Pharmacokinetics, safety, and tolerability of intravenous brivaracetam in neonates with seizures: interim analysis of a phase 2/3, open-label trial

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Background

- Seizures occur more often during the neonatal period than at any other period of life. In addition, management of neonatal seizures is challenging, with little evidence base.[1]
- Brivaracetam (BRV) is indicated for the treatment of focal (partial-onset) seizures in patients ≥4 years of age as monotherapy (United States) and adjunctive therapy (United States and European Union).[2,3]
  - In the United States, BRV injection is indicated for the treatment of focal seizures only in patients ≥16 years of age.[3]
- Currently, none of the antiseizure medications (ASMs) used to treat neonatal seizures is approved, and overall there is limited information on the efficacy.

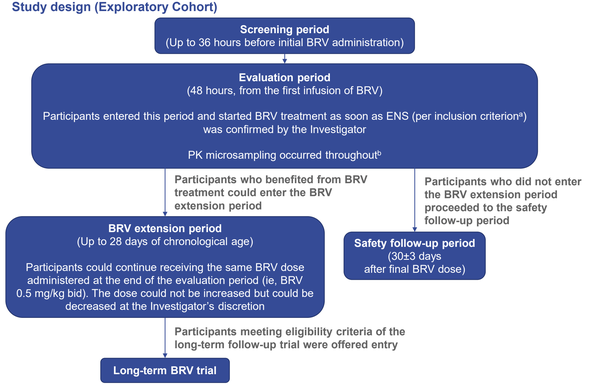
Objective

- To evaluate the pharmacokinetics (PK), safety, and tolerability of BRV in neonates with repeated electroencephalographic (EEG) seizures not controlled with previous ASM treatment, and to identify the optimal dose (Exploratory Cohort) for the treatment of participants enrolled into the Confirmatory Cohorts of this trial.

Methods

- N01349 (the PETITE trial/NCT03325439) is an ongoing, phase 2/3, multicenter, open-label, single-arm trial in neonates with repeated EEG seizures.
- This poster reports data from the completed Exploratory Cohort, which aimed to confirm or adapt the dose predictions of the initial modeling. The trial is currently ongoing and has opened enrollment in the Confirmatory Cohort.
- It was planned to enroll into the Exploratory Cohort six or more neonates (postmenstrual age [PMA] ≥34 weeks; term neonates ≤27 days of chronological age and preterm neonates ≤40 weeks of PMA and ≤27 days of chronological age; bodyweight ≥2.3 kg at enrollment) who did not have adequate seizure control after receiving at least one ASM per standard of care (SOC) for the treatment of EEG neonatal seizures.
  - With the ASM treatment per SOC, the choice of first-line, second-line, or subsequent treatment, dose, and dosing regimen were at the Investigator's discretion.
- Patients were excluded if they had seizures responding to previous ASM treatment immediately before BRV treatment, pyridoxine treatment, or correction of metabolic disturbances; required extra corporeal membrane oxygenation; had seizures related to prenatal maternal drug use or withdrawal; had known severe disturbance of hemostasis; or had a poor prognosis for survival.
- At any time after the initiation of ASM treatment per SOC, an initial low dose of BRV (0.5 mg/kg twice daily [bid]) was administered as an approximately 15-minute intravenous (IV) infusion at the Investigator's discretion during a 48-hour evaluation period. An additional three IV BRV doses, up to a total of four doses (0.5 mg/kg bid), could be administered during the evaluation period at the Investigator's discretion.
  - 0.5 mg/kg bid in neonatal patients is estimated to give a similar exposure to 25 mg bid in adults.
- ASM treatment per SOC could be continued when BRV dosing was initiated. Otherwise, another ASM treatment (choice of treatment, dose, and dosing regimen at Investigator's discretion) had to be initiated and continue in parallel with BRV treatment.
- Participants benefiting from BRV could enter the extension period, during which they could switch to oral BRV and enter into a long-term follow-up trial; the remaining participants proceeded to the safety follow-up period.

