PROTOCOL N01349 AMENDMENT 7

A MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE THE PHARMACOKINETICS, EFFICACY, AND SAFETY OF BRIVARACETAM IN NEONATES WITH REPEATED ELECTROENCEPHALOGRAPHIC SEIZURES

PHASE 2/3

EudraCT Number: 2015-002756-27

Sponsor:

UCB Biopharma SRL
Allée de la Recherche 60
1070 Brussels
BELGIUM

Protocol/Amendment number	Date	Type of amendment
Final Protocol	14 Oct 2016	Not applicable
Protocol Amendment (1.0)	14 Dec 2016	Non-Substantial
Protocol Amendment (2.0)	28 Feb 2017	Non-Substantial
Protocol Amendment (2.1, Germany)	19 Jul 2017	Non-Substantial
Protocol Amendment (2.2, Czech Republic)	19 Jul 2017	Non-Substantial
Protocol Amendment (3.0)	23 Oct 2017	Non-Substantial
Protocol Amendment (4.0)	22 Jan 2018	Non-Substantial
Protocol Amendment (5.0)	10 Oct 2019	Substantial
Protocol Amendment (6.0)	28 Oct 2019	Non-Substantial
Protocol Amendment (6.1, Germany)	08 Nov 2019	Non-Substantial
Protocol Amendment (6.2, Czech Republic)	08 Nov 2019	Non-Substantial
Protocol Amendment (6.3, France)	07 Oct 2020	Substantial
Protocol Amendment (6.4, Czech Republic)	10 Nov 2020	Substantial
Protocol Amendment (6.5, Germany)	02 Dec 2020	Substantial
Protocol Amendment (7.0)	24 May 2021	Substantial

STUDY CONTACT INFORMATION

Sponsor

UCB Biopharma SRL

Allée de la Recherche 60

1070 Brussels

BELGIUM

Principal/Coordinating Investigator

Name:	Ronit Pressler, [redacted]
Affiliation:	University College London
Address:	Gower Street 1 London, WC1E 6BT United Kingdom
Phone:	[redacted]
Fax:	[redacted]

Sponsor Study Physician

Name:	[redacted], [redacted]
Address:	UCB BioSciences, Inc. 8010 Arco Corporate Drive [redacted] Raleigh, NC 27617 USA
Phone:	[redacted]
Fax:	[redacted]

Clinical Project Manager

Name:	[redacted], [redacted]
Address:	Alfred-Nobel-Strasse 10 40789 Monheim GERMANY
Phone:	[redacted]
Fax:	[redacted]

Clinical Trial Biostatistician

Name:	[redacted], [redacted]
Address:	UCB BioSciences, Inc. 8010 Arco Corporate Drive, [redacted] Raleigh, NC 27617 USA
Phone:	[redacted]
Fax:	[redacted]

Clinical Monitoring Contract Research Organization

Name:	PRA Health Sciences
Address:	Green Park 500 South Oak Way Reading, RG2 6AD United Kingdom
Phone:	+44 118 918 1000
Fax:	+44 118 918 1001

Data Monitoring Committee

Name:	Affiliation/Job title:
[redacted]	Pediatric Clinical Pharmacologist
[redacted]	Pediatric Neonatologist
[redacted]	Pediatric Neonatologist

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	**Europe:** +32 238 66561
Email	PSRapidalert@ucb.com

TABLE OF CONTENTS

LIST OF ABBREVIATIONS 10
1 SUMMARY 12
2 INTRODUCTION 15
2.1 Epidemiology and treatment of targeted disease 15
2.2 Background information regarding product 15
2.3 Rationale for the study 17
3 STUDY OBJECTIVES 18
3.1 Primary objective 18
3.2 Secondary objectives 18
4 STUDY VARIABLES 18
4.1 PK variables (Exploratory and Confirmatory Cohorts) 18
4.1.1 Primary PK variable 18
4.1.2 Other PK variables 18
4.2 Efficacy variables (Confirmatory Cohorts only) 19
4.2.1 Secondary efficacy variables 19
4.2.2 Other efficacy variables 20
4.3 Safety variables (Exploratory and Confirmatory Cohorts) 21
4.3.1 Secondary safety variable 21
4.3.2 Other safety variables 21
5 STUDY DESIGN 22
5.1 Study description 22
5.1.1 Exploratory Cohort 24
5.1.2 Confirmatory Cohorts 25
5.1.3 Study duration per subject 28
5.1.4 Planned number of subjects and sites 28
5.1.5 Anticipated regions and countries 29
5.2 Schedule of study assessments 29
5.3 Schematic diagrams 40
5.4 Rationale for study design and selection of dose 45
5.4.1 Rationale for study design 45
5.4.2 Rationale for dose selection 45
6 SELECTION AND WITHDRAWAL OF SUBJECTS 47
6.1 Inclusion criteria 47
6.2 Exclusion criteria 47
6.3 Withdrawal criteria 48
6.3.1 Potential drug-induced liver injury IMP discontinuation criteria 49
7 STUDY TREATMENTS 50

7.1 Description of investigational medicinal products 50
7.2 Treatments to be administered 50
7.3 Packaging 51
7.4 Labeling 51
7.5 Handling and storage requirements 51
7.6 Drug accountability 51
7.7 Procedures for monitoring subject compliance 52
7.8 Concomitant treatments and medications 52
7.8.1 Permitted concomitant treatments (medications and therapies) 52
7.8.2 Prohibited concomitant treatments (medications and therapies) 53
7.8.3 Rescue medication 53
7.9 Blinding 53
7.10 Randomization and numbering of subjects 53
8 STUDY PROCEDURES BY VISIT 53
8.1 Exploratory Cohort 54
8.1.1 Screening Period 54
8.1.2 Evaluation Period 55
8.1.3 BRV Extension Period 56
8.1.3.1 Extension Period Visit 1 57
8.1.3.2 Extension Period Visit 2 57
8.1.3.3 Unscheduled Visit 58
8.1.3.4 Telephone Contact 58
8.1.4 Safety Follow-Up Period 58
8.2 Confirmatory Cohorts 59
8.2.1 Screening Period 59
8.2.1.1 Baseline Period 59
8.2.2 Evaluation Period 60
8.2.3 BRV Extension Period 62
8.2.3.1 Extension Period Visit 1 63
8.2.3.2 Extension Period Visit 2 63
8.2.3.3 Unscheduled Visit 64
8.2.3.4 Telephone Contact 64
8.2.4 Down-Titration Period 64
8.2.5 Safety Follow-Up Period 65
9 ASSESSMENT OF PHARMACOKINETIC VARIABLES 65
9.1 Pharmacokinetic sampling and handling 65
9.2 Pharmacokinetic sample shipment 67
10 ASSESSMENT OF EFFICACY 67

10.1 Assessment of the secondary efficacy variables (Confirmatory Cohort[s] only) 67
10.2 Assessment of other efficacy variables 68
10.3 Seizure burden 69
11 ASSESSMENT OF SAFETY 69
11.1 Adverse events 69
11.1.1 Definitions 69
11.1.1.1 Adverse event 69
11.1.1.2 Serious adverse event 70
11.1.1.3 Adverse events of special interest 72
11.1.2 Procedures for reporting and recording adverse events 72
11.1.2.1 Description of adverse events 75
11.1.2.2 Rule of repetition of an adverse event 75
11.1.2.3 Additional procedures for reporting serious adverse events 75
11.1.2.4 Immediate reporting of adverse events 76
11.1.3 Follow-up of adverse events 76
11.1.4 Suspected transmission of an infectious agent 76
11.1.5 Overdose of investigational medicinal product 76
11.1.6 Safety signal detection 77
11.2 Laboratory measurements 77
11.2.1 Evaluation of PDILI 79
11.2.1.1 Consultation with Medical Monitor and local hepatologist 81
11.2.1.2 Immediate action: determination of IMP discontinuation 81
11.2.1.3 Testing: identification/exclusion of alternative etiology 81
11.2.1.4 Follow-up evaluation 83
11.3 Other safety measurements 83
11.3.1 Physical and neurological examinations 83
11.3.2 Medical history including Apgar score 84
11.3.3 Vital signs 84
11.3.4 Biometric parameters 84
11.3.5 N-PASS 84
11.3.6 Video-EEG Parameters 84
11.3.7 HIE (Thompson score) 85
11.3.8 Withdrawal and rebound phenomena 85
11.3.9 Mechanical ventilation 85
11.3.10 Bayley Scales of Infant and Toddler Development, Third Edition 85
12 STUDY MANAGEMENT AND ADMINISTRATION 86
12.1 Adherence to protocol 86
12.2 Monitoring 86

12.2.1 Definition of source data 86
12.2.2 Source data verification 87
12.3 Data handling 87
12.3.1 Case Report form completion 87
12.3.2 Database entry and reconciliation 87
12.3.3 Subject Screening and Enrollment log/Subject Identification Code list 87
12.4 Termination of the study 88
12.5 Archiving and data retention 88
12.6 Audit and inspection 88
12.7 Good Clinical Practice 88
13 STATISTICS 89
13.1 Definition of analysis sets 89
13.2 General statistical considerations 89
13.3 Pharmacokinetic variable analysis 89
13.3.1 Exploratory Cohort 89
13.3.2 Confirmatory Cohorts 90
13.4 Safety analyses 90
13.5 Planned efficacy analyses 90
13.5.1 Analysis of the secondary efficacy variables 90
13.5.2 Analysis of the other efficacy variables 92
13.6 Handling of protocol deviations 93
13.7 Handling of dropouts or missing data 93
13.8 Planned PK data review and safety data monitoring 93
13.8.1 Exploratory Cohort 93
13.8.2 Confirmatory Cohorts 93
13.8.3 DMC and stopping rules 94
13.9 Determination of sample size 94
14 ETHICS AND REGULATORY REQUIREMENTS 94
14.1 Informed consent 94
14.2 Subject identification cards 95
14.3 Independent Ethics Committees 95
14.4 Subject privacy 96
14.5 Protocol amendments 96
15 FINANCE, INSURANCE, AND PUBLICATION 96
16 REFERENCES 97
17 APPENDICES 100
17.1 Protocol Amendment 1 100
17.2 Protocol Amendment 2 122

17.3 Protocol Amendment 3 135
17.4 Protocol Amendment 4 173
17.5 Protocol Amendment 5 174
17.6 Protocol Amendment 6 239
17.7 Protocol Amendment 7 241
18 DECLARATION AND SIGNATURE OF INVESTIGATOR 253
19 SPONSOR DECLARATION 254

LIST OF TABLES

Table 5–1: Schedule of study assessments – Screening and Evaluation Periods (Exploratory Cohort) 30
Table 5–2: Schedule of study assessments – Screening and Evaluation Periods (Confirmatory Cohorts) 32
Table 5-3: Schedule of study assessments - BRV Extension Period and Safety Follow-Up Period (Exploratory and Confirmatory Cohorts) 37
Table 5–4: Schedule for PK Sampling (Exploratory Cohort) 39
Table 5–5: Schedule for PK Sampling (Confirmatory Cohorts) 40
Table 11–1: Mandatory laboratory measurements 78
Table 11–2: Optional laboratory measurements 78
Table 11–3: Required investigations and follow-up for PDILI 80
Table 11–4: Recommended PDILI laboratory measurements[a] 82
Table 11–5: PDILI information to be collected 83

LIST OF FIGURES

Figure 5–1: Schematic overview of the study (Exploratory Cohort) 41
Figure 5–2: Screening and Evaluation Periods (Exploratory Cohort) 42
Figure 5–3: Schematic overview of the study (Confirmatory Cohorts) 43
Figure 5–4: Screening and Evaluation Periods (Confirmatory Cohorts) 44
Figure 11–1: Adverse event reporting flowchart 74

LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
Bayley-III®	Bayley Scales of Infant and Toddler Development®, Third Edition
bid	(bis in die) twice daily
BRV	brivaracetam
BZD	benzodiazepine
CDMS	clinical data management system
CI	confidence interval
CGA	corrected gestational age
CNS	central nervous system
CPMP	Committee for Proprietary Medicinal Products
CRO	contract research organization
CTD	Clinical Trials Directive
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic Case Report form
EEG	electroencephalogram
EMA	European Medicines Agency
ENS	electroencephalographic neonatal seizures
EPV	Extension Period Visit
EudraCT	European Union Drug Regulating Authorities Clinical Trials
GA	gestational age
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIE	hypoxic-ischemic encephalopathy
IB	Investigator's Brochure
ICF	Informed Consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee

IMP	investigational medicinal product
IRT	interactive response technology
iv	intravenous(ly)
LDC	lidocaine
LEV	levetiracetam
LFT	liver function test
MDZ	midazolam
N-PASS	neonatal pain, agitation and sedation scale
PB	phenobarbital
PDCO	Paediatric Committee
PDILI	potential drug-induced liver injury
PHT	phenytoin
PNA	postnatal age
PK	pharmacokinetic
POS	partial-onset seizure
PS	Patient Safety
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOC	standard of care
SOP	Standard Operating Procedure
SS	Safety Set
SV2A	synaptic vesicle protein 2A
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VEEG	(multichannel) video-electroencephalography

1 SUMMARY

N01349 is a Phase 2/3, multicenter, open-label, single-arm study to evaluate the pharmacokinetics (PK), seizure activity/efficacy (interpreted as "efficacy on seizure activity" and referred to as "efficacy" in the protocol), and safety of brivaracetam (BRV) in neonates with repeated electroencephalographic (EEG) seizures. Subjects will first receive antiepileptic drugs (AEDs) for the treatment of electroencephalographic neonatal seizures (ENS) (first-line, second-line, or subsequent treatment, which may have started prior to the subject's admission into the study site; dose and dosing regimen at the Investigator's discretion). If they do not have adequate seizure control after the treatment with AEDs, they may be enrolled into N01349.

As the patient population of neonates with ENS is limited, N01349 is designed with a 2-step approach to allow for confirmation (or adjustment) of BRV dosing based on results from the first step (Exploratory Cohort) and evaluation of BRV efficacy in the second step (Confirmatory Cohorts). This adaptive design allows for the determination of dose and the collection of PK, safety, and efficacy data, thereby potentially providing rapid access to alternative treatment in neonates.

For the Exploratory Cohort (first step), enrolled subjects will receive 1 or more of the following AEDs prior to or at the time of enrollment: phenobarbital (PB), midazolam (MDZ), phenytoin (PHT), levetiracetam (LEV), or lidocaine (LDC) for the treatment of ENS (first-line, second-line, or subsequent treatment; choice of treatment, dose, and dosing frequency is at the discretion of the Investigator) prior to receiving BRV. Subsequently, an initial low dose of BRV intravenous (iv) solution for injection will be administered. At the discretion of the Investigator, 3 additional iv BRV doses can be administered, up to a total of 4 iv BRV doses (0.5mg/kg twice daily [bid]), during the 48-hour Evaluation Period to determine the PK of BRV in neonates. This treatment represents the first use of BRV in neonates (0.5mg/kg bid), which is 4-fold less than the highest dosage of 4mg/kg/day that has been used previously in study N01263 (Section 2.2).

In BRV PK modeling studies CL0187 and N01331, PK profiles were extrapolated allometrically to the neonatal age group from the pediatric data collected in N01263 (age range of ≥1 month to <16 years). A total of 600 samples from 96 subjects were used for this modeling. The results of this modeling suggest that a dosing regimen of 2mg/kg bid in pediatric subjects ≥1 month to <16 years of age with a maximum of 100mg bid (for patients with a bodyweight of 50kg or more) would result in plasma concentration profiles similar to those attained in older children and adults who received therapeutic doses of BRV (up to 100mg bid). Since extrapolation of data from subjects ≥1 month to subjects ≤2 weeks may be imprecise due to variability in ontogeny in the metabolic and excretory functions in neonates, actual PK measurements conducted in the Exploratory Cohort of N01349 will be used to confirm the relationship between dose and plasma concentration in neonates.

