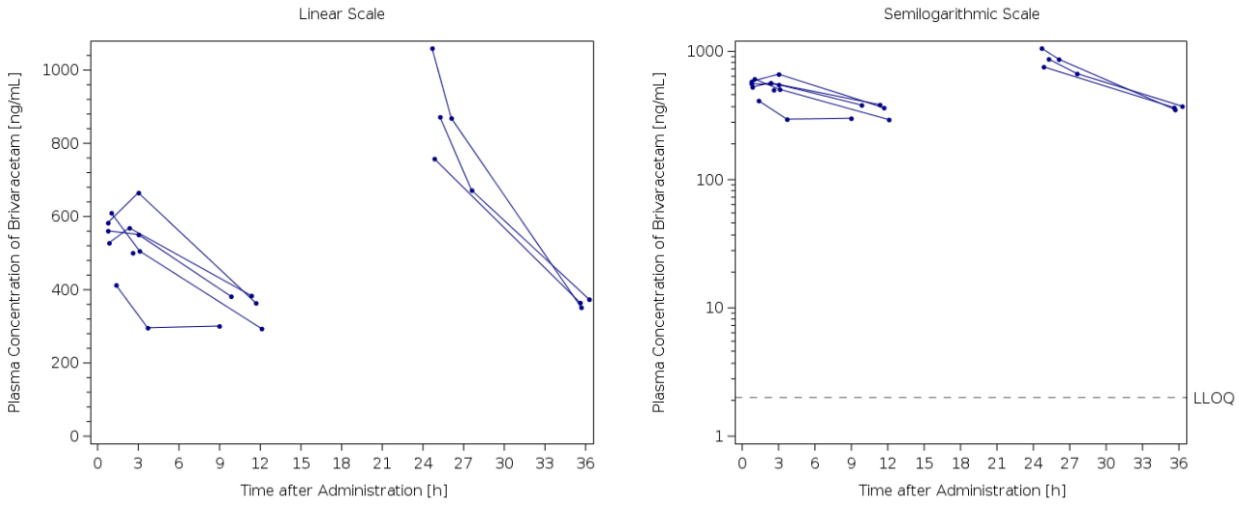
EEG=electroencephalogram; FAS=Full Analysis Set; n=number of study participants; NA=not applicable; PK-PPS=Pharmacokinetic Per-Protocol Set; SS=Safety Set
Note: FAS did not apply to study participants from the Exploratory Cohort since EEG was not required in this Cohort under Protocol Amendment 6.
Data source: Table 1.3

All 6 eligible study participants in the Exploratory Cohort completed the study and composed the SS and the PK-PPS (Table 3). No study participants were included in the FAS due to the lack of enrolment for the Confirmatory Cohorts. Therefore, no efficacy analyses were conducted.

PK results

Due to the small number of study participants enrolled, a planned analysis related to the concomitant use of hypothermia could not be conducted. In addition, since sparse sampling was used in the study, noncompartmental analysis could not be used to analyze the BRV data, and, instead, modeling and simulation were used to analyze the BRV data.

A spaghetti plot of individual BRV plasma concentrations over time is provided for the PK-PPS in Figure 1. A summary of BRV plasma concentrations over time on Day 1 is presented for the PK-PPS in Table 4.



BRV=Brivaracetam, LLOQ=Lower limit of quantification.
Note: LLOQ=2 ng/mL.

Figure 1 Spaghetti Plot of Individual BRV Plasma Concentrations vs Scheduled Time by Cohort

Table 4 Plasma concentrations of BRV (ng/mL) after iv administration on Day 1

	Day 1 relative time		
Variable	**0.5 to 1 hour**	**2 to 4 hours**	**8 to 12 hours**
n	5	6	5
GeoMean (GeoCV [%])	534.2 (15.4)	500.1 (28.2)	342.7 (13.2)
Mean (SD)	539.0 (76.6)	514.7 (122.4)	345.0 (44.1)
Median (min, max)	561.0 (413, 610)	528.5 (296, 665)	364.0 (294, 384)

BRV=brivaracetam; CV=coefficient of variation; geo=geometric; iv=intravenous; LLOQ=lower limit of quantification; max=maximum; min=minimum; n=number of study participants; PK-PPS=Pharmacokinetic Per-Protocol Set; SD=standard deviation
Note: Values below the limit of quantification were replaced by the value of LLOQ/2 in the calculation of means, SDs, and CVs.
Note: Means, SDs, and CVs were only calculated if at least two-thirds of the concentrations were quantified at the respective timepoint.
Data source: N01349 CSR Table 12.1