Study design (Exploratory Cohort)



[a]Confirmation on VEEG of ≥2 minutes of cumulative ENS or ≥3 identifiable ENS before entering the evaluation period (ENS was defined as a seizure lasting ≥10 seconds on VEEG), despite receiving previous ASM for the treatment of electroencephalographic seizures. The occurrence of ENS during an up to 1-hour period had to be confirmed either by the local or central VEEG reader before drug administration; [b]Following the first BRV infusion, 3-6 blood microsamples (60 µL/sample) were collected from each participant. On day 1, samples were collected at 30-60 minutes after the start of BRV infusion and then at 2-4 and 8-12 hours after the start of the most recent BRV infusion. On day 2, samples were only collected if the participant received BRV on that day; the timepoints for sample collection were 30-60 minutes, 2-4 hours, and 8-12 hours after the start of the most recent BRV infusion. In addition, opportunistic blood samples for PK analysis may have been used at the Investigator's discretion at any time during the evaluation period. ASM, antiseizure medication; bid, twice daily; ENS, electroencephalographic neonatal seizures; PK, pharmacokinetic; VEEG, video-electroencephalography.

OUTCOMES

- BRV plasma concentrations following the first dose on day 1 (primary variable), area under the curve, maximum plasma concentration, volume of distribution, clearance, and elimination half-life were assessed during the evaluation period.
- Treatment-emergent adverse events were assessed throughout BRV treatment.

PK ANALYSES

- BRV doses and concentration measurements in participants were analyzed to provide PK profiles and associated PK parameters.
- PK 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 that describes BRV PK after 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 3/4 and 1, respectively.
- As a reference, adult profiles were simulated using the weight distribution from a National Health and Nutrition Examination Survey database (with age >18 years), and using the parameters estimated in an adult population PK model using freely estimated allometric exponents.

ANALYSIS SETS

- The Safety Set (SS) consisted of all enrolled participants who took at least one dose of BRV.
- The PK Per-Protocol Set consisted of all participants who provided at least one measurable plasma sample (with recorded sampling time) on at least one post-baseline visit with documented trial drug intake times.

Results

PARTICIPANT DISPOSITION AND DEMOGRAPHICS

- Six participants were enrolled into the Exploratory Cohort, all of whom were included in the SS and completed the trial.
- Of the six participants who completed the evaluation period, two (33.3%) entered and completed the BRV extension period.
- The median BRV treatment duration was 30.0 (min, max: 12.0, 231.6) hours.

Baseline characteristics

	Safety Set (N=6)
Participant demographics	
Chronological age, mean (SD), days	2.5 (2.1)
Postmenstrual age, mean (SD), weeks	38.7 (1.5)
Female, n (%)	4 (66.7)
Weight at baseline, mean (SD), g	3255.0 (684.8)
Apgar score (5 minutes), mean (SD)	7 (2.9)
HIE status: suffered from HIE, n (%)	3 (50.0)
Previous and ongoing medical history conditions[a], n (%)	
At least one condition	4 (66.7)
Conditions in ≥30% of participants	
Asphyxia	2 (33.3)
Brain edema	2 (33.3)
Cardiovascular insufficiency	2 (33.3)
Respiratory failure	2 (33.3)
ASMs taken at trial entry[b], n (%)	
At least one ASM	5 (83.3)
Phenobarbital	5 (83.3)
Midazolam	3 (50.0)
Phenytoin	3 (50.0)
Levetiracetam	1 (16.7)
Concomitant ASMs[c], n (%)	
At least one ASM	3 (50.0)
Phenobarbital	3 (50.0)
Midazolam	2 (33.3)
Levetiracetam	1 (16.7)

Baseline was defined as the latest assessment before the first dose of BRV. [a]Previous and ongoing medical conditions that occurred before or at the time of trial entry; [b]ASMs ongoing at trial entry; [c]ASMs taken during the administration of BRV. ASM, antiseizure medication; HIE, hypoxic-ischemic encephalopathy.