For the Confirmatory Cohorts (second step with 3 consecutive cohorts planned), the efficacy of BRV will be evaluated. Subjects may have received 1 or more of the following AEDs prior to or at the time of enrollment: PB, MDZ, LEV (≤60mg/kg/day), PHT, or LDC. The iv dose and dosing frequency of BRV selected for the Confirmatory Cohorts will be determined by the evaluation of BRV plasma concentrations from the Exploratory Cohort, as well as by the PK modeling of N01263 data described above, to be within the range of plasma concentrations observed in children ≥1 month old who received BRV 4mg/kg/day. A dosage of BRV 4mg/kg/day for neonates is predicted to be approximately equivalent to the highest BRV dose

(200mg/day) approved as adjunctive therapy for partial-onset seizures (POS) in patients ≥16 years of age.

The recommendation to confirm or adjust the originally calculated BRV dose of the Confirmatory Cohorts of study N01349 will be given by the Data Monitoring Committee (DMC) after review of PK and safety data of the Exploratory Cohort. Based on the DMC meeting held on 05 Nov 2020, the BRV dose and frequency selected for the Confirmatory Cohorts is 1mg/kg bid (2mg/kg/day). Based on data from the Confirmatory Cohorts, the BRV dose may be further adjusted in a staggered approach as determined by the DMC.

The safety and PK of BRV will be evaluated in all 4 cohorts. At the end of the Evaluation Period, subjects from both the Exploratory and Confirmatory Cohorts may enter the BRV Extension Period.

The primary objective of this study is to evaluate the PK of BRV in neonates who have seizures that are not adequately controlled with previous AED treatment, and to identify the optimal BRV dose (Exploratory Cohort) for the treatment of subjects enrolled into the Confirmatory Cohorts of this study. Secondary objectives include the evaluation of the short-term safety and tolerability of BRV in neonates and the evaluation of the efficacy of BRV in severe and nonsevere seizure burden (defined as total minutes of ENS per hour) in neonates with seizures that are not adequately controlled with previous AED treatment.

This study will enroll at least 42 evaluable subjects (at least 6 subjects in the Exploratory Cohort, at least 36 subjects in the Confirmatory Cohorts, including at least 2 subjects undergoing hypothermia treatment in the Exploratory Cohort and each of the 3 Confirmatory Cohorts). At enrollment, subjects must be at least 34 weeks of corrected gestational age (CGA). In addition, term neonates up to 27 days of postnatal age (PNA) and preterm neonates up to 40 weeks of CGA and 27 days of PNA can be enrolled.

Subjects must have a confirmed diagnosis of ENS by multichannel video-electroencephalography (VEEG) of ≥2 minutes of cumulative ENS or ≥3 identifiable ENS prior to entering the Evaluation Period (ENS is defined as a seizure lasting for at least 10 seconds on VEEG), despite receiving AED treatment. The maximum study duration per subject is expected to be up to 75 days, which consists of a Screening Period, Baseline Period (Confirmatory Cohorts only), Evaluation Period, BRV Extension Period, Down-Titration Period (Confirmatory Cohorts only), and Safety Follow-Up Period. There is a possibility that in certain regions sites may not be ready to transition subjects to EP0156 at the time enrollment into N01266 will be closed. To avoid that enrollment into N01349 must pause from early Sep 2021 onwards, subjects will then be allowed to stay in N01349 for up to 90 days of PNA until rollover to the long-term study is possible. In this event, the maximum study duration for subjects who remain in the study for up to 90 days of PNA and do not enter the long-term study will then be up to 130 days (90 days of PNA, up to 7 days for the Down-Titration Period, and up to 33 days for the Safety Follow-Up Period). All subjects who participate in the BRV Extension Period must be offered entry into a long-term study, if they meet the eligibility criteria. Before entering the long-term study, subjects must be on oral BRV.

The PK variables are the plasma concentrations of BRV, the area under the curve (AUC), volume of distribution, and clearance of BRV in neonates. Further, PK assessments will include plasma concentrations of concomitant PB and/or PHT if administered.

The safety variables are adverse events (AEs) as reported by the Investigator, withdrawal and rebound phenomena, and mechanical ventilation over the Evaluation Period of the Exploratory Cohort and the Confirmatory Cohorts. In addition, safety variables also include the change from Baseline to the end of the Evaluation Period for the following variables: vital signs, safety laboratory tests, heart rate, physical and neurological examination (Sarnat scale for subjects with hypoxic-ischemic encephalopathy [HIE]), psychometric parameters (neonatal pain, agitation, and sedation scale [N-PASS]), EEG-parameters, the severity of HIE (Thompson score for subjects with HIE); and change from Baseline to the Safety Follow-Up Visit for biometric parameters (length, body weight, and head circumference).

The efficacy of BRV will be analyzed for the Confirmatory Cohorts based on the following variables:

The proportion of responders to BRV treatment from Baseline to 3 hours after the initial BRV dose. A BRV responder is defined as a subject who achieves a reduction in seizure burden (ENS in minutes per hour), without need for rescue medication, compared to the seizure burden measured during the Baseline Period immediately prior to BRV administration, evaluated for a 2-hour period starting 1 hour after the start of initial BRV treatment. Reduction in seizure burden is defined as at least 80% reduction in nonsevere seizure burden (nonsevere seizure burden is defined as ≤50% seizure activity on VEEG in all 30-minute timespans) or at least 50% reduction in severe seizure burden (severe seizure burden is defined as >50% seizure activity on VEEG in any 30-minute timespan). Timespans of 30 minutes refer to the following intervals within the 2-hour period: 0 to ≤30 minutes, >30 to ≤60 minutes, >60 to ≤90 minutes, and >90 to ≤120 minutes.

Secondary efficacy variables will also include the proportion of subjects with at least 80% reduction in nonsevere seizure burden from Baseline to 3 hours after the initial BRV treatment, the proportion of subjects with at least 50% reduction in severe seizure burden from Baseline to 3 hours after the initial BRV treatment, the absolute and percentage reduction in average seizure burden measured by continuous VEEG from Baseline to the end of the 96-hour Evaluation Period, the proportion of BRV responders at the end of the 96-hour Evaluation Period, the proportion of subjects who are seizure-free (100% reduction in seizure burden from Baseline) at 24 hours following the start of initial BRV treatment, categorized by subjects with nonsevere or severe seizure burden at Baseline, the time to reduction in seizure burden for BRV responders (defined as the first timepoint when BRV responder criteria are met), seizure freedom at the end of the Down-Titration Period, rate of at least 50% reduction in ENS frequency per hour from Baseline to the end of the 96-hour Evaluation Period, the proportion of subjects who are seizure-free by time interval (at 3 hours, at 3 hour intervals thereafter through 24 hours, and every 12 hours to 24 hours following the start of the initial BRV treatment), and the absolute and percent difference in clinical seizures at the end of the 24-hour Evaluation Period from Baseline for neonates with motor seizures at the time of inclusion.

Other efficacy variables are the absolute and percentage reduction from Baseline in seizure burden at the defined evaluation periods, the categorized percentage reduction from Baseline to the end of the 96-hour Evaluation Period in seizure burden, the proportion of BRV responders by time interval at the defined evaluation periods, the proportion of subjects who switch over from BRV to another AED during the 96-hour Evaluation Period, and the proportion of responders to other treatment during the 96-hour Evaluation Period.

2 INTRODUCTION

2.1 Epidemiology and treatment of targeted disease

Seizures occur more often during the neonatal period than at any other time during life (Volpe, 2008). The most common cause of neonatal seizures is HIE as a result of perinatal asphyxia (van Rooij et al, 2013a). A population-based study suggested that 42% of neonatal seizures were observed following HIE (van Rooij et al, 2013a). Other causes include intracranial hemorrhage and stroke, infections of the central nervous system (CNS), congenital malformations, inborn errors of metabolism, transient metabolic disturbances, maternal drug abuse, or rare neonatal epilepsy syndromes (benign familial neonatal-infantile seizures or fifth-day seizures) (Volpe, 2008; Ronen et al, 1999).

Clinical recognition of seizures in newborns is not always simple due to a highly variable clinical expression (Volpe, 2008; Mizrahi and Kellaway, 1987). As demonstrated by prolonged VEEG recordings, especially following AED treatments, ENS patterns are not always accompanied by clinical signs (Scher et al, 2003; Boylan et al, 2002; Clancy et al, 1988; Mizrahi and Kellaway, 1987).

First-generation AEDs, such as PB and PHT, remain the drugs of first (and second) choice because of extensive clinical experience, despite their limited clinical effectiveness and potential neurotoxicity (van Rooij et al, 2013b).

In addition to MDZ, other benzodiazepines (BZDs; eg, lorazepam and clonazepam) are used for the treatment of neonatal seizures, often in PB-refractory cases. As one of the most lipophilic BZDs, MDZ readily crosses the blood-brain barrier and provides the advantage of very rapid onset of action. The formation of pharmacologically active (glucuronidated) metabolites of MDZ is considered a disadvantage of MDZ use since drug-drug interactions or renal impairment could cause an undesired accumulation of these metabolites (van Rooij et al, 2013a).

Current treatments for neonatal seizure include PB, PHT, LEV, LDC, and MDZ (Slaughter et al, 2013).

2.2 Background information regarding product

Brivaracetam ((2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1H-pyrrol-1-yl] butanamide) displays a high and selective affinity for the synaptic vesicle protein 2A (SV2A) in the brain. Binding to SV2A is believed to be the primary mechanism for BRV anticonvulsant activity. Between 2016 and 2018, marketing authorization for the use of oral and iv BRV as adjunctive treatment for POS was granted in the EU, US, Russia, Turkey, Mexico, Australia, India, Argentina, Israel, United Arab Emirates, Qatar, Hong Kong, and Korea (film coated tablet, oral solution) for patients 16 years of age and older with epilepsy and in Switzerland and Canada for patients 18 years of age and older with epilepsy. Brivaracetam is approved in the US as monotherapy, based on extrapolation, for the treatment of POS in patients with epilepsy aged 16 years and older. An application for the extension of indication to the pediatric population from 4 years of age in the EU (adjunctive) and the US (adjunctive and monotherapy) based on the concept of extrapolation of efficacy data from the adult population was approved in 2018. Of note, in the US, BRV injection is indicated for the treatment of POS only in adult patients (16 years of age and older).

Brivaracetam is weakly bound (≤20%) to plasma proteins. The volume of distribution is 0.5L/kg, a value close to that of the total body water.

Brivaracetam is rapidly and evenly distributed in most tissues and penetrates rapidly into the brain. The main metabolic pathway of BRV is by hydrolysis of the acetamide group to the corresponding carboxylic acid, ucb-42145, while a second pathway is the ω1-hydroxylation into ucb-100406-1 mediated by cytochrome P450 (CYP)2C19. The combination of these 2 pathways results in the terminal metabolite (hydroxyacid), ucb-107092-1. These metabolites are not pharmacologically active. Brivaracetam is eliminated primarily by metabolism and by excretion in the urine. More than 95% of the dose, including metabolites, is excreted in the urine within 72 hours after dosing in adults. The terminal half-life is approximately 9 hours.

The first BRV pediatric study was N01263, which is described as follows:

N01263 was a completed open-label, multicenter, fixed 3-step up-titration, adjunctive therapy study of the PK, safety, and efficacy of BRV in subjects ≥1 month old to <16 years of age with epilepsy. The study enrolled 100 subjects with either focal or generalized epilepsy. Doses of BRV (oral solution) were adjusted by body weight and did not exceed a maximum of 50mg/day, 100mg/day, and 200mg/day for each titration step.

A total of 100 subjects were enrolled in N01263: 99 subjects received the study drug and were included in the Safety Set (SS). Results from N01263 indicate that BRV was generally well-tolerated and that the safety profile in pediatric subjects was consistent with the known safety profile in adult subjects. Six subjects discontinued the study due to treatment-emergent adverse events (TEAEs), including 1 serious adverse event (SAE) that was moderate in intensity. All severe TEAEs and 11 out of 12 treatment-emergent SAEs were considered to be not related to study drug by the Investigator. No deaths were reported. The TEAE profile in pediatric subjects in this study was consistent with the known BRV safety profile in adults with a low incidence of dizziness as the main difference. There was no dose dependency observed in the overall incidence of TEAEs. In general, there were no clinically meaningful changes in laboratory parameters, vital signs, or electrocardiograms (ECGs).

Pharmacokinetic analyses performed for N01263 demonstrated that BRV plasma concentrations increased with increasing age and increased proportionally to the dose, which was indicated by the approximate doubling of trough BRV plasma concentration with every doubling of the BRV dose. Trough plasma concentration in the ≥1 month to <2 years age group was approximately 30% to 45% lower than in adolescents.

For the 97 subjects included in the efficacy analysis, 47 subjects (58.8%) had a -25% to <25% reduction in the number of seizure days from Baseline to the end of the Evaluation Period, and 26 subjects (32.5% of all subjects) had a ≥25% reduction. Similar observations were made overall across age groups and by seizure category. Six subjects (7.5% of all subjects) experienced a 100% reduction in the number of seizure days from Baseline to the end of the Evaluation Period, and 7 subjects (8.8% of all subjects) experienced a <-25% reduction.

Overall, 14 subjects (14.4%) experienced seizure freedom over the Evaluation Period, based on the Data Record Card data. The number of subjects with seizure freedom was highest in the ≥2 years to <12 years age group (9 subjects [18.0%]), with a similar number of subjects in the ≥1 month to <2 years and ≥12 years to <16 years age groups (3 subjects [10.0%] and 2 subjects

[11.8%], respectively). The overall mean proportion of seizure-free days was 0.5 days (±0.4 days) and was similar regardless of age group or seizure type (range: 0.3 days to 0.7 days).

N01266, an ongoing, open-label, multicenter study, was designed as a long-term follow-up study for subjects who had enrolled in N01263 and the other studies conducted with BRV in the pediatric population from birth to 18 years of age. The objectives of this study include evaluation of the long-term safety and efficacy of bid administration of BRV oral solution and tablets in pediatric subjects with epilepsy; the maximum allowable BRV dosage is 5mg/kg/day, not to exceed 200mg/day in subjects with body weights >40kg.

Based on the results of population PK modeling studies CL00187 and N01331, it was concluded that a dosing regimen of 2.0mg/kg bid in pediatric subjects ≥1 month to <16 years of age with a maximum of 100mg bid should result in plasma concentration profiles similar to those attained in older children and adults who receive therapeutic doses of BRV (up to 200mg per day). Extrapolation of the model to neonates suggested that doses of 2mg/kg to 3mg/kg bid might be required to achieve exposure similar to adults receiving the maximum dose of 200mg bid. Since extrapolation of data from subjects more than 1 month old to subjects 2 weeks of age or younger may be imprecise due to variability in ontogeny in the metabolic and excretory functions in neonates, actual PK measurements (ie, those conducted in the Exploratory Cohort of N01349) are needed to confirm the relationship between dose and plasma concentration in neonates.

Additional information about BRV, including the current information pertaining to the pediatric development program, is provided in the Investigator's Brochure (IB).

2.3 Rationale for the study

Neonatal seizures are described in the International League Against Epilepsy report as "subtle because the manifestations are often overlooked." Most neonatal seizures do not comply with the usual term epilepsy (enduring predisposition to seizures) because they are symptomatic (provoked, reactive) seizures most commonly caused by HIE, cerebral infarction, or infection.

Due to growing evidence that neonatal seizures contribute to an adverse neurodevelopmental outcome, physicians are increasingly focused on the diagnosis and treatment of this condition (Glass et al, 2012). The current available data from randomized controlled studies to support the choice of AEDs for this indication are limited, and there are currently no definite recommendations on the most suitable treatment option to use (Pressler and Mangum, 2013; van Rooij et al, 2013a). Thus, there is a need to investigate which AEDs should be used to treat neonatal seizures and their most appropriate dosages (Pressler and Mangum, 2013; Glass et al, 2012). Furthermore, although newer AEDs are efficacious for the treatment of seizures in adults and older children, limited progress has been made in the treatment of neonatal seizures (Pressler et al, 2015; Tulloch et al 2012). Therefore, clinical studies to assess the efficacy and safety of new treatment options in neonates are warranted.