Brivaracetam was detectable in the plasma at all PK timepoints assessed in participants with evaluable samples. Following iv administration of BRV, on Day 1 the highest geometric mean (GeoMean [GeoCV]) plasma concentration of BRV was observed during the 0.5-hour to 1-hour time period (534.2 ng/mL [15.4%]); plasma concentrations declined with time thereafter. Inter-individual variability in GeoMean plasma concentration varied between 13.2% and 28.2%.

A summary of plasma PK parameters for BRV is presented in Table 5.

Table 5 Plasma PK parameters of BRV after iv administration

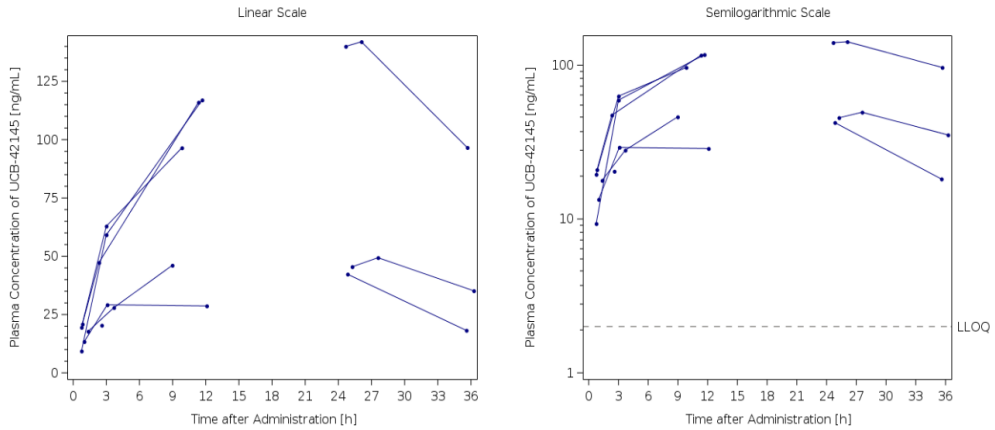
Variable	$AUC_{(0\text{-}12)}$ (h*mg/L)	AUC (h*mg/L)	C_{max} (mg/L)	t_{max} (min)	V_d (L)	CL (L/h)	CL (mL/min)	$t_{½}$ (h)
n	6	6	6	6	6	6	6	6
GeoMean (GeoCV [%])	4.437 (9.1)	6.751 (12.8)	0.604 (7.3)	16.837 (28.9)	2.570 (27.1)	0.233 (30.4)	3.884 (30.3)	7.647 (8.3)
Mean (SD)	4.452 (0.382)	6.795 (0.822)	0.605 (0.042)	17.500 (6.124)	2.650 (0.748)	0.242 (0.079)	4.038 (1.320)	7.668 (0.634)
Median (min, max)	4.545 (3.71, 4.75)	6.975 (5.39, 7.68)	0.616 (0.52, 0.63)	15.000 (15.00, 30.00)	2.515 (1.85, 3.97)	0.221 (0.16, 0.39)	3.680 (2.71, 6.50)	7.765 (6.87, 8.60)

AUC=area under the curve; BRV=brivaracetam; CL=clearance; C_{max}=maximum plasma concentration; CV=coefficient of variation; geo=geometric; iv=intravenous; max=maximum; min=minimum; n=number of study participants; PK=pharmacokinetic(s); PK-PPS=Pharmacokinetic Per-Protocol Set; SD=standard deviation; $t_{½}$=elimination half-life; t_{max}=time to reach C_{max}; V_d=volume of distribution
Note: Data are shown for the Exploratory Cohort.
Note: GeoMeans, SDs, and CVs were only calculated if at least two-thirds of the parameters were properly determined parameters (ie, calculated and flagged).
Data source: N01349 CSR Table 12.8