PHARMACOKINETICS

- BRV was detectable in the plasma at all PK timepoints assessed in all participants with evaluable samples.

Plasma concentrations of BRV after IV BRV administration on day 1

BRV plasma concentration, geometric mean (GeoCV, %), mg/L	PK Per-Protocol Set (N=6)
0.5-1 hours	0.5342 (15.4)[a]
2-4 hours	0.5001 (28.2)
8-12 hours	0.3427 (13.2)[a]

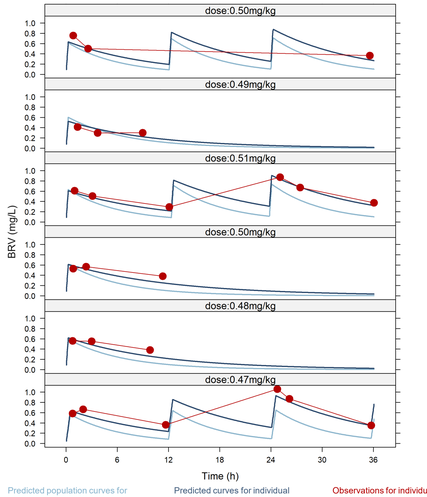
[a]n=5. GeoCV, geometric coefficient of variation; IV, intravenous; PK, pharmacokinetic.

Plasma PK parameters of BRV after IV BRV administration

Geometric mean (GeoCV, %)	PK Per-Protocol Set (N=6)
AUC, h.mg/L	4.4 (9.1)
C_{max}, mg/L	0.604 (7.3)
VD, L	2.6 (27.1)
CL/F, L/h	0.23 (30.4)
$t_{1/2}$, h	7.6 (8.3)

AUC, area under the curve; CL/F, clearance; C_{max}, maximum plasma concentration; GeoCV, geometric coefficient of variation; IV, intravenous; PK, pharmacokinetic; $t_{1/2}$, elimination half-life; VD, volume of distribution.

Observed and predicted BRV profiles for individual participants



Individual predicted pediatric curves were calculated using Bayesian feedback.

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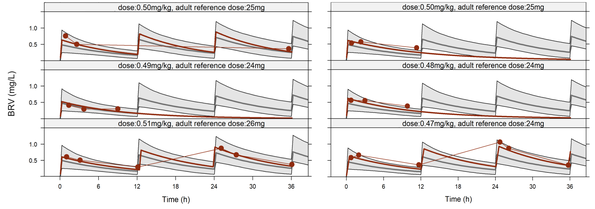
Observed and predicted BRV profiles for individual participants, compared with reference profiles for adults receiving IV BRV



Pediatric predicted individual curves were calculated using Bayesian feedback.
bid, twice daily; IV, intravenous.

- Generally, the plasma concentrations were in the range of the simulated adult levels.

SAFETY AND TOLERABILITY

- IV BRV was generally well tolerated in this Exploratory Cohort of neonatal participants, with no drug-related treatment-emergent adverse events being reported.
- One (16.7%) participant experienced a serious treatment-emergent adverse event.
- No participants permanently discontinued BRV treatment due to treatment-emergent adverse events.

Treatment-emergent adverse events during the trial

Participants, n (%)	Safety Set (N=6)
Any treatment-emergent adverse events	3 (50.0)
Serious treatment-emergent adverse events	1 (16.7)
Permanent discontinuation of BRV due to treatment-emergent adverse events	0
Deaths	0
Drug-related treatment-emergent adverse events	0
Severe treatment-emergent adverse events	1 (16.7)
Incidence of treatment-emergent adverse events	
Anemia	1 (16.7)
Hyperglycemia	1 (16.7)
Apnea	1 (16.7)
Incidence of serious treatment-emergent adverse events	
Apnea	1 (16.7)

Conclusions

- In this first BRV trial in neonatal participants, observed BRV plasma concentrations were consistent with data from adults receiving a nominal IV dose of 25 mg bid.
- Treatment with IV BRV up to 0.5 mg/kg bid was generally well tolerated.

References

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