Thus far, BRV is well-tolerated orally up to 200mg/day in adult subjects with epilepsy and in children 1 month old to 16 years of age receiving up to 4mg/kg/day. Intravenously administered BRV is bioequivalent to the same dosage given orally in healthy adults when given as a bolus or as a 15-minute infusion. Results have shown that a single iv BRV dose of up to 150mg as a 15-minute infusion or as a bolus dose is well-tolerated in adults. Based on these results, the iv route of administration and the proposed dosages to be used in N01349 are justified.

N01349 represents the first study of BRV in neonatal subjects, and will evaluate the PK, efficacy, and safety of BRV in neonates (up to 27 days of PNA and preterm neonates up to 40 weeks of CGA and 27 days of PNA).

3 STUDY OBJECTIVES

3.1 Primary objective

The primary objective is to evaluate the PK of BRV in neonates who have seizures that are not adequately controlled with previous AED treatment, and to identify the optimal BRV dose (Exploratory Cohort) for the treatment of subjects enrolled into the Confirmatory Cohorts of this study.

3.2 Secondary objectives

The secondary objectives are:

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

4 STUDY VARIABLES

4.1 PK variables (Exploratory and Confirmatory Cohorts)

4.1.1 Primary PK variable

The primary PK variable is as follows:

- Plasma concentrations of BRV following first dose on Day 1

4.1.2 Other PK variables

- Plasma concentrations of BRV on other occasions
- Plasma concentrations of BRV metabolites ucb-42145 (acid), ucb-100406-1 (hydroxy), and ucb-107092-1 (hydroxyacid)
- AUC, volume of distribution, and clearance of BRV
- Plasma concentrations of concomitant AEDs if administered

4.2 Efficacy variables (Confirmatory Cohorts only)

The variables for the evaluation of BRV efficacy are described in Section 4.2.1 (Secondary efficacy variables) and Section 4.2.2 (Other efficacy variables).

4.2.1 Secondary efficacy variables

The main secondary efficacy variable is as follows:

- Proportion of responders to BRV treatment from Baseline to 3 hours after the initial BRV dose

  A BRV responder is defined as a subject who achieves the following reduction in seizure burden (ENS in minutes per hour) without need for rescue medication, compared to the seizure burden measured during the Baseline Period immediately prior to BRV administration, evaluated for a 2-hour period starting 1 hour after the start of initial BRV treatment:

  – At least 80% reduction in nonsevere seizure burden

    (Nonsevere seizure burden is defined as ≤50% seizure activity on VEEG in all 30-minute timespans)

  OR

  – At least 50% reduction in severe seizure burden

(Severe seizure burden is defined as >50% seizure activity on VEEG in any 30-minute timespan). Timespans of 30 minutes refer to the following intervals within the 2-hour period: 0 to ≤30 minutes, >30 to ≤60 minutes, >60 to ≤90 minutes, and >90 to ≤120 minutes.

For this study, an ENS is defined as an EEG seizure lasting for at least 10 seconds on VEEG. Baseline seizure burden is defined as seizure burden measured on the continuous VEEG (total ENS in minutes per hour) during a period of up to 1 hour immediately prior to the first administration of study drug.

In addition, the secondary efficacy variables will include:

- Proportion of subjects with at least 80% reduction in nonsevere seizure burden from Baseline to 3 hours after the initial BRV treatment
- Proportion of subjects with at least 50% reduction in severe seizure burden from Baseline to 3 hours after the initial BRV treatment
- Absolute reduction in average seizure burden measured by continuous VEEG from Baseline to the end of the 96-hour Evaluation Period
- Percent reduction in average seizure burden measured by continuous VEEG from Baseline to the end of the 96-hour Evaluation Period
- Proportion of BRV responders at the end of the 96-hour Evaluation Period
- Proportion of subjects who are seizure-free (100% reduction in seizure burden from Baseline) at 24 hours following the start of initial BRV treatment, categorized by subjects with nonsevere or severe seizure burden at Baseline

- Time to reduction in seizure burden for BRV responders (defined as the first timepoint when BRV responder criteria are met)
- Seizure freedom at the end of the Down-Titration Period
- Rate of at least 50% reduction in ENS frequency per hour from Baseline to the end of the 96-hour Evaluation Period
- Proportion of subjects who are seizure-free by time interval at 3 hours, at 3-hour intervals thereafter through 24 hours, and every 12 hours to 24 hours thereafter up until the end of the 96-hour Evaluation Period following the start of the initial BRV treatment
- Absolute difference in clinical seizures at the end of the 24-hour Evaluation Period from Baseline for neonates with motor seizures at the time of inclusion
- Percent difference in clinical seizures at the end of the 24-hour Evaluation Period from Baseline for neonates with motor seizures at the time of inclusion

The use of rescue medication will affect the analysis of the main secondary efficacy variable(see Section 13.5.1). The factors affecting the definition of BRV responders for the analysis of the secondary efficacy variables are described in Section 10.1.

4.2.2 Other efficacy variables

Other efficacy variables will include:

- Absolute reduction from Baseline in seizure burden at evaluation periods of 0 hours to 3 hours, >3 hours to 6 hours, >6 hours to 12 hours, >12 hours to 24 hours, >24 hours to 36 hours, >36 hours to 48 hours, >48 hours to 72 hours, and >72 hours to 96 hours after the start of initial BRV treatment
- Percent reduction from Baseline in seizure burden at evaluation periods of 0 hours to 3 hours, >3 hours to 6 hours, >6 hours to 12 hours, >12 hours to 24 hours, >24 hours to 36 hours, >36 hours to 48 hours, >48 hours to 72 hours, and >72 hours to 96 hours after the start of initial BRV treatment
- Categorized percentage reduction from Baseline to the end of the 96-hour Evaluation Period in seizure burden (<-25% [worsening], -25% to <25% [no change], 25% to <50%, 50% to <80%, and ≥80%)
- Proportion of BRV responders by time interval at evaluation periods of 0 hours to 3 hours, >3 hours to 6 hours, >6 hours to 12 hours, >12 hours to 24 hours, >24 hours to 36 hours, >36 hours to 48 hours, >48 hours to 72 hours, and >72 hours to 96 hours after the start of initial BRV treatment
- Proportion of subjects who switch over from BRV to another AED during the 96-hour Evaluation Period
- Proportion of responders to other treatment during the 96-hour Evaluation Period (including at the end of the 96-hour Evaluation Period, and by time intervals: 0 hours to 3 hours, >3 hours to 6 hours, >6 hours to 12 hours, >12 hours to 24 hours, >24 hours to 36 hours, >36 hours to 48 hours, >48 hours to 72 hours, and >72 hours to 96 hours after the start of initial BRV treatment)

(A responder to other treatment is defined as at least 80% reduction in nonsevere seizure burden from start of other treatment to end of other treatment or at least 50% reduction in severe seizure burden from the initiation of other treatment to end of other treatment during the 96-hour Evaluation Period).

4.3 Safety variables (Exploratory and Confirmatory Cohorts)

4.3.1 Secondary safety variable

The secondary safety variable is as follows:

- AEs as reported by the Investigator

4.3.2 Other safety variables

- Change from Baseline in vital signs (blood pressure, heart rate, respiratory rate [including apneas], oxygen saturation [pulse oximetry], and body temperature)
- 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 subjects with HIE only)
- Change from Baseline in EEG-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 subjects with HIE only)
- Change from Baseline in 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 should be taken within 7 days prior to drug administration, or at birth for subjects ≤7 days old)
- Withdrawal and rebound phenomena
- Mechanical ventilation:
  - Number and percentage of subjects requiring mechanical ventilation during the Evaluation Period
  - Duration of mechanical ventilation during the Evaluation Period

Neurodevelopmental tests validated for age and language will be done after 1 year for subjects who enter 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 is available.

5 STUDY DESIGN

5.1 Study description

N01349 is a Phase 2/3, multicenter, open-label, single-arm study to evaluate the PK, efficacy, and safety of BRV in neonates with repeated EEG seizures.

N01349 consists of a 2-step design and includes a descriptive comparison with a historical control group (matched in age and condition) from literature treated with AEDs per SOC and diagnostic methods.

For the Exploratory Cohort (first step), enrolled subjects will have received 1 or more of following AEDs prior to or at the time of enrollment: PB, MDZ, PHT, LEV, or LDC for the treatment of ENS (first-line, second-line, or subsequent treatment; choice of treatment, dose, and dosing frequency are at the discretion of the Investigator) prior to receiving BRV. Subsequently, a low dose of BRV iv solution for injection will be 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), can be administered during the 48-hour Evaluation Period. This treatment, which is the first use of BRV in neonates, is 4-fold less than the highest dose of 4mg/kg/day dosage (2mg/kg bid) that has been used previously in infants ≥1 month old.

For the Confirmatory Cohorts (second step), 3 consecutive cohorts are planned, and the efficacy of BRV will be evaluated. Subjects may receive 1 or more of the following AEDs prior to or at the time of enrollment: PB, MDZ, PHT, LEV (≤60mg/kg/day), PHT, or LDC. The iv dose of BRV selected for the Confirmatory Cohorts will be determined by the evaluation of BRV plasma concentrations from the Exploratory Cohort, as well as by previous PK modeling of N01263 data, to be within the range of plasma concentrations observed in children ≥1 month old who received 4mg/kg/day. A dosage of BRV 4mg/kg/day for neonates is predicted to be approximately equivalent to the highest BRV dosage (200mg/day) that has been studied in the adult Phase 3 program (eg, N01358 and N01258).

The PK and safety of BRV will be evaluated in all cohorts. The recommendation to confirm or adjust the originally calculated BRV dose of the Confirmatory Cohorts of study N01349 will be given by the DMC after review of PK and safety data of the Exploratory Cohort. Based on the DMC meeting held on 05 Nov 2020, the BRV dose and frequency selected for the Confirmatory Cohorts is 1mg/kg bid (2mg/kg/day). Based on data from the Confirmatory Cohorts, the BRV dose may be further adjusted in a staggered approach as determined by the DMC.

At the end of the Evaluation Period, subjects from both the Exploratory and Confirmatory Cohorts may enter the BRV Extension Period.

All subjects who participate in the BRV Extension Period must be offered entry into a long-term study, if they meet the eligibility criteria. Before entering the long-term study, subjects must be on oral BRV.

Blood samples for routine assay of hematology, biochemistry, liver enzymes, and endocrinology will be collected in line with Section 13.2 of the "Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population" (European Union Commission ad hoc group, 2008), and according to the schedule of study assessments in Table 5–1 (Exploratory Cohort) and Table 5–2 (Confirmatory Cohorts). The local laboratories will perform the routine analysis of blood samples. For Screening and determination of eligibility, use of laboratory data

acquired prior to Screening per standard of care inside or outside the study site within 36 hours prior to the start of the Evaluation Period is allowed.

Interpretation of VEEGs recorded for the Confirmatory Cohorts will be done by local readers but may be supported by the blinded central reader, as needed. Start and stop of BRV treatment and the administration of rescue medication or alternative AEDs will be digitally marked as treatment events on VEEGs. The VEEG recordings will subsequently be evaluated by a blinded, independent central reader at the end of the study. The independent central reader will be blinded from site-specific information and the subject's medical history.

Subjects assigned to the Confirmatory Cohorts will be evaluated with VEEG monitoring at least during the Baseline, Evaluation, and Down-Titration Period. Interruption of the VEEG is allowed up to 30 minutes per day. Depending on medical needs related to SOC (eg, MRIs to be performed), interruptions longer than this are acceptable. However, every effort should be made to avoid VEEG interruption of the Baseline VEEG and during the first 3 hours after the start of the initial BRV administration. The video portion of the VEEG monitoring will assist Investigators in accurately diagnosing ENS and distinguishing artifacts from epileptiform discharges/seizures.

For subjects undergoing therapeutic hypothermia treatment, the target low body temperature achieved and age since birth when cooling began will be recorded. Rewarming of subjects will be documented in the same way.

If appropriate (in the event of screening failures), re-screening will be allowed for the study. Re-screening for screen-failed subjects will be allowed with prior consultation of the Medical Monitor whenever feasible. Subjects can be re-screened only once. Once a subject has received at least one dose of BRV or has left the study because a "must withdrawal" criterion is met, re-screening will no longer be possible.

A continuous consent process will be followed. Parent(s) or legal representative(s) will be informed about the study as early as possible and asked to sign the Informed Consent form (ICF) after the occurrence of seizures has been confirmed by VEEG; subjects will then be considered to be enrolled. During the course of the study, parent(s) or legal representative(s) will be updated about the care of their neonate, and continuous consent will be ensured by meetings between the Investigator (or designee) and the subject's parent(s) or legal representative(s). Parent(s) or legal representative(s) will not be asked to re-sign and re-date the ICF, but they will be informed that they can withdraw their neonate from the study at any time and that this decision will not affect the care of their neonate. Continuous consent will be documented in the subjects' medical charts and electronic Case Report form (eCRF).

A DMC will be in place for the duration of this study. The DMC will meet after completion of the 6 subjects in the Exploratory Cohort and after completion of each of the 3 Confirmatory Cohorts (12 subjects each). Although it was planned that the DMC will meet at no longer than 6-month intervals between meetings, due to the low enrollment rate observed, the intervals between meetings may be increased per the discretion of the DMC.

The schedules of assessments during the Screening and Evaluation Periods for the Exploratory and Confirmatory Cohorts are presented in Table 5–1 and Table 5–2, respectively. The schedule of assessments during the BRV Extension, Down-Titration (Confirmatory Cohorts only), and

Safety Follow-Up Periods for both the Exploratory and Confirmatory Cohorts are presented in Table 5-3.

Details of the study periods for the Exploratory and Confirmatory Cohorts are described in Section 5.1.1 and Section 5.1.2, respectively.

5.1.1 Exploratory Cohort

For the Exploratory Cohort, at least 6 subjects who do not have adequate seizure control after they received 1 or more of the following AEDs: PB, MDZ, PHT, LEV, or LDC prior to or at the time of enrollment for the treatment of ENS (first-line, second-line, or subsequent treatment, which may have started prior to the subject's admission into the study site; choice of treatment, dose, and dosing regimen at the Investigator's discretion) will be enrolled. The AED treatment per SOC can be continued when BRV dosing is initiated. Alternatively, another AED treatment (choice of treatment, dose, and dosing regimen at the Investigator´s discretion) must be initiated and continue in parallel with BRV treatment.

At any time after AED treatment per SOC for the treatment of ENS (first-line, second-line, or subsequent treatment) was initiated, an initial low dose of BRV (0.5mg/kg [bid]) will be administered at the Investigator´s discretion. After the Exploratory Cohort completes the study, a PK and safety data review will be performed by the DMC. During the review of data from the Exploratory Cohort, the enrollment of subjects will be on hold.

At least 2 subjects undergoing hypothermia treatment will be included. Subjects in the Exploratory Cohort might be replaced due to lack of data, as deemed necessary following the review of PK and safety data by the DMC.

The study periods for the Exploratory Cohort are as follows:

- Screening Period: from signing and dating of the written ICF up to initiation of the first BRV dose.

  The Screening Period starts up to 36 hours prior to the first administration of BRV. Phenobarbital, MDZ, PHT, LEV, or LDC may have been administered prior to the subject's enrollment into the study and/or at a location other than the study site.

  Subjects will enter the Evaluation Period and start BRV treatment as soon as the occurrence of ENS per inclusion criterion 2a is confirmed by the Investigator based on local EEG. If preferred by the Investigator, the central VEEG reader can be consulted to confirm the required ENS.

- Evaluation Period (48 hours): The first BRV infusion marks the starting point of the Evaluation Period. At any time after AED treatment per SOC for the treatment of ENS (first-line, second-line, or subsequent treatment) was initiated, a low dose of BRV (0.5mg/kg) will be administered as an approximately 15-minute iv infusion; additional 3 doses of BRV(0.5mg/kg) can be administered every 12 hours for 48 hours (at the discretion of the Investigator). The AED treatment per SOC can be continued when BRV dosing is initiated. Otherwise, another AED treatment (choice of treatment, dose, and dosing regimen at the Investigator´s discretion) must be initiated and continue in parallel with BRV treatment.