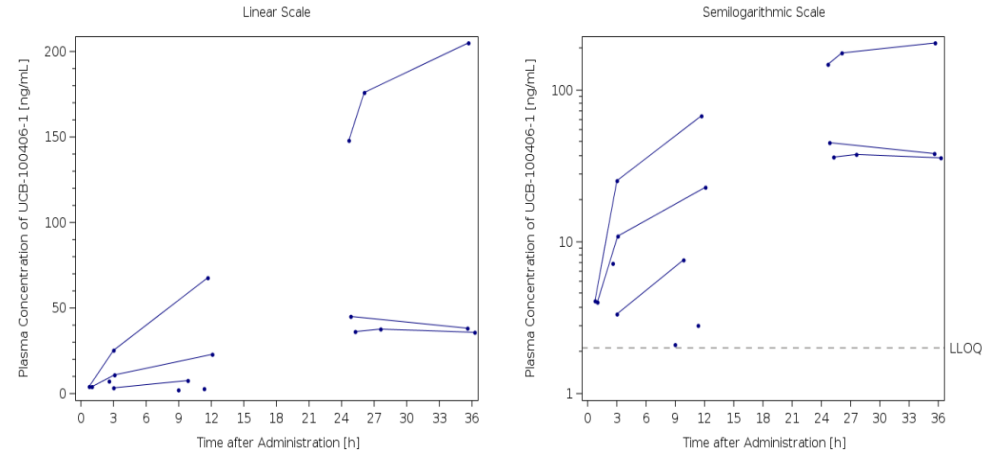
The GeoMean (GeoCV) AUC(0-12), AUC and Cmax values were 4.437h*mg/L (9.1%), 6.751h*mg/L (12.8%), and 0.604 mg/L (7.3%), respectively (Table 8-2). The median tmax was 15 minutes (minimum 15 minutes, maximum 30 minutes), and the GeoMean (GeoCV) t1/2 was 7.647 hours (8.3%). The GeoMean (GeoCV) Vd, and CL values were 2.570L (27.1) and 3.884mL/min (30.3%).

Spaghetti plots of individual plasma concentrations of BRV metabolites ucb-42145, ucb-100406-1, and ucb-107092-1 over time are provided in Figure 2. Plasma concentrations of the 3 BRV metabolites (ucb-42145, ucb-100406-1, and ucb-107092-1) were lower than BRV plasma concentrations.

ccb-42145



ucb-100406-1



ucb-107092-1

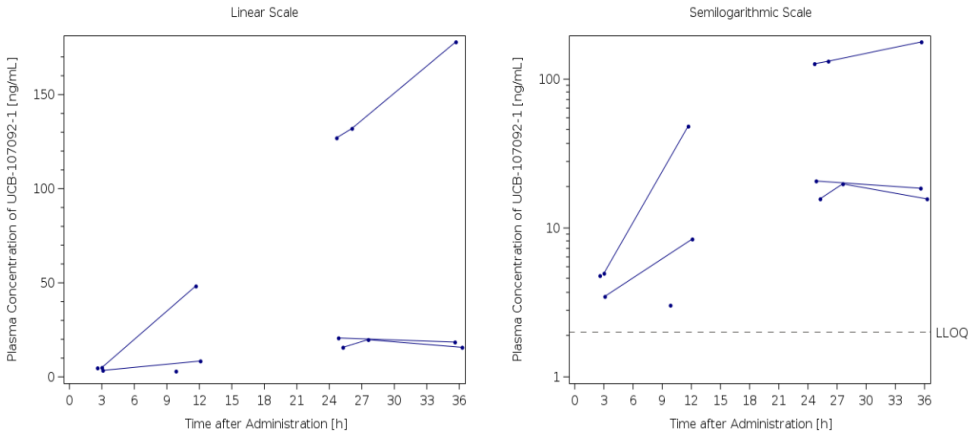


Figure 2 Spaghetti plots of individual metabolite plasma concentrations vs time

Plasma concentrations of concomitant AEDs were collected (data not shown).

In summary, brivaracetam was quantifiable in plasma at all PK timepoints assessed in participants with evaluable samples, and plasma concentrations were consistent with data from adults receiving an equivalent iv dose (25mg bid). The highest GeoMean BRV plasma concentration was observed between the 0.5-hour to 1-hour time period following iv administration of BRV; concentration declined with time thereafter. Plasma concentrations of the 3 BRV metabolites were lower than the BRV concentrations. Pharmacokinetic parameters were estimated using a model previously developed for participants aged 1 month to 16 years. The plasma concentrations observed in the current study were consistent with the PK observed in these older children, the data of which were similar to results obtained in adults.