  Following the first BRV infusion, 3 to 6 PK blood microsamples (60µL/sample) will be collected during the 48-hour Evaluation Period from each subject for the determination of

plasma concentrations of BRV and its metabolites, as described in Table 5–4. The first set of 3 PK samples will be collected on the first day within specific timeframes (Table 5–4), with the second set of 3 PK samples to be collected within the same timeframes on the second day of the 48-hour Evaluation Period. In addition, opportunistic blood samples for the PK analysis may be used at the Investigator's discretion at any time during the Evaluation Period (see Section 9.1). Blood for PK samples should be drawn from a line different to that of the BRV infusion. The AED PK sample should be collected 3 hours after the start of the initial BRV administration. The number of subjects in the Exploratory Cohort may be increased, if deemed necessary following the analysis of PK data.

At the end of the Evaluation Period, subjects who benefit from BRV treatment may enter the BRV Extension Period in accordance with the Investigator's opinion. Subjects not entering the BRV Extension Period will proceed immediately to the Safety Follow-Up Period (a visit will occur 30±3 days after the final BRV administration).

- BRV Extension Period (up to 28 days of postnatal age [+7 days]): Subjects can proceed to the BRV Extension Period if they benefit from BRV treatment during the Evaluation Period, in accordance with the Investigator's opinion. All subjects who participate in the BRV Extension Period must be offered entry into the long-term study, if they meet the eligibility criteria. Subjects will participate in the BRV Extension Period until they reach a stable condition that will allow them to enter the long-term study. The anticipated duration of the BRV Extension Period per subject is up to 28 days of postnatal age (+7 days). Subjects must switch to BRV oral solution before entering the long-term study. The timing of the switch from iv to oral solution will be at the discretion of the Investigator; subjects who are not able to be dosed with BRV oral solution when they reach 28 days of postnatal age may continue in the BRV Extension Period for an additional 7 days; subjects who are not able to be switched to BRV oral solution by the end of the additional 7 days of the BRV Extension Period will not be eligible for enrollment in the long-term study.

  During the BRV Extension Period, subjects may continue receiving the same BRV dose administered at the end of the Evaluation Period (ie, BRV 0.5mg/kg bid); the BRV dose should not be increased but may be decreased at the discretion of the Investigator.

- Safety Follow-Up Period: Subjects will proceed to the Safety Follow-Up Period if they do not enter the BRV Extension Period. The visit will occur 30±3 days after the final administration of BRV.

5.1.2 Confirmatory Cohorts

For the Confirmatory Cohorts, enrollment will only start after the dosing of BRV is determined based on the PK findings of the Exploratory Cohort and an existing PK model from N01263. A total of at least 36 subjects without adequate seizure control after receiving one or more of the following AEDs prior to or at the time of enrollment: PB, MDZ, PHT, LEV (≤60mg/kg/day), or LDC (first-line, second-line, or subsequent treatment, which may have started prior to the subject's admission into the study site; dose and dosing regimen at the Investigator's discretion) will enter the Confirmatory Cohorts. The AED treatment can be continued if the subject is on a stable dose for at least 1 hour at the time the first BRV infusion is initiated.

Three consecutive Confirmatory Cohorts (n=12 each) are planned; each cohort must have at least 2 subjects undergoing hypothermia treatment. A PK and safety data review will be performed by

the DMC after completion of each of the 3 Confirmatory Cohorts. Based on the DMC meeting held on 05 Nov 2020, the BRV dose and frequency selected for the Confirmatory Cohorts is 1mg/kg bid (2mg/kg/day). Based on data from the Confirmatory Cohorts, the BRV dose may be further adjusted in a staggered approach as determined by the DMC. During the PK and safety data review of data from the first and second Confirmatory Cohorts, the recruitment of subjects into subsequent cohorts will continue.

The study periods for the Confirmatory Cohorts are as follows:

Screening Period: from signing and dating of the written ICF up to initiation of the first BRV dose.

- The Screening Period starts up to 36 hours prior to the first administration of BRV. Phenobarbital, MDZ, PHT, LEV (≤ 60mg/kg/day), or LDC may have been administered prior to the subject's enrollment into the study and/or at a location other than the study site.
- Baseline Period (included in the Screening Period):
    - For subjects with **intermittent ENS**: at least 1 hour prior to entering the Evaluation Period
    - For subjects in **status epilepticus:** up to 30 minutes prior to entering the Evaluation Period. At least 15 minutes of continuous seizures, or 50% of cumulative seizure activity during a 30-minute interval are to be confirmed on EEG before the administration of BRV can start.

      As soon as subjects are considered to be in status epilepticus, steps required for the preparation of the initial BRV infusion can be initiated (eg, assignment of BRV kits through interactive response technology [IRT] and the dilution of BRV solution for iv infusion), even if the required EEG recording is not completed by that time.

      Status epilepticus in neonates for the purpose of this study is defined as follows:

        - 15 minutes of continuous or cumulative electrographic or electroclinical seizure within 30 minutes

      The occurrence of ENS during the Baseline Period must be confirmed either by the local or central VEEG reader prior to BRV administration. Preferably, the central VEEG reader should confirm the required ENS. Video-EEGs that are acquired per standard of care prior to consenting and meet study-specific technical and quality requirements (eg, ability for immediate cloud-based central review) can be used as part of the Baseline assessment VEEG.
- Evaluation Period (96 hours): The first administration of BRV marks the starting point of the Evaluation Period. Subjects in the Confirmatory Cohorts will receive iv BRV 1mg/kg bid (2mg/kg/day), as recommended by the DMC on 05 Nov 2020 based on the results of the PK analysis of the Exploratory Cohort as well an existing PK model from N01263. The DMC will continue to monitor the PK and safety of the subjects and dosing may be adjusted as new data are available. If subjects do not benefit from BRV treatment after 96 hours of BRV administration, BRV administration will be stopped and replaced by another AED.

Following the first BRV infusion, 6 PK blood microsamples (60µL/sample) will be collected during the 96-hour Evaluation Period for each subject for the determination of plasma concentrations of BRV and its metabolites, as described in Table 5–5. Blood for PK samples should be drawn from a line different to that of the BRV infusion.

The AED PK sample should be collected 3 hours after the start of the initial BRV administration. In addition, opportunistic blood samples for the PK analysis may be used at the Investigator's discretion at any time during the Evaluation Period (see Section 9.1).

At the end of the Evaluation Period, subjects who benefit from BRV treatment may enter the BRV Extension Period in accordance with the Investigator's opinion. Subjects not entering the BRV Extension Period will proceed to the Down-Titration Period.

- BRV Extension Period (28 days [up to 90 days] of PNA): Subjects can proceed to the BRV Extension Period if they benefit from BRV treatment during the Evaluation Period, in accordance with the Investigator's opinion. All subjects who participate in the BRV Extension Period must be offered entry into the long-term study, if they meet the eligibility criteria. Subjects will participate in the BRV Extension Period until they reach a stable condition that will allow them to enter the long-term study, if epilepsy is confirmed.

  The anticipated duration of the BRV Extension Period per subject is up to 28 (+7) days of PNA. Subjects who are not able to be dosed with BRV oral solution at a PNA of 28 days may continue in the BRV Extension Period for an additional 7 days; subjects who are not able to be switched to BRV oral solution by the end of the additional 7 days of the BRV Extension Period will not be eligible for enrollment in the long-term study.

  In the event that a long-term study is temporarily not available, subjects are allowed to remain in the BRV Extension Period until they reach a PNA of up to 90 days. For those subjects, the assessments planned for Unscheduled Visits (see Section 8.1.3.3) will be conducted in intervals of approximately 30 days during the prolonged Extension Period. The treatment with BRV will be managed through IVRS. Before subjects can roll-over to the long-term study, they must have switched to BRV oral solution.

- Subjects must switch to BRV oral solution before entering the long-term study. The timepoint of the switch from iv to oral solution will be at the discretion of the Investigator.

  During the BRV Extension Period, subjects may continue receiving the same BRV dose administered at the end of the Evaluation Period; the BRV dose should not be increased, but may be decreased at the discretion of the Investigator.

  Down-Titration Period (up to 1 week): A Down-Titration Period of up to 1 week is recommended for subjects in the Confirmatory Cohorts who discontinue BRV treatment prior to completion of the Evaluation Period, who do not proceed to the BRV Extension Period, or start the BRV Extension Period but do not enter the long-term study. The Down-Titration steps and duration may be adjusted at the Investigator's discretion.

- Safety Follow-Up Period: Subjects will proceed to the Safety Follow-Up Period once they complete the Down-Titration Period. The visit will occur 30±3 days after the final administration of BRV.

Rescue medication should be given if the following occurs:

- There is no improvement in seizure burden within the first 3 hours after administration of BRV.
- Seizure burden is unacceptable to the Investigator, in which case rescue medication can be given earlier at any time, but ideally not in the first 3 hours after the initial administration of BRV.

Subjects in the Confirmatory Cohorts are allowed to switch over from BRV to another AED (eg, MDZ or PHT), if needed. Subjects discontinuing BRV treatment during the Evaluation Period should start the Down-Titration Period while completing the Evaluation Period in parallel for the full 96 hours. In this case, subjects will complete all study assessments, except the collection of blood microsamples for the determination of BRV plasma concentrations. Ideally, changing or adding a new treatment should not occur during the first 3 hours after the initial administration of BRV. Subjects who are switched from BRV to another AED will not be eligible to participate either in the BRV Extension Period or the long-term study.

5.1.3 Study duration per subject

The maximum study duration per subject is expected to be up to 75 days (Screening Period [including Baseline Period (Confirmatory Cohorts only)], Evaluation Period, BRV Extension Period, Down-Titration Period [Confirmatory Cohorts only], and Safety Follow-Up Period). In the event that a long-term study is not available at the time of a subject's planned transition, the maximum study duration for subjects who remain in the study for up to 90 days of PNA and do not enter the long-term study will then be up to 130 days (90 days of PNA, up to 1 week for the Down-Titration Period, and up to 33 days for the Safety Follow-Up Period). The individual study duration will be shorter depending on the type of cohort to which subjects will be assigned, the age at enrollment, and the decision to enter the BRV Extension Period.

The maximum BRV exposure per subject is expected to be up to 42 days, which comprises up to 4 days during the Evaluation Period (depending on type of cohort), up to 28 (+7) days of PNA during the BRV Extension Period, and up to 1 week during the Down-Titration Period for subjects in the Confirmatory Cohorts only. For subjects who remain in the study for up to 90 days of PNA and do not enter the long-term study, maximum BRV exposure per subject is expected to be up to 97 days (up to 90 days of PNA and up to 1 week for the Down-Titration Period).

All subjects who do not continue into the long-term study will proceed to the Safety Follow-Up Period, and a visit will occur 30±3 days after the final dose of BRV.

The end of the study is defined as the date of the last visit of the last subject in the study.

5.1.4 Planned number of subjects and sites

At least 42 evaluable subjects will be enrolled in this study, with at least 6 subjects in the Exploratory Cohort evaluable for the determination of BRV plasma concentrations and at least 36 subjects with evaluable PK data in the Confirmatory Cohorts (at least 12 subjects in each of the 3 Confirmatory Cohorts). At least 2 subjects undergoing hypothermia treatment will be included in the Exploratory Cohort and each of the 3 Confirmatory Cohorts.

The number of subjects in the Exploratory Cohorts might be increased, if deemed necessary, following the analysis of PK data.

5.1.5 Anticipated regions and countries

Only sites in Europe are planned.

5.2 Schedule of study assessments

The schedules of study assessments during the Screening and Evaluation Periods for the Exploratory and Confirmatory Cohorts are presented in Table 5–1 and Table 5–2, respectively. The PK sampling will be performed according to the schedule provided in Table 5–4 for the Exploratory Cohort and in Table 5–5 for each Confirmatory Cohort.

The schedule of study assessments during the BRV Extension, Down-Titration (Confirmatory Cohorts only), and Safety Follow-Up Periods are presented in Table 5-3.

Table 5–1: Schedule of study assessments – Screening and Evaluation Periods (Exploratory Cohort)

Assessments	Screening Period[a]		Evaluation Period													
	Up to 36h		BRV													
	-36h to 0h	Timepoint immediately before first BRV administration	0h	1h	2h	3h	4h	6h	8h	10h	12h	24h	27h	34h	36h	48h
(Assessment window)	-	-	-			(±15min)	(±30min)									
Informed consent[b]	X		-X-													
Subject identification card dispensing	X															
Inclusion/exclusion criteria	X	X[c]														
Demographic data	X															
Medical history including Apgar score and HIE	X															
Vital signs		X	X			X		X			X	X				X
Physical and neurological examination: Sarnat scale for subjects with HIE		X										X				X
Length		X														
Body weight[d]	X	X										X				X
Head circumference[e]		X														
Primary cause of seizure	X															X
Psychometric parameters: N-PASS and EEG-parameters	X															X
AED treatment (PB, MDZ, PHT, LEV, or LDC)	X[j]	-X -														
Cohort Assignment			X													
BRV infusion			X								X	X			X	
Heart rate monitoring		X		X	X	X		X		X	X	X	X	X	X	X
BRV PK samples[f]			X[g]			X				X		X	X	X		
AED PK sample (only when PB and PHT are used)						X										

Table 5–1: Schedule of study assessments – Screening and Evaluation Periods (Exploratory Cohort)

Assessments	Screening Period[a]		Evaluation Period													
	Up to 36h															
	-36h to 0h	Timepoint immediately before first BRV administration	BRV													
			0h	1h	2h	3h	4h	6h	8h	10h	12h	24h	27h	34h	36h	48h
(Assessment window)	-	-		-		(±15min)					(±30min)					
Laboratory assessments (safety)		X[h]														X
Thompson score[i]		X														X
Mechanical ventilation		-X-														
AE(s)	-X-															
Concomitant medications	-X-															
Medical procedures	-X-															
Infusion site reaction monitoring[k]			X	X	X	X		X			X	X			X	X
Dispense BRV dosing diary																X[l]
Dispense BRV for the BRV Extension Period[m]																X

AE(s)=adverse event(s); AED(s)=antiepileptic drug(s); BRV=brivaracetam; BZD(s)=benzodiazepine(s); COVID-19=coronavirus disease 2019; ENS=electroencephalographic neonatal seizures; HIE=hypoxic-ischemic encephalopathy; ICF=Informed Consent form; LDC=lidocaine; LEV=levetiracetam; MDZ=midazolam; N-PASS=neonatal pain, agitation, and sedation scale; PB=phenobarbital; PHT=phenytoin; PK=pharmacokinetic(s); SOC=standard of care

[a] Screening Period is from signing and dating of the written ICF up to initiation of the first BRV dose.

[b] Parent(s) or legal representative(s) will be informed about the study as early as possible and asked to sign the informed consent after the occurrence of seizures is confirmed on local VEEG. Continuous consent will be ensured by meetings between the Investigator (or designee) and the subject's parent(s) or legal representative(s), during the conduct of the study.

[c] The occurrence of ENS prior to entering the Evaluation Period must be confirmed by the local VEEG reader prior to initial BRV administration.

[d] Measurement of body weight is mandatory prior to BRV treatment and optional at 24 and 48 hours. Dosage of BRV during the Evaluation Period will be based on the subject's weight measured prior to the start of the first BRV administration. However, dosage calculation can be adjusted to a more recent weight measurement, upon discretion of the Investigator, if weight is measured during the Evaluation Period.

[e] Head circumference Baseline measurement should be taken within 7 days prior to drug administration, or at birth for subjects ≤7 days old.

[f] Following the first BRV infusion, 3 to 6 blood microsamples (60µL/sample) will be collected from each subject in the Exploratory Cohort.

[g] The schedule of PK sampling for the Exploratory Cohort is also provided in Table 5–4.

Table 5–1: Schedule of study assessments – Screening and Evaluation Periods (Exploratory Cohort)

Assessments	Screening Period[a]		Evaluation Period													
	Up to 36h															
	-36h to 0h	Timepoint immediately before first BRV administration	BRV													
			0h	1h	2h	3h	4h	6h	8h	10h	12h	24h	27h	34h	36h	48h
(Assessment window)	-	-	-			(±15min)	(±30min)									

[h] For Screening and determination of eligibility, use of laboratory data acquired prior to Screening per standard of care inside or outside the study site within 36 hours prior to the start of the Evaluation Period is allowed.
[i] Thompson score will be used to measure the severity of HIE for subjects with HIE.
[j] The recording of AEDs will include BZDs and opiates taken by the mother at the time of delivery. In addition, details regarding COVID-19 vaccination will be recorded as concomitant medication if the mother was pregnant or breastfeeding when vaccinated.
[k] Monitoring for BRV infusion site reactions should take place during and 30 minutes after the end of the infusion.
[l] The BRV dosing diary will be dispensed only if the subject enters the BRV Extension Period.
[m] Dispensing of BRV is only applicable if the subject enters the BRV Extension Period.

Table 5–2: Schedule of study assessments – Screening and Evaluation Periods (Confirmatory Cohorts)

Assessments	Screening Period[a]		Evaluation Period																		
	Up to 36h																				
	-36h to up to -1h	Base-line Period[b] up to -1h to 0h	0h	3h	6h	8h	9h	10h	12h	15h	18h	21h	24h	27h	34h	36h	48h	60h	72h	84h	96h[c]
(Assessment window)	-	-	-	(±15min)	(±30min)																
Informed consent[d]	X	X	-X-																		
Subject identification card dispensing	X																				
Inclusion/exclusion criteria	X	X[e]																			

Table 5–2: Schedule of study assessments – Screening and Evaluation Periods (Confirmatory Cohorts)

Assessments	Screening Period[a]		Evaluation Period																	
	Up to 36h																			
	-36h to up to -1h	Base-line Period[b] up to -1h to 0h	0h	3h	6h	8h	9h	10h	12h	15h	18h	21h	24h	27h	34h	36h	48h	60h	72h	84h	96h[c]
(Assessment window)	-	-	-	(±15min)	(±30min)																
Demographic data		X																			
Medical history including Apgar score and HIE		X																			
Vital signs		X	X	X	X		X		X	X	X	X	X				X		X		X
Physical and neurological examination: Sarnat scale for subjects with HIE		X											X				X		X		X
Length		X																			
Body weight[f]	X	X											X				X		X		X
Head circumference		X[g]																			
Primary cause of seizure		X																			X
Psychometric parameters: N-PASS and EEG-parameters		X																			X
AED treatment (PB, MDZ, PHT, LEV	X[n]	X			(X)																

Table 5–2: Schedule of study assessments – Screening and Evaluation Periods (Confirmatory Cohorts)

Assessments	Screening Period[a]		Evaluation Period																	
	Up to 36h																			
	-36h to up to -1h	Base-line Period[b] up to -1h to 0h	0h	3h	6h	8h	9h	10h	12h	15h	18h	21h	24h	27h	34h	36h	48h	60h	72h	84h	96h[c]
(Assessment window)	-	-	-	(±15min)	(±30min)																
[≤60mg/kg/day], or LDC)																					
Cohort Assignment			X																		
BRV infusion[h]			X						X				X			X	X	X	X	X	X
VEEG[i]	-X-																				
Heart rate monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BRV PK samples[j]			X[j]	X	X								(X)[j]				(X)[j]		(X)[k]		
AED PK sample (only when PB and PHT are used)				X																	
Laboratory assessments (safety)[l]		X											X								X
Thompson score[m]		X																			X
Mechanical ventilation		-X-																			
AEs	-X-																				
Concomitant medications	-X-																				
Medical procedures	-X-																				

Table 5–2: Schedule of study assessments – Screening and Evaluation Periods (Confirmatory Cohorts)

Assessments	Screening Period[a]		Evaluation Period																	
	Up to 36h																			
	-36h to up to -1h	Base-line Period[b] up to -1h to 0h	0h	3h	6h	8h	9h	10h	12h	15h	18h	21h	24h	27h	34h	36h	48h	60h	72h	84h	96h[c]
(Assessment window)	**-**	**-**	**-**	**(±15min)**	**(±30min)**																
AEDs[n]	-X-																				
Infusion site reaction monitoring[o]			X	X	X				X				X			X	X	X	X	X	X
Neurodevelop-mental testing (Bayley-III score)																					X[p]
Dispense BRV dosing diary																					X[q]
Dispense BRV for the BRV Extension Period[r]																					X

AE(s)=adverse events(s); AED(s)=antiepileptic drug(s); bid=twice daily; BRV=brivaracetam; BZD(s)=benzodiazepine(s); EEG=electroencephalography; ENS=electroencephalographic neonatal seizures; HIE=hypoxic-ischemic encephalopathy; ICF=Informed Consent form; iv=intravenous; LDC=lidocaine; LEV=levetiracetam; MDZ=midazolam; N-PASS=neonatal pain, agitation and sedation scale; PB=phenobarbital; PHT=phenytoin; PK=pharmacokinetic(s); VEEG=(multichannel) video-electroencephalography; (X)=optional for that day

[a] Screening Period is from signing and dating of the written ICF up to initiation of the first BRV dose.

[b] The duration of the Baseline EEG depends on seizure activity. Subjects with intermittent seizures will enter the Evaluation Period based on at least 1 hour of EEG recording. Subjects in status epilepticus will enter the Evaluation Period based on up to 30 minutes of EEG recording, ie, as soon as 15 minutes of continuous seizures or 50% of cumulative seizure activity is confirmed on EEG.

[c] If subjects do not benefit from BRV treatment after 96 hours of BRV administration, BRV administration will be stopped and replaced by another AED; however, the subject's participation in the study will continue. Subjects discontinuing BRV treatment during the Evaluation Period should start the Down-Titration Period while completing the Evaluation Period in parallel for the full 96 hours.

[d] Parent(s) or legal representative(s) will be informed about the study as early as possible and asked to sign the informed consent after the occurrence of seizures is confirmed on VEEG. Continuous consent will be ensured by meetings between the Investigator (or designee) and the subject's parent(s) or legal representative(s), during the conduct of the study.

Table 5–2: Schedule of study assessments – Screening and Evaluation Periods (Confirmatory Cohorts)

Assessments	Screening Period[a]		Evaluation Period																	
	Up to 36h																			
	-36h to up to -1h	Base-line Period[b] up to -1h to 0h	0h	3h	6h	8h	9h	10h	12h	15h	18h	21h	24h	27h	34h	36h	48h	60h	72h	84h	96h[c]
(Assessment window)	-	-	-	(±15min)	(±30min)																

[e] The occurrence of ENS during the Baseline Period must be confirmed either by the local or central VEEG reader prior to drug administration. Preferably, the central VEEG reader should confirm the required ENS.

[f] Measurement of body weight is optional at 24, 48, 72, and 96 hours. Dosage of BRV during the Evaluation Period will be based on the subject's weight measured prior to the start of the first BRV administration. However, dosage calculation can be adjusted to a more recent weight measurement, upon discretion of the Investigator, if weight is measured during the Evaluation Period.

[g] Head circumference Baseline measurement should be taken within 7 days prior to drug administration, or at birth for subjects ≤7 days old.

[h] Subjects will receive iv BRV 1mg/kg bid (2mg/kg/day), as recommended by the DMC on 05 Nov 2020 based on the results of the PK analysis of the Exploratory Cohort as well as an existing PK model from N01263.

[i] Video-EEGs that are acquired per standard of care prior to consenting and meet study-specific technical and quality requirements can be used as part of the Baseline assessment VEEG.

[j] Following the first BRV infusion, 6 blood microsamples (60µL/sample) will be collected during the Evaluation Period from each subject.

[k] The schedule of PK sampling for the Confirmatory Cohorts is also provided in Table 5–5.

[l] For Screening and determination of eligibility, use of laboratory data acquired prior to Screening per standard of care inside or outside the study site within 36 hours prior to the start of the Evaluation Period is allowed.

[m] Thompson score will be used to measure the severity of HIE for subjects with HIE.

[n] The recording of AEDs will include BZDs and opiates taken by the mother at the time of delivery. In addition, details regarding COVID-19 vaccination will be recorded as concomitant medication if mother was pregnant or breastfeeding when vaccinated.

[o] Monitoring for BRV infusion site reactions should take place during and 30 minutes after the end of the infusion. The assessment will be conducted hourly from 0h to 3h of the BRV Evaluation Period.

[p] The assessment of the Bayley-III score at 96-hour time point only applies to subjects who directly roll-over from the Evaluation Period to the long-term study due to their age at enrollment into N01349.

[q] The BRV dosing diary will be dispensed only if the subject enters the BRV Extension Period.

[r] Dispensing of BRV is only applicable if the subject enters the BRV Extension Period.

Table 5-3: Schedule of study assessments - BRV Extension Period and Safety Follow-Up Period (Exploratory and Confirmatory Cohorts)

Assessments	BRV Extension Period				Down-Titration Period[a]	Safety Follow-Up Period[b]
	EPV1[c]	EPV2[d]	Unscheduled Visit	Telephone Contact	Up to 1 week	30 days
(Assessment window)	(±2 days)	-			-	(±3 days)
Informed consent[e]	X	X			X	
Vital signs		X	X		X	X
Physical and neurological examination: Sarnat scale for subjects with HIE		X	X		X[f]	X
Biometric parameters: length, body weight and head circumference						X
Primary cause of seizure					X[f]	X
Psychometric parameters: N-PASS					X	X
BRV administration or dispense	X	X[g]			X[h]	
BRV return		X				
1-hour VEEG					X[i]	
Laboratory assessments (safety)		X	X[o]			X
Neurodevelopmental testing (Bayley-III score)		X[j]				
AE(s)	-X-					
Concomitant medications	-X-					
Medical procedures	-X-					
AEDs[k]	-X-					
Infusion site reaction monitoring[l]	X	X	X		X	
Confirmation/diagnosis of epilepsy		X				
Update on Medical History		X[m]				X[n]
Review BRV dosing diary	X	X	X	X		

AE(s)=adverse event(s); AED(s)=antiepileptic drug(s); BRV=brivaracetam; BZD(s)=benzodiazepine(s); EEG=electroencephalography; EPV=Extension Period Visit; HIE=hypoxic-ischemic encephalopathy; iv=intravenously; N-PASS=neonatal pain, agitation, and sedation scale; VEEG=(multichannel) video-electroencephalography

Note: An Unscheduled Visit and a Telephone Contact are only applicable to subjects receiving oral BRV at home.

[a] A Down-Titration Period of up to 1 week applies only to subjects in the Confirmatory Cohorts. The Down-Titration Period is recommended for subjects who discontinue BRV treatment prior to completion of the Evaluation Period, who do not proceed to the BRV Extension Period, or start the BRV Extension Period but do not enter the long-term study. Subjects discontinuing BRV treatment during the Evaluation Period can continue assessments pertaining to the Evaluation Period, except the collection of blood microsamples for the determination of BRV plasma

Table 5-3: Schedule of study assessments - BRV Extension Period and Safety Follow-Up Period (Exploratory and Confirmatory Cohorts)

Assessments	BRV Extension Period				Down-Titration Period[a]	Safety Follow-Up Period[b]
	EPV1[c]	EPV2[d]	Unscheduled Visit	Telephone Contact	Up to 1 week	30 days
(Assessment window)	(±2 days)	-			-	(±3 days)

concentrations. Those subjects should start the Down-Titration Period in parallel to completing the Evaluation Period.

[b] Subjects will enter the Safety Follow-Up Period if they withdraw from the study at any time, or do not proceed to the BRV Extension Period, or complete the Down-Titration Period. This visit will occur 30±3 days after the last administration of BRV. For subjects unable to return to the hospital due to COVID-19, the Safety Follow-up Visit can be performed remotely. In this case vital signs, the physical and neurological examination, biometric and psychometric parameters, and the laboratory assessment may not be performed.

[c] Subjects will attend EPV1 at 7±2 days after completion of the Evaluation Period. For subjects unable to return to the hospital due to COVID-19, EPV1 can be performed remotely if BRV oral solution was dispensed at the time when the subject completed the Evaluation Period.

[d] Subjects will attend EPV2 when they enter the long-term study. Before entering the long-term study, subjects must have been switched to BRV oral solution and be able to tolerate it. Subjects who have not been switched to BRV oral solution will not be permitted to continue into the long-term study. The timing of switching from iv to oral solution will be at the discretion of the Investigator. Subjects will continue to receive the same BRV dose administered at the end of the Evaluation Period.

[e] Parent(s) or legal representative(s) will be informed about the study as early as possible and asked to sign the informed consent after the occurrence of seizures is confirmed on VEEG. Continuous consent will be ensured by meetings between the Investigator (or designee) and the subject's parent(s) or legal representative(s), during the conduct of the study.

[f] To be performed on the first day of the Down-Titration Period only.

[g] If the subject enters the long-term study, no study drug from N01349 will be dispensed in EPV2. If the subject does not enter the long-term study, BRV from N01349 will be administered for down-titration (only applicable to subjects from the Confirmatory Cohorts).

[h] The Down-Titration steps and duration may be adjusted at the Investigator's discretion.

[i] Video-EEG will only apply to subjects of the Confirmatory Cohorts who complete the study after the Evaluation Period. The VEEG will be recorded for at least 1 hour on the final day of the Down-Titration Period. Additional VEEGs can be performed at any time during the Down-Titration Period at the Investigator´s discretion.

[j] Bayley-III assessment will be assessed for subjects continuing into the long-term study, in countries where a validated translation is available.

[k] The recording of AEDs will include AEDs (BZDs and opiates) taken by the mother at the time of delivery. In addition, details regarding COVID-19 vaccination will be recorded as concomitant medication if mother was pregnant or breastfeeding when vaccinated.

[l] Infusion site reactions will only be monitored for subjects receiving iv BRV. Monitoring for BRV infusion site reactions should take place during and 30 minutes after the end of the infusion.

[m] Updated Medical History should be recorded at EPV2 for subjects entering the long-term study.

[n] Updated Medical History should be recorded for subjects not entering the long-term study.

[o] Laboratory assessment (safety) only required for Unscheduled Visits performed during the BRV Extension Period.

Table 5–4: Schedule for PK Sampling (Exploratory Cohort)

Assessment	48-hour Evaluation Period					
	Time relative to the start of the most recent BRV infusion					
	Day 1			Day 2[a]		
	30-60min[b]	2-4h	8-12h	30-60min	2-4h	8-12h
BRV PK samples[c]	X	X	X	X	X	X
AED PK sample		X[d]				

AED=antiepileptic drug; BRV=brivaracetam; h=hours; min=minutes; PK=pharmacokinetic(s)
Note: Blood for PK samples should be drawn from a line different to that of the BRV infusion.
[a] Blood sampling is only needed on Day 2 if subjects are dosed with BRV on Day 2.
[b] The first PK sample should be collected 30 to 60 minutes after the start of the BRV infusion.
[c] The BRV PK sampling timepoints for the first 3 samples of the Exploratory Cohorts are as follows: 30 to 60 minutes, 2 to 4 hours, and 8 to 12 hours after the start of the most recent BRV infusion. The second set of 3 samples will be collected at the same timepoints on the second day of the 48-hour Evaluation Period.
[d] The AED PK sample should be collected 3 hours after the start of the initial BRV administration.

Table 5–5: Schedule for PK Sampling (Confirmatory Cohorts)

Assessment	96-hour Evaluation Period											
	Time relative to the start of the most recent BRV infusion											
	Day 1			Day 2			Day 3			Day 4		
	30-60min[a]	2-4 h	8-12 h	30-60min	2-4 h	8-12 h	30-60min	2-4 h	8-12 h	30-60min	2-4 h	8-12 h
BRV PK samples[b]	X	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
AED PK sample		X[c]										

AED=antiepileptic drug; BRV=brivaracetam; h=hours; PK=pharmacokinetic(s); min=minutes; (X)=optional for that day

Note: Blood for PK samples should be drawn from a line different to that of the BRV infusion.

[a] The first PK sample will be collected 30 to 60 minutes after the start of the BRV infusion.