Discussion on Pharmacokinetics

In study N01349, brivaracetam PK and safety were characterized in a limited number of neonates who had seizures that were not adequately controlled with previous AED treatment. Due to problems with recruitment, the study was stopped before any patient was enrolled in the Confirmatory Cohort. PK and safety data are available from 6 patients in the Exploratory Cohort; No data on efficacy are available.

The MAH concludes the plasma concentrations observed in the current study were consistent with the PK observed in adults receiving an equivalent iv dose (25mg bid). Overall, the Assessor agrees that PK

parameters appears to be comparable to the equivalent adult dose, however, since only a limited number of patients were available (n=6), it is not possible to draw any firm conclusions regarding similarity between neonates and adults.

The limited amount of data is the main limitation of this analysis. Another limitation is that the only observed dose level (0.5 mg/kg) is most likely subtherapeutic in most subjects. Nevertheless, the PK data was presented and analysed in a reasonable manner; the observed data collected with a sparse design were presented graphically in spaghetti plots and several PK parameters were estimated using modelling and simulation (Bayesian feedback of a previous paediatric PopPK model).

Efficacy results

Not applicable (see above).

Safety results

The duration of BRV exposure in N01349 is presented in Table 5 1.

Table 5-1: BRV exposure by study period (SS)

Study period	Statistic	BRV duration (days)	iv BRV duration (days)	iv BRV duration (hours)	BRV oral solution (days)
Overall	n	6	6	6	2
	Mean (SD)	10.333 (14.081)	5.500 (6.863)	119.222 (159.429)	15.500 (4.950)
	Median (min, max)	1.500 (1.00, 29.00)	1.500 (1.00, 17.00)	30.000 (12.00, 387.58)	15.500 (12.00, 19.00)
Evaluation Period	n	6	6	6	NA
	Mean (SD)	1.833 (0.983)	1.833 (0.983)	30.014 (19.734)	NA
	Median (min, max)	1.500 (1.00, 3.00)	1.500 (1.00, 3.00)	29.875 (12.00, 48.33)	NA
BRV Extension Period	n	2	2	2	2
	Mean (SD)	26.500 (0.707)	12.000 (4.243)	266.000 (98.995)	15.500 (4.950)
	Median (min, max)	26.500 (26.00, 27.00)	12.000 (9.00, 15.00)	266.000 (196.00, 336.00)	15.500 (12.00, 19.00)

BRV=brivaracetam; iv=intravenous; IMP=investigational medicinal product; max=maximum; min=minimum; n=number of study participants; NA=not applicable; os=oral solution; SD=standard deviation; SS=Safety Set
Note: The duration of BRV exposure (hours) was defined as the start date and time of last administration of IMP (BRV) minus the start date and time of first administration of IMP (BRV) plus duration of dosing interval (12 hours).
Note: BRV os was administered during the BRV Extension Period only.
Data source: N01349 CSR Table 7.1

Three study participants (50.0%) received 1 dose of BRV and 3 participants (50.0%) received >1 dose. During the Evaluation Period, BRV was administered as iv infusion only. During the BRV Extension Period, participants switched from BRV iv to oral solution before entering the long term study. Six participants (100%) received iv BRV during the Evaluation Period; only 2 study participants (33.0%) entered the BRV Extension Period and were treated with BRV oral solution. Overall, the median treatment duration of iv BRV was 30.00 hours (range: 12.00 hours to 387.58 hours).

CHMP comments

Even though 3 additional doses of BRV were allowed during the 48 hours evaluation period only 3 patients received more than 1 dose. Also, it is noted that only 2 patients entered extension period of the study. The reasons why 3 patients did not receive additional BRV doses as well as 4 patients did not enter extension period are not really discussed.

Adverse events

Overall summary of treatment-emergent adverse events

An overview of the incidence of treatment-emergent adverse events (TEAEs) is provided for the All Study Participants Screened Set in Table 5 2.