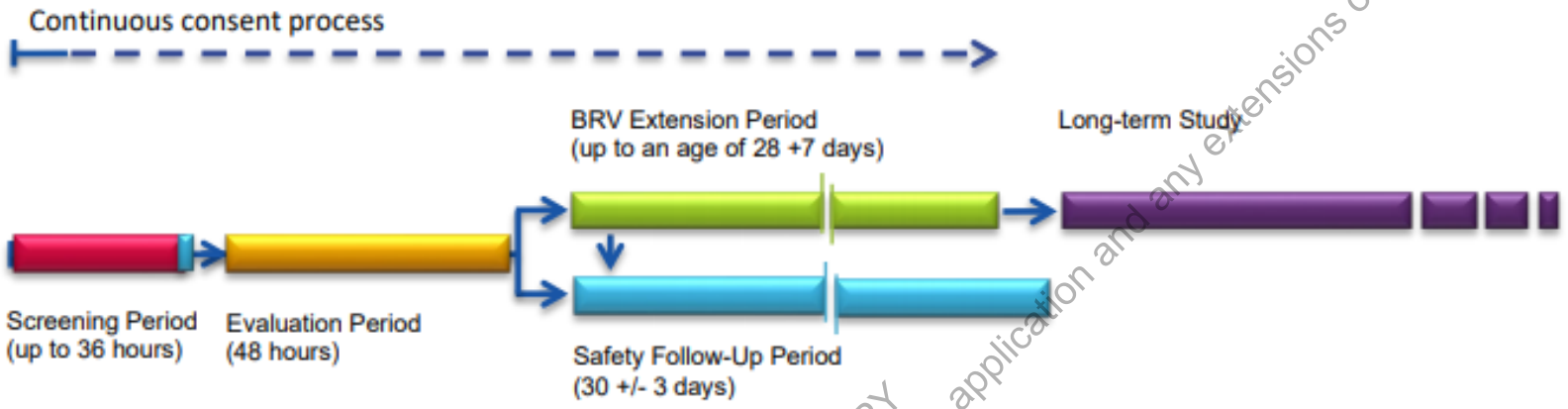
[b] The BRV PK sampling timepoints for the first 3 samples of the Confirmatory Cohorts are as follows: 30 to 60 minutes, 2 to 4 hours, and 8 to 12 hours after the start of the most recent BRV infusion. The second set of 3 PK samples will be collected within the same timeframes as the first set on one of the following days: either Day 2 (post-24 hours), OR Day 3 (post-48 hours) OR Day 4 (post-72 hours). It is acceptable if these samples are drawn on different days.

[c] The AED PK sample should be collected 3 hours after the start of the initial BRV administration.

5.3 Schematic diagrams

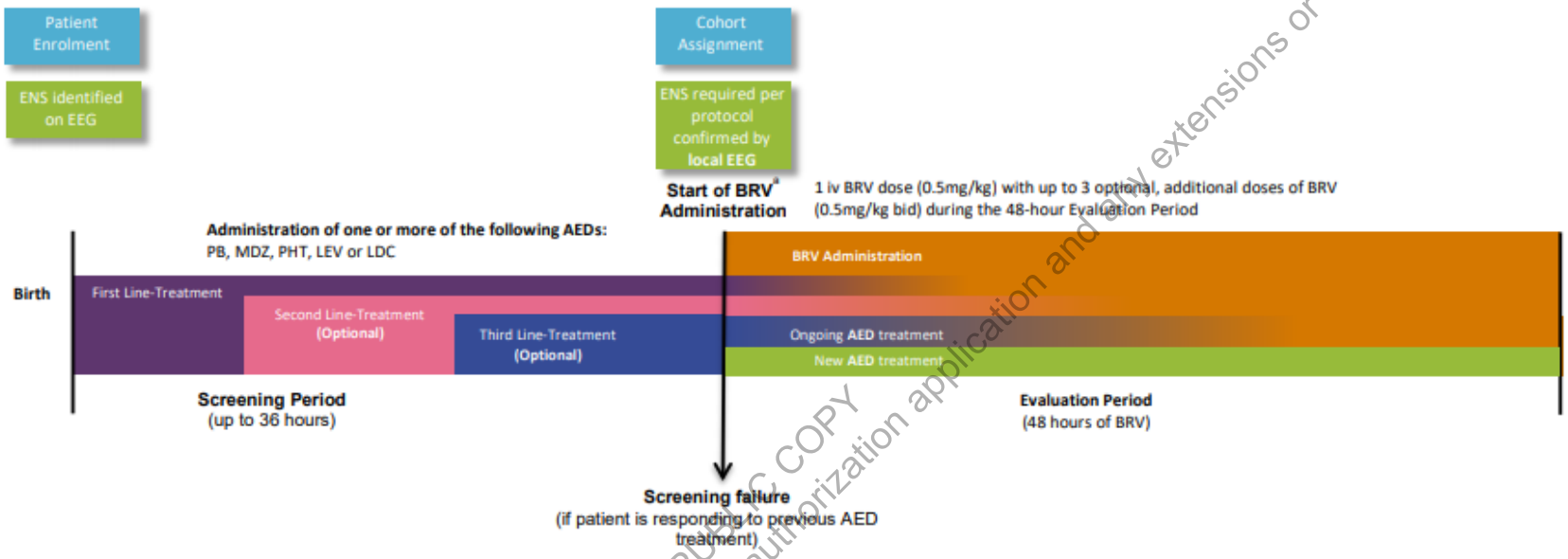
Figure 5–1 displays a schematic overview of the study for the Exploratory Cohort and the Screening and Evaluation Periods of this Cohort are presented in detail in Figure 5–2. Figure 5–3 displays a schematic overview of the study for the Confirmatory Cohorts and the Screening and Evaluation Periods of these Cohorts are presented in detail in Figure 5–4.

Figure 5–1: Schematic overview of the study (Exploratory Cohort)



AED=antiepileptic drug; BRV=brivaracetam
[a] BRV to be administered in addition to another AED.

Figure 5–2: Screening and Evaluation Periods (Exploratory Cohort)

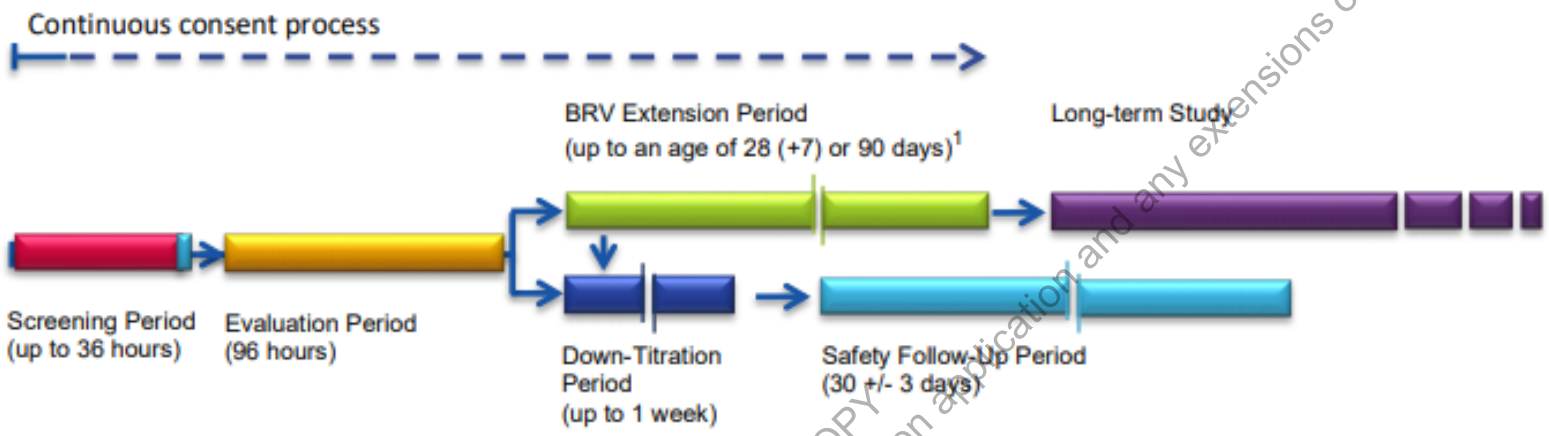


AED=antiepileptic drug; bid=twice daily; BRV=brivaracetam; EEG=electroencephalogram; ENS=electroencephalographic neonatal seizures; ICF=Informed Consent form; iv=intravenous; LEV=levetiracetam; LDC=lidocaine; MDZ=midazolam; PB=phenobarbital; PHT=phenytoin

Note: The Screening Period is from signing and dating of the written ICF up to initiation of the first BRV dose.

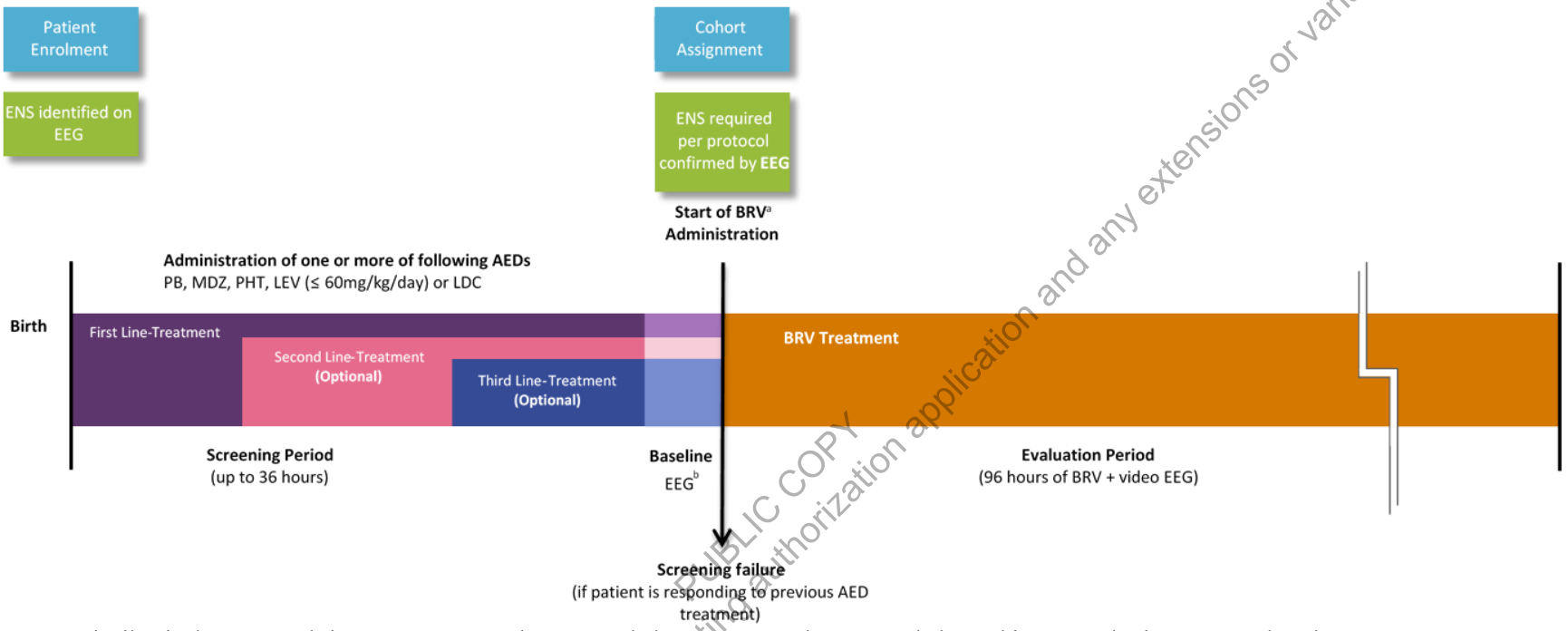
[a] BRV to be administered in addition to another AED.

Figure 5–3: Schematic overview of the study (Confirmatory Cohorts)



BRV=brivaracetam; PNA=postnatal age
[1] BRV Extension Period up to a PNA of 90 days is only applicable if subjects can intermittently not transition to a long-term study.

Figure 5–4: Screening and Evaluation Periods (Confirmatory Cohorts)



AED=antiepileptic drug; BRV=brivaracetam; EEG=electroencephalogram; ENS=electroencephalographic neonatal seizure; LEV=levetiracetam; LDC=lidocaine; MDZ=midazolam; PB=phenobarbital; PHT=phenytoin

[a] Concomitant treatment with AEDs is permitted to continue in parallel with BRV treatment if subjects are on a stable dose from 1 hour prior to initiation of BRV treatment. Changes to concomitant AEDs are permitted from 3 hours onward following first BRV administration).

[b] Duration of the Baseline EEG depending on seizure activity:

- for subjects with intermittent ENS: 1 hour
- for subjects in status epilepticus: up to 30 minutes

5.4 Rationale for study design and selection of dose

5.4.1 Rationale for study design

The current accepted medical practice (ie, standard of care) for neonatal seizures is initial treatment with PB with rapid progression to treatment with MDZ for patients without adequate seizure control after 2 doses of PB. In more than 50% of subjects, seizures are not controlled after first-line treatment with PB or other AEDs, and subsequent treatment with additional AEDs does not significantly improve seizure control (van Rooij et al, 2013b; Castro Conde et al, 2005; Boylan et al, 2004; Painter et al, 1999). Thus, study N01349 was designed for a flexible treatment of ENS, and only those subjects who do not have adequate seizure control with previous AED treatment will be permitted to continue in the study.

As the patient population of neonates with ENS is limited, the 2-step design of this study will allow confirmation (or adjustment) of dosing based on results from the first step (Exploratory Cohort) and evaluation of BRV efficacy in the second step (Confirmatory Cohorts). This adaptive design allows confirmation of dose and collection of PK, safety, and efficacy data, thereby potentially providing rapid access to alternative treatment in neonates.

The frequency, voltage, and morphology of the discharges may change within an individual seizure and between seizures in an individual neonate. At enrollment, subjects must be at least 34 weeks of 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 can be enrolled. Neonates undergoing hypothermia treatment (eg, for the treatment of HIE) will also be enrolled.

Although newer AEDs are efficacious for the treatment of seizures in adults and older children, limited progress has been made in the treatment of neonatal seizures (Pressler et al, 2015; Pressler and Mangum 2013; Tulloch et al, 2012). Thus, clinical studies to assess the efficacy and safety of new treatment options in neonates are warranted.

5.4.2 Rationale for dose selection

The doses planned to be applied in this study are based on pediatric data collected in N01263 subjects (overall 96 subjects in the age range of 1 month to 17 years with the following number of subjects per pediatric age group: 1 month to <2 years of age, 29 subjects; 2 years to <6 years of age, 26 subjects; 6 years to <12 years of age, 24 subjects; 12 years to <16 years of age, 17 subjects). A physiological-based PK model was used to extrapolate the PK of BRV from older children. It is estimated that a dose of BRV 0.5mg/kg bid, administered to neonatal subjects, should yield the same BRV exposure range in plasma as observed in older children receiving the same dose on a mg/kg body weight basis. In adults, a similar exposure is achieved with a dose of 25mg bid, which represents the lowest dose approved for adults. A dose of 2mg/kg bid should result in similar exposure in neonates as compared to adults receiving 100mg bid (the highest approved dose in adults). Given the uncertainties of the extrapolation, as well as the variability and rapid changes in neonatal physiology, these predictions may or may not be precise; however, large discrepancies are not expected.

Based on the extrapolation explained above, subjects who enter the Exploratory Cohort will receive an initial low dose of BRV (0.5mg/kg [bid]). A starting dose of BRV 0.5mg/kg was selected because this dose offers a wide safety margin (4-fold) with respect to the highest BRV dose administered and tolerated in older children and adults with epilepsy. Simultaneously, a

dose of BRV 0.5mg/kg is potentially therapeutically beneficial to subjects in this study. In adjunctive treatment studies, a dosage of BRV 25mg bid is effective for POS in adult subjects with epilepsy.

For subjects who enter the Confirmatory Cohorts, the dosing frequency of BRV will be determined based on the PK findings of the Exploratory Cohort (see Section 5.1). The dose of BRV to be administered in the Confirmatory Cohorts will be determined by the evaluation of plasma samples collected in the Exploratory Cohort, as well as by the PK modeling of N01263 data described above, and should not exceed the range of plasma concentrations observed in children ≥1 month old who received BRV 4mg/kg/day. The plasma concentration of BRV 4mg/kg/day for neonates is predicted to be approximately equivalent to the plasma concentrations observed in adults who receive BRV 200mg/day. The dose in neonates to reach the same plasma concentrations will be confirmed or adapted upon completion of enrollment and analysis of PK and safety data from the Exploratory Cohort involving the DMC.

The BRV dose used in the Confirmatory Cohorts will be based on recommendations made by the DMC. Based on the DMC meeting held on 05 Nov 2020, the BRV dose and frequency selected for the Confirmatory Cohorts is 1mg/kg bid (2mg/kg/day). Based on data from the Confirmatory Cohorts, the BRV dose may be further adjusted in a staggered approach as determined by the DMC.

Furthermore, the posology of BRV for the Confirmatory Cohorts is proposed as an approximately 15-minute iv infusion in consideration of the following and is based on PK and safety data available from subjects ≥1 month old in N01263 and N01266:

BRV is well-tolerated orally up to 200mg/day in adult subjects with epilepsy and in children 1 month old to 16 years of age receiving up to 4mg/kg/day. In adults, a single iv infusion over 15 minutes or a bolus of BRV up to 150mg/day is well-tolerated. A dose of BRV 4mg/kg/day is predicted to be approximately equivalent to the highest BRV dosage (200mg/day) received by adults. In addition, iv BRV is bioequivalent to the same dose given orally in healthy adults when given as a bolus or as a 15-minute infusion.

Dose adjustment of BRV for the change in the formulation (switching from iv to oral solution) used during this study is not required as the AUC of BRV is bioequivalent between the following formulations: a tablet, a 15-minute iv infusion, and a bolus iv injection. In adults, iv BRV was administered to healthy volunteers, as well as subjects with epilepsy. Results showed that iv BRV was well-tolerated at all doses, up to 150mg per iv injection. Furthermore, the dose of BRV oral solution is bioequivalent to BRV tablets; therefore, dose adjustment is not required when switching between these formulations.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met:

1. An Independent Ethics Committee (IEC)-approved written ICF is signed and dated by the parent(s) or legal representative(s).

2a. Confirmation on VEEG of ≥2 minutes of cumulative ENS or ≥3 identifiable ENS prior to entering the Evaluation Period (ENS is defined as a seizure lasting for at least 10 seconds on VEEG), despite receiving previous AED treatment for the treatment of electroencephalographic seizures.

The occurrence of ENS during an up to 1-hour period must be confirmed either by the local or central VEEG reader prior to drug administration. Preferably, the central VEEG reader should confirm the required ENS.

3. Subject is male or female and must be at least 34 weeks of 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 can be enrolled.

4. Subject weighs at least 2.3kg at the time of enrollment.

5. Subjects with or without concomitant hypothermia treatment.

6.2 Exclusion criteria

Subjects are not permitted to be enrolled in the study if any of the following criteria are met:

1a. Subject receiving AED treatment other than PB, MDZ, PHT, LEV (≤60mg/kg/day), or LDC for the treatment of seizures prior to or at the time of enrollment (Confirmatory Cohorts only).

2. Subject with seizures responding to any of the following: previous AED treatment immediately prior to BRV treatment, pyridoxine treatment, or correction of metabolic disturbances (hypoglycemia, hypomagnesemia, or hypocalcemia).

3. Subject requires extra corporeal membrane oxygenation.

4. Subject has seizures related to prenatal maternal drug use or drug withdrawal.

5. Subject has known severe disturbance of hemostasis, as assessed by the Investigator.

6. Subject has a poor prognosis for survival, as judged by the Investigator.

7a. Subject has 2x upper limit of normal (ULN) of any of the following: aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP), with the following exception:

For subjects with perinatal asphyxia, elevation of AST, ALT or ALP <5x ULN is acceptable, if initial and peak elevation of liver function tests (LFTs) occurs within 5 days after birth, and the time course of LFT elevation is compatible with hepatic injury due to perinatal asphyxia.

The determination of ULN will be based on the subject's gestational age (GA) and the site's normal range values for the respective GA.8a. Subject has direct (conjugated) bilirubin levels >2mg/dL.

9. Subject requiring or expected to require phototherapy or exchange transfusion due to elevated bilirubin.

10. Subject with rapidly increasing bilirubin that may preclude the subject from inclusion in the study at the discretion of the Investigator.

11 Subject with a severe cardiac condition, including subject with a diagnosis or signs of long QT syndrome (LQTS), and subject with a family history of LQTS.

6.3 Withdrawal criteria

Parent(s) or legal representative(s) are free to withdraw the subject from the study at any time, without prejudice to continued care.

Subjects **must** be withdrawn from the study if any of the following occur:

1. The Sponsor or a regulatory agency requests withdrawal of the subject.
2. Parent(s) or legal representative(s) withdraw their consent for the subject to participate.
3. Subject is treated with prohibited concomitant medications as defined in this protocol.

4a. Subject has direct (conjugated) bilirubin levels >2mg/dL.

5. Subject requires phototherapy or exchange transfusion due to elevation of total bilirubin.

6a. Subject has AST, ALT or ALP values 3x ULN, with the following exception:

For subjects with perinatal asphyxia, elevation of AST, ALT or ALP <5x ULN is acceptable for continuation in the study, if initial and peak elevation of LFTs occurs within 5 days after birth, and if the time course of LFT elevation is compatible with hepatic injury due to perinatal asphyxia (ie, peak LFT elevation within a few days after birth, and subsequent normalization until up to day 14 after birth).

In case AST, ALT or ALP elevation ≥5x ULN occurs within 5 days after birth, study drug must be discontinued and LFTs retested within 24 hours. If AST, ALT and ALP are confirmed to be <5x ULN, the subject may restart study drug after consultation with and approval by the Medical Monitor.

The determination of ULN will be based on the subject's GA and the site's normal range values for the respective GA.

Subjects **may** be withdrawn from the study if any of the following events occur:

7a. Subject experiences prolongation of seizure duration, a worsening of seizure burden, or emergence of new seizure type considered by the Investigator to require intervention.

8. Investigator may withdraw subject due to any medical condition, based on clinical judgment and discretion.

9a. Subject has AST, ALT or ALP values between >2x and ≤3x ULN, with the following exception:

For subjects with perinatal asphyxia, elevation of AST, ALT or ALP <5x ULN is acceptable for continuation in the study, if initial and peak LFT elevation occurs within 5 days after birth, and if the time course of LFT elevation is compatible with hepatic injury due to perinatal asphyxia (ie, peak LFT elevation within a few days after birth, and subsequent normalization until up to day 14 after birth).

The determinations of ULN will be based on the subject's GA and the site's normal range values for the respective GA.

10. Subject has rapidly increasing total bilirubin without requiring or being expected to require phototherapy or exchange transfusion; the subject's withdrawal will be at the discretion of the Investigator.

Investigators should attempt to obtain information on subjects in the case of withdrawal. The Investigator should document his/her effort (date and summary of the phone call and copy of the written message in the source documents) to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the subject, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal.

Investigators should contact the Medical Monitor, whenever possible, to discuss the withdrawal of a subject in advance.

6.3.1 Potential drug-induced liver injury IMP discontinuation criteria

Subjects with potential drug-induced liver injury (PDILI) must be assessed to determine if the investigational medicinal product (IMP) must be discontinued. In addition, all concomitant medications that are not medically necessary should also be discontinued.

The PDILI criteria below require immediate and permanent discontinuation of IMP:

- Subject has direct (conjugated) bilirubin >2mg/dL.
- Subject has AST, ALT or ALP values >3x ULN, with the following exception:

  For subjects with perinatal asphyxia, elevation of AST, ALT or ALP <5x ULN is acceptable for continuation in the study, if initial and peak LFT elevation occurs within 5 days after birth, and if the time course of LFT elevation is compatible with hepatic injury due to perinatal asphyxia (ie, peak LFT elevation within few days after birth, and subsequent normalization until up to day 14 after birth).

  In case AST, ALT or ALP elevation ≥5x ULN occurs within 5 days after birth, study drug must be discontinued and LFTs retested within 24 hours. If AST, ALT and ALP are confirmed to be <5x ULN, the subject may restart study drug after consultation with and approval by the Medical Monitor.

  The determination of ULN will be based on the subject's GA and the site's normal range values for the respective GA.
- Subject requires or is expected to require phototherapy or exchange transfusion due to elevation of total bilirubin values.

Investigators should attempt to obtain information on subjects in the case of IMP discontinuation to complete the final evaluation. Subjects with PDILI should not be withdrawn from the study

until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for IMP discontinuation and subject withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for IMP discontinuation.

7 STUDY TREATMENTS

7.1 Description of investigational medicinal products

Only the following study drug will be supplied by UCB for N01349:

- BRV 10mg/mL iv solution in a 5mL vial.

For subjects who are switched to BRV oral solution in the BRV Extension Period, the following will be supplied by UCB:

- BRV oral solution, at concentrations of 10mg/mL, will be supplied in 300mL glass bottles.

Refer to the IMP Handling Manual for further details on the handling of BRV.

There is no placebo or reference product.

After the completion of the study, BRV treatment per SOC may be continued as prescribed but will not be provided by the Sponsor.

7.2 Treatments to be administered

Subjects in the Exploratory Cohort will be dosed during the Evaluation Period with BRV (0.5mg/kg bid) according to the sites standard procedures. Treatment with AEDs per SOC (first-line, second-line, or subsequent treatment) will continue in parallel with BRV treatment.

For subjects who enter the Confirmatory Cohorts, the dosing of BRV (1mg/kg bid [2mg/kg/day]) has been determined based on the PK findings of the Exploratory Cohort. The DMC will continue to monitor the PK and safety of the subjects and dosing may be adjusted as new data are available. Administration of BRV is proposed as approximately 15-minute iv infusions. Treatment with previous AEDs (PB, MDZ, PHT, LEV [≤60mg/kg/day], or LDC) during the Evaluation Period is permitted to continue if the subject is on a stable dose from 1 hour prior to initiation of the BRV treatment.

Subjects can switch from iv to oral BRV at any time during the BRV Extension Period.

For subjects who are switched to BRV oral solution, the dose will be measured using the appropriate syringes (1mL, 3mL or 10mL) with an adaptor able to fit all the bottle sizes. Oral solution should not be mixed with other liquids prior to administration.

7.3 Packaging

Brivaracetam (sterile solution for iv infusion and oral solution) is manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) guidelines and applicable laws or regulations. Brivaracetam is suitably packaged in such a way as to be protected from deterioration during transport and storage.

Brivaracetam sterile solution for iv infusion 10mg/mL will be packaged in 5ml vials.

Brivaracetam 10mg/mL oral solution will be packaged in 300mL type-III amber glass bottles with child-resistant tamper evident polypropylene screw closures. Syringes of 1mL, 3mL or 10mL will be provided with an adaptor able to fit all the bottle sizes.

Other AED treatments will be used for this study and will not be provided or covered by the Sponsor.

7.4 Labeling

Clinical drug supplies will be labeled in accordance with the current International Council on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and GMP and will include any locally required statements. If necessary, labels will be translated into the local language.

7.5 Handling and storage requirements

The Investigator (or pharmacist/designee) is responsible for the safe and proper storage of BRV at the site. Brivaracetam stored by the Investigator is to be kept in a secured area with limited access according to the storage conditions mentioned on the label.

Appropriate storage conditions must be ensured either by controlling the temperature (eg, room, refrigeration unit) or by completing a temperature log in accordance with local requirements on a regular basis (eg, once per working day), showing actual minimum/maximum temperatures reached over the time interval.

Additional information pertaining to the handling of BRV, a Schedule V drug, is provided in the IMP Handling Manual.

In case an out-of-range temperature is noted, it must be immediately reported as per instructions contained in the IMP Handling Manual.

The Investigator (or designee) will instruct the subject to store the IMP following the instructions on the label.

7.6 Drug accountability

A Drug Accountability form will be used to record BRV dispensing and return information on a by-subject basis and will serve as source documentation during the course of the study. Details of any BRV lost, damaged (due to breakage or wastage), not used, partially used, disposed of at the study site, or returned to the Sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

The Investigator (or designee) is responsible for retaining all used, unused, and partially used containers/ bottles of BRV until returned or destroyed.

The Investigator may assign some of the Investigator's duties for drug accountability at the study site to an appropriate pharmacist/designee.

The Investigator must ensure that BRV is used only in accordance with the protocol.

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers)/partially used, unused, damaged and/or expired IMP containers/ bottles must be reconciled and either destroyed at the site according to local laws, regulations, and UCB Standard Operating Procedures (SOPs), or returned to UCB (or designee). Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

7.7 Procedures for monitoring subject compliance

After each iv BRV administration, empty/used BRV containers must be kept.

All unused IMP and empty IMP containers/bottles must be accounted for or returned to the site. For subjects treated at home during the BRV Extension Period, parent(s) or legal representative(s) should be advised to return all unused IMP and empty IMP bottles to the site. Drug accountability must be done in the presence of the subject's parent(s) or legal representative(s) and site staff to obtain explanations regarding discrepancies in compliance with the dosing regimen. Drug accountability must be recorded on the Drug Accountability form.

Site personnel who are administering iv BRV will record information about all doses administered, including the target dose, actual dose administered, and the dates and times of initiation and completion of each iv administration. If the actual dose is less or more than the target dose, the reason a partial or excessive dose was administered will be recorded.

Intravenous BRV solution will be administered under supervision of the Investigator or his/her designee. The noninjected volume will be recorded in the eCRF. Compliance with the recommended duration of the iv administration will also be assessed by recording the start time and the stop time in the eCRF.

Noncompliance will be recorded for subjects who are administered <75% or >125% of the planned BRV dose. If, in the Investigator's opinion, there is persistent noncompliance with the subject's BRV administration, the Sponsor, in conjunction with the Investigator, will make a decision as to whether the subject should be withdrawn from the study.

7.8 Concomitant treatments and medications

7.8.1 Permitted concomitant treatments (medications and therapies)

Concomitant treatment with non-AEDs is permitted for the Exploratory and Confirmatory Cohort(s) at any time throughout the study.

For the Exploratory Cohort, concomitant treatment with AEDs is permitted at any time.

For the Confirmatory Cohorts, concomitant treatment with AEDs is permitted to continue in parallel with BRV treatment if subjects are on a stable dose from 1 hour prior to initiation of BRV treatment. Changes to concomitant AEDs are permitted from 3 hours onward following first BRV administration.

7.8.2 Prohibited concomitant treatments (medications and therapies)

For the Confirmatory Cohorts, subjects will not be permitted to change concomitant treatment for neonatal seizures for the first 3 hours after the first BRV administration.

The initiation of LEV treatment after the first time BRV is introduced is prohibited throughout the study for the Confirmatory Cohorts.

7.8.3 Rescue medication

Any treatment initiation with a new AED, or any increase of dose or frequency of an existing concomitant AED for the treatment of seizures during the Evaluation Period is considered rescue treatment. Rescue medication can be given at any time if considered necessary by the Investigator.

However, during the Evaluation Period rescue medication should not be administered – if possible – in the following time frames:

- During the first 3 hours after the initial dose of BRV for the Confirmatory Cohorts. If this occurs, subjects will be considered BRV nonresponders for the evaluation of the main efficacy variable.

7.9 Blinding

This is an open-label study and, therefore, no blinding is required.

7.10 Randomization and numbering of subjects

Because N01349 is an open-label, single-arm study, subjects will not be randomized to any treatment groups. The first 6 subjects meeting the eligibility criteria will be assigned to the Exploratory Cohort. Subsequent subjects will be assigned to the Confirmatory Cohorts.

An IRT system will be used to assign eligible subjects to a treatment regimen based on a predetermined packaging schedule provided by the Sponsor. The IRT will generate individual assignments for subject kits of BRV, as appropriate, according to the cohort assignment and dosing schedule.

After the ICF has been signed and dated, the subject will be enrolled in the study. The Investigator or designee will contact the IRT and provide brief details about the subject enrolled. Each subject will be assigned a 5-digit number that serves as the subject identifier throughout the study. The IRT will allocate kit numbers to the subject based on the subject number during the course of the study. The subject number will be required in all communications between the Investigator or designee and the IRT on a particular subject. Subject numbers and kit numbers will be tracked via the IRT.