Table 5-2: Overview of the incidence of TEAEs (ASPS)

Category	Exploratory Cohort N=6 n (%) [#]	All participants N=9 n (%) [#]
Any AEs	3 (50.0) [5]	5 (55.6) [8]
Any TEAEs	3 (50.0) [4]	3 (33.3) [4]
Serious TEAEs	1 (16.7) [1]	1 (11.1) [1]
Nonserious TEAEs	3 (50.0) [3]	3 (33.3) [3]
Permanent withdrawal of IMP due to TEAEs	0	0
Drug-related TEAEs	0	0
Drug-related serious TEAEs	0	0
Severe TEAEs	1 (16.7) [1]	1 (11.1) [1]
Deaths (AEs leading to death)	0	0
Deaths (TEAEs leading to death)	0	0
Death prior to first dose of BRV	0	0

AE=adverse event; ASPS=All Study Participants Screened; BRV=brivaracetam; IMP=investigational medicinal product; TEAE=treatment-emergent adverse event
Note: "n" was the number of study participants reporting at least 1 TEAE in the category.
Note: "[#]" was the number of individual occurrences of TEAEs in the category.
Note: Treatment-emergent AEs were defined as AEs which had onset on or after the start date and time of initial IMP (BRV) administration.
Data source: N01349 CSR Table 8.1

For two of the study participants who were screen failures, a total of 4 AEs were reported; none of the AEs were severe, serious, or attributed to IMP as the participants did not receive IMP. Of the 6 study participants enrolled in the Exploratory Cohort, for 3 study participants (50.0%) 4 TEAEs were reported, none of which were considered to be drug related by the Investigator (Table 5 2). For 1 study participant (16.7%), 1 serious TEAE was reported that was considered severe in intensity.

No study participant discontinued from the study. No deaths were reported during the study.

Most common TEAEs

Treatment-emergent adverse events following investigational medicinal product (IMP) administration were in the System Organ Classes (SOCs) of Blood and lymphatic system disorders, Eye disorders, Metabolism and nutrition disorders, and Respiratory, thoracic and mediastinal disorder (1 participant [16.7%] each). For 1 study participant (16.7%) each, by preferred term (PT), the following TEAEs were reported: anemia, dry eye, hyperglycemia, and apnea during the study.

CHMP comments

The most TEAEs reported were mild or moderate in intensity. It is noted that neither of reported TEAEs, - anemia, dry eye, hyperglycemia, and apnea - are currently listed in the SmPC of BRV. However, single reports in very few patients which received even concomitant ASD (MDZ, Phenytoin, phenobarbital, levetiracetam) does not allow to draw any conclusions.

Treatment-emergent adverse events by maximum intensity

For 1 study participant (16.7%), 1 TEAE of severe apnea was reported (see Section 5.1.2.6 for details). All other TEAEs were of mild to moderate intensity (N01349 CSR Table 8.1.4).

Treatment-emergent adverse events by relationship

No TEAEs were considered related to IMP by the Investigator (N01349 CSR Table 8.15).

Other serious adverse events

For 1 study participant (16.7%), a serious TEAE of apnea was reported during the study and was related to MDZ. The study participant's apnea was severe in intensity, was not assessed as related to IMP by the Investigator and did not lead to discontinuation from the study.

Other significant adverse events

For 1 study participant (16.7%), hyperglycemia was reported which was considered as an AE of interest (N01349 CSR Table 8.25, N01349 CSR Table 8.28). This AE was moderate in intensity, was not assessed as related to IMP by the Investigator and did not lead to discontinuation from the study.

Clinical laboratory evaluation

Mean and median changes from Baseline for hematology and clinical chemistry variables were generally small and not considered to be clinically meaningful during the study. No trends were identified. The values were generally within normal ranges. Due to the limited number of study participants, no definite conclusions could be drawn.

One study participant (1/4 participants; 25.0%) had possibly clinically significant treatment emergent (PCST) Grade 2 high post-Baseline hemoglobin levels at the 48 hour timepoint during the Evaluation Period. No TEAEs related to abnormal hematology findings were reported during the study.

One study participant (1/5 participants; 20.0%) each had PCST Grade 2 high post-Baseline potassium and sodium levels at the 48-hour timepoint during the Evaluation Period. One study participant (20.0%) had PCST Grade 2 low post-Baseline sodium levels at the 48 hour timepoint during the Evaluation Period. One study participant (20.0%) had PCST Grade 2 high post-Baseline glucose levels at the 24-hour timepoint during the Evaluation Period. This participant had PCST Grade 2 high glucose levels at Baseline and also experienced a TEAE of hyperglycemia.

No study participants showed evidence of potential drug-induced liver injury (PDILI) during the study.

Vital signs

Changes in important vital signs, including systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, and respiration rate, were temporary and returned to Baseline within 24 hours to 48 hours. No significant signals were observed.

No critical PCST vital signs, including SBP, DBP, respiration rate, and heart rate, were observed in study participants treated with BRV in the Exploratory Cohort.

Other observations related to safety

Due to the limited number of study participants, no definite conclusions could be drawn.

The values for physical and neurological examination findings, Thompson score, and biometric parameters were generally within normal ranges. No trends were identified. No participant had withdrawal and rebound phenomenon.

One study participant (16.7%) required mechanical ventilation during the Evaluation Period. The mean duration of ventilation for this participant was 1.017 hours. No other study participants required mechanical ventilation.

Due to the small number of participants (n=3) undergoing hypothermia treatment, it was not possible draw conclusions regarding hypothermia treatment.

The Bayley-III scales were not used for analysis in this study.

Safety conclusions by the MAH

- The median treatment duration of iv BRV was 30.00 hours (range: 12.00 hours to 387.58 hours).
- For 3 study participants (50.0%), 4 TEAEs were reported, none of which were drug-related as assessed by the Investigator.
- The reported TEAEs following IMP administration were in the SOCs of Blood and lymphatic system disorders, Eye disorders, Metabolism and nutrition disorders, and Respiratory, thoracic and mediastinal disorder. For 1 study participant (16.7%) each, by PT, the following TEAEs were reported: anemia, dry eye, hyperglycemia, and apnea.
- There were no deaths or TEAEs leading to discontinuation during the study. All reported TEAEs were of mild to moderate intensity except for 1 participant (16.7%) who experienced a serious TEAE of apnea that was severe in intensity.
- For 1 study participant (16.7%), a TEAE of hyperglycemia was reported, which was moderate in intensity and was considered an AE of interest.
- Hematology and clinical chemistry values were generally within the normal ranges. No trends were identified. Due to the limited number of study participants, no definite conclusions could be drawn.
- Changes in vital signs (SBP, DBP, heart rate, respiration rate) were temporary. No critical PCST vital signs were observed in study participants treated with BRV.
- The values for physical and neurological examination findings, Thompson score, N-PASS score, and biometric parameters were generally within normal ranges. No trends were identified. No participant had withdrawal and rebound phenomenon.
- No PDILI events were reported by any participant.

2.3.3. Discussion on clinical safety aspects

The planned N01349 study was a Phase 2/3, multicenter, open-label, single-arm study to evaluate the PK, efficacy, and safety of BRV in neonates with repeated electroencephalographic seizures. Only the first step of the N01349 study from a planned 2 step design (step 1=Exploratory Cohort; step 2=Confirmatory Cohorts) was completed. In agreement with PDCO the study was terminated since completion of it was considered to be infeasible.

Only six patients were included into the first exploratory cohort. The most common TEAEs reported were mild or moderate in intensity. It is noted that neither of reported TEAEs, - anemia, dry eye, hyperglycemia, and apnea - are currently listed in the SmPC of BRV. However, single reports in very few patients which received even concomitant ASD (MDZ, Phenytoin, phenobarbital, levetiracetam) does not allow to draw any conclusions.

The benefit risk balance of brivaracetam when used in patients according to approved indication remains unchanged.

Currently, the following statement is included in section 4.8 of the SmPC under the heading "Paediatric population":

"<…> *No clinical data are available in neonates. <…>*"

Since safety information is currently available from 6 neonates, this statement may be considered as not correctly reflecting the current level of knowledge and it could be recommended to modify it as follows (new text in **bold**, removed text – ~~strikethrough~~):

"<…> ***Limited*** ~~*no*~~ *clinical data are available in neonates. <…>*"

3. Rapporteur's overall conclusion and recommendation

☒ **Fulfilled:**

Only the first exploratory part of the planned N01349 study was completed. In agreement with PDCO the study was terminated since completion of it was considered to be infeasible.

No efficacy data were generated. Only limited pharmacokinetic and safety data from 6 patients were available.

It is considered acceptable to not update the Briviact SmPC based on the pharmacokinetic results from study N01349.

In view of the available limited clinical safety data regarding use of brivaracetam in neonates from the N01349 study and the information currently present in the SmPC stating that no clinical data in neonates are available, this discrepancy should be corrected, and the MAH should 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.