8 STUDY PROCEDURES BY VISIT

A continuous consent process will be followed. Parent(s) or legal representative(s) will be informed about the study as early as possible and asked to sign the ICF after the occurrence of seizures has been confirmed by VEEG. During the course of the study, parent(s) or legal representative(s) will be updated about the care of their neonate, and continuous consent will be ensured by meetings between the Investigator (or designee) and the subject's parent(s) or legal

representative(s). Continuous consent will be documented in the subjects' medical charts and eCRF.

8.1 Exploratory Cohort

8.1.1 Screening Period

The Screening Period will be from the signing and dating of the written ICF by the parent(s) or legal representative(s) up to initiation of the first BRV dose. Any AEs, AEDs, concomitant medications, and medical procedures will be collected after the ICF is signed. The subject's eligibility to participate in this study will be assessed. The subject identification card will be dispensed.

The Screening Period starts up to 36 hours prior to the first administration of BRV. Phenobarbital, MDZ, PHT, LEV, or LDC may have been administered prior to the subject's enrollment into the study and/or at a location other than the study site.

Subjects will enter the Evaluation Period and start BRV treatment as soon as the occurrence of ENS per inclusion criterion 2a is confirmed by the Investigator based on local EEG. If preferred by the Investigator, the central VEEG reader can be consulted to confirm the required ENS.

The following assessments will be performed immediately before the first administration of BRV is initiated:

- Verification of inclusion/exclusion criteria. Confirmation on VEEG of ≥2 minutes of cumulative ENS or ≥3 identifiable ENS prior to entering the Evaluation Period (ENS is defined as a seizure lasting for at least 10 seconds on VEEG), despite treatment with 1 or more AEDs administered per SOC
- Vital signs (blood pressure, heart rate, respiratory rate [including apneas], oxygen saturation [pulse oximetry], and body temperature)
- Physical and neurological examination (Sarnat scale for subjects with HIE; physical examination will include a check for the presence of skin rash and skin hypersensitivity)
- Length
- Body weight
- Head circumference (to be taken within 7 days prior to drug administration, or at birth for subjects ≤7 days old)
- Heart rate monitoring
- Safety laboratory assessments (hematology, biochemistry, liver enzymes, and endocrinology)
- Thompson score (for subjects with HIE)
- Mechanical ventilation
- AEs as reported by the Investigator
- Recording of AEDs, concomitant medications, and medical procedures

Laboratory measurements will be performed by local laboratories unless historical data is available. Historical safety laboratory assessments, previously collected as standard of care, may

be accepted from referring hospitals as measurement prior to first use of BRV if performed 36 hours prior to the start of the Evaluation Period. In this case, test results will be considered medical history. Prior laboratory assessment results should be available and verified prior to initiation of the first BRV infusion.

At the determination of the Investigator, subjects achieving adequate seizure control following AED treatment per SOC will be considered AED responders. Those subjects will be classified as screen failures and will not be assigned to BRV treatment.

8.1.2 Evaluation Period

The first BRV infusion marks the starting point of the 48-hour Evaluation Period.

An initial iv dose of BRV (0.5mg/kg) will be administered as an approximately 15-minute infusion. At the discretion of the Investigator, 3 additional iv BRV doses can be administered, up to a total of 4 iv BRV doses (0.5mg/kg bid) during the 48-hour BRV Evaluation Period.

The following assessments will be performed after the end of the first BRV infusion:

- Vital signs (blood pressure, heart rate, respiratory rate [including apneas], oxygen saturation [pulse oximetry], and body temperature; at 0, 3, 6, 12, 24, and 48 hours)
- Physical and neurological examination (Sarnat scale for subjects with HIE; physical examination will include a check for the presence of skin rash and skin hypersensitivity; at 24 hours and 48 hours)
- Body weight (optional [at 24 and 48 hours]; dosage of BRV during the Evaluation Period will be based on the subject's weight measured prior to the start of the first BRV administration. However, dosage calculation can be adjusted to a more recent weight measurement, upon discretion of the Investigator, if weight is measured during the Evaluation Period)
- Confirmation of the primary cause of seizure (HIE, hemorrhage, or infarction; CNS malformations; CNS infections; undetermined causes [at 48 hours])
- N-PASS and EEG parameters for the assessment of sedation (at 48 hours)
- Video-EEG
- Heart rate monitoring (1, 2, 3, 6, 10, 12, 24, 27, 34, 36, and 48 hours)
- Three to 6 PK samples (30 to 60 minutes, 2 to 4 hours, and 8 to 12 hours after the start of the most recent BRV infusion; the same timepoints apply to the first and second day of the 48-hour Evaluation Period)
- Collection of AED PK sample 3 hours after the start of the initial BRV administration
- Safety laboratory assessments (hematology, biochemistry, liver enzymes, and endocrinology [at 48 hours])
- Thompson score (for subjects with HIE [at 48 hours])
- Mechanical ventilation
- AEs as reported by the Investigator

- AEDs, concomitant medications, and medical procedures
- Infusion site reaction monitoring

8.1.3 BRV Extension Period

The BRV Extension Period is intended to bridge the time until subjects are old enough to participate in the long-term study. Subjects completing the Evaluation Period at a PNA of at least 28 days may directly roll over to the long-term study, if they meet the eligibility criteria. Those patients are not required to enter the BRV Extension Period.

At the end of the Evaluation Period, subjects who benefit from BRV treatment may enter the BRV Extension Period in accordance with the Investigator's opinion. Subjects participating in the BRV Extension Period will need to remain at the study site as long as BRV is administered iv or via the enteral route. Only subjects able to swallow oral BRV should be allowed to be treated at home during the BRV Extension Period. In this case the parent(s) or legal representative(s) will receive a dosing diary to record the home administration of oral BRV. If oral BRV administration is not possible, the subjects will be invited to return to the study site and receive iv BRV as indicated below. It will not be possible for subjects to receive iv BRV at any institutions other than the study site.

All subjects who participate in the BRV Extension Period must be offered entry into the long-term study, if they meet the eligibility criteria. Subjects will participate in the BRV Extension Period until they reach a stable condition that will allow them to enter the long-term study, if epilepsy is confirmed. The maximum anticipated duration of the BRV Extension Period per subject is up to 28 days of PNA (+7 days). For subjects entering the BRV Extension Period, study drug will be dispensed at the end of the Evaluation Period. Subjects not continuing the BRV treatment after they completed the Evaluation Period will not enter the BRV Extension Period but proceed immediately to the Safety Follow-Up Period (see Section 8.1.4).

For subjects treated at home with oral BRV during the BRV Extension Period, a total of 2 on-site visits may take place (Extension Period Visit 1 [EPV1], Extension Period Visit 2 [EPV2]). Extension Period Visit 1 will be performed at 7±2 days after completion of the Evaluation Period (see Section 8.1.3.1). Extension Period Visit 2 will be performed on the same day when the subject enters the long-term study (see Section 8.1.3.2). If the long-term study is performed outside the N01349 hospital, an interval of up to 3 days between the N01349 EPV2 and follow-up study Entry Visit is allowed. In addition, an Unscheduled Visit or Telephone Contact can be performed, as needed. For subjects treated during the BRV Extension Period at the study site with iv BRV, assessments will be performed at timepoints described for EPV1 and EPV2.

During the BRV Extension Period, subjects may continue receiving iv BRV but must switch to BRV oral solution before entering the long-term study. The timepoint of the switch from iv to oral solution will be at the discretion of the Investigator. Subjects who are not able to be dosed with BRV oral solution when they reach 28 days of postnatal age may continue in the BRV Extension Period for an additional 7 days; subjects who are not able to be switched to BRV oral solution by the end of the additional 7 days of the BRV Extension Period will not be eligible for enrollment in the long-term study.

Subjects who participate in the BRV Extension Period will continue to receive the same BRV dosage administered at the end of the Evaluation Period (ie, BRV 0.5mg/kg bid). The BRV dose should not be increased, but may be decreased at the discretion of the Investigator.

8.1.3.1 Extension Period Visit 1

The EPV1 will be performed at 7±2 days after completion of the Evaluation Period. The following assessments will be performed:

- BRV dispense
- AEs as reported by the Investigator
- AEDs, concomitant medications, and medical procedures
- Review of BRV dosing diary (only if oral BRV is administered at home)
- Infusion site reaction monitoring (for subjects treated with iv BRV)

For subjects unable to return to the hospital due to COVID-19, EPV1 can be performed remotely if BRV oral solution was dispensed at the time when the subject completed the Evaluation Period.

8.1.3.2 Extension Period Visit 2

The EPV2 should be performed on the same day when the subject enters the long-term study. The following assessments will be performed:

- Vital signs (blood pressure, heart rate, respiratory rate [including apneas], oxygen saturation [pulse oximetry], and body temperature)
- Physical and neurological examination (Sarnat scale for subjects with HIE; physical examination will include a check for the presence of skin rash and skin hypersensitivity)
- BRV administration/dispense. If the subject enters the long-term study, no study drug from N01349 will be dispensed at EPV2. If the subject does not enter the long-term study, BRV from N01349 will be administered for down-titration (only applicable to subjects from the Confirmatory Cohorts).
- BRV return
- Safety laboratory assessments (hematology, biochemistry, liver enzymes, and endocrinology)
- Bayley-III (for subjects continuing into the long-term study only and only for subjects enrolled in countries where a validated translation is available)
- AEs as reported by the Investigator
- AEDs, concomitant medications, and medical procedures
- Review of BRV dosing diary (only if oral BRV is administered at home)
- Infusion site reaction monitoring
- Confirmation/diagnosis of epilepsy
- Medical History (for subjects entering the long-term study)

8.1.3.3 Unscheduled Visit

An Unscheduled Visit can take place at any time during the BRV Extension Period. The following assessments will be performed:

- Vital signs (blood pressure, heart rate, respiratory rate [including apneas], oxygen saturation [pulse oximetry], and body temperature)
- Physical and neurological examination (Sarnat scale for subjects with HIE; physical examination will include a check for the presence of skin rash and skin hypersensitivity)
- AEs as reported by the Investigator
- AEDs, concomitant medications, and medical procedures
- Review of BRV dosing diary Infusion site reaction monitoring

8.1.3.4 Telephone Contact

For subjects receiving oral BRV at home, a Telephone Contact can be performed at any time during the BRV Extension Period. The following information will be collected by the Investigator:

- AEs
- AEDs, concomitant medications, and medical procedures
- Discussion of BRV dosing diary

8.1.4 Safety Follow-Up Period

Subjects will proceed to the Safety Follow-Up Period if they do not enter the BRV Extension Period. The visit will occur 30±3 days after the final administration of BRV. The following assessments will be performed:

- Vital signs (blood pressure, heart rate, respiratory rate [including apneas], oxygen saturation [pulse oximetry], and body temperature)
- Physical and neurological examination (Sarnat scale for subjects with HIE; physical examination will include a check for the presence of skin rash and skin hypersensitivity)
- Body weight and length and head circumference
- Primary cause of seizure (HIE, hemorrhage, or infarction; CNS malformations; CNS infections; undetermined causes)
- N-PASS
- Safety laboratory assessments (hematology, biochemistry, liver enzymes, and endocrinology)
- AEs as reported by the Investigator
- AEDs, concomitant medications, and medical procedures
- Medical history (for subjects not entering the long-term study)

For subjects unable to return to the hospital due to COVID-19, the Safety Follow-Up Visit can be performed remotely. In this case vital signs, the physical and neurological examination, biometric and psychometric parameters, and the laboratory assessment may not be performed.

8.2 Confirmatory Cohorts

Based on the PK and safety data review of the Exploratory Cohort by the DMC, enrollment and BRV dosing for the Confirmatory Cohorts will begin. Three consecutive Confirmatory Cohorts (n=12 each) are planned. A PK and safety data review will be performed after completion of each of the 3 Confirmatory Cohorts. During the PK and safety data review, the recruitment of subjects will continue.

8.2.1 Screening Period

The Screening Period will be from the signing and dating of the written ICF by the parent(s) or legal representative(s) of the subject up to initiation of the first BRV dose. Any AEs, AEDs, concomitant medications, and medical procedures will be collected after the ICF is signed. The subject's eligibility to participate in this study will be assessed. The subject identification card will be dispensed.

The Screening Period starts up to 36 hours prior to the first administration of BRV. The treatment with one or more of the following AEDs prior to or at the time of enrollment: PB, MDZ, PHT, LEV (≤60mg/kg/day), or LDC (first-line, second-line, or subsequent treatment; choice of treatment, dose, and dosing regimen at the Investigator's discretion) may have started prior to the subject's enrollment in the study and/or at a location other than the study site.

At the determination of the Investigator, subjects achieving adequate seizure control following any of the following AEDs: PB, MDZ, PHT, LEV (≤60mg/kg/day), or LDC will be considered AED responders. Those subjects will be classified as screen failures and will not be assigned to BRV treatment.

8.2.1.1 Baseline Period

The Baseline Period will be up to 1 hour immediately prior to the start of initial BRV infusion and depend on seizure activity:

- For subjects with intermittent ENS: at least 1 hour prior to entering the Evaluation Period
- For subjects in status epilepticus: up to 30 minutes prior to entering the Evaluation Period. At least 15 minutes of continuous seizures, or 50% of cumulative seizure activity during a 30-minute interval are to be confirmed on EEG before the administration of BRV can start.

As soon as subjects are considered to be in status epilepticus, steps required for the preparation of the initial BRV infusion can be initiated (eg, assignment of BRV kits through interactive IRT and the dilution of BRV solution for iv infusion), even if the required EEG recording is not completed by that time.

The occurrence of ENS during the Baseline Period must be confirmed either by the local or central VEEG reader prior to drug administration. Preferably, the central VEEG reader should confirm the required ENS. Video-EEGs that are acquired per standard of care prior to consenting and meet study-specific technical and quality requirements (eg, ability for immediate cloud-based central review) can be used as part of the Baseline assessment VEEG.

The following assessments will be performed during the Baseline Period:

- Verification of inclusion/exclusion criteria. Confirmation on VEEG of ≥2 minutes of cumulative ENS or ≥3 identifiable ENS within the up to 1 hour prior to entering the Evaluation Period (ENS is defined as a seizure lasting for at least 10 seconds on VEEG), despite treatment with one or more AEDs per SOC
- Demographic data
- Medical history (including Apgar score)
- Vital signs (blood pressure, heart rate, respiratory rate [including apneas], oxygen saturation [pulse oximetry], and body temperature)
- Physical and neurological examination (Sarnat scale for subjects with HIE; physical examination will include a check for the presence of skin rash and skin hypersensitivity)
- Length
- Body weight
- Head circumference (Baseline measurement should be taken within 7 days prior to drug administration, or at birth for subjects ≤7 days old)
- Primary cause of seizure (HIE, hemorrhage, or infarction; CNS malformations; CNS infections; undetermined causes)
- N-PASS and EEG parameters for the assessment of sedation
- Video-EEG
- Heart rate monitoring
- Safety laboratory assessments (hematology, biochemistry, liver enzymes, and endocrinology)
- Thompson score (for subjects with HIE)
- Mechanical ventilation
- AEs as reported by the Investigator
- AEDs, concomitant medications, and medical procedures

Baseline laboratory measurements will be performed by local laboratories unless historical data is available. Historical safety laboratory assessments, previously collected as standard of care, may be accepted from referring hospitals as Baseline measurement if performed 36 hours prior to the start of the Evaluation Period. In this case, test results will be considered medical history. Prior laboratory assessment results should already be available at Baseline and verified prior to initiation of BRV administration.

8.2.2 Evaluation Period

The first administration of BRV marks the starting point of the Evaluation Period.

Up to 8 iv doses of BRV (1mg/kg bid) will be administered as an approximately 15-minute infusion during the 96-hour BRV Evaluation Period. The AED treatment initiated prior to first

administration of BRV can be continued if the subject is on a stable dose for at least 1 hour at the time the first BRV infusion is initiated.

If subjects do not benefit from BRV treatment after 96 hours of BRV administration, BRV administration will be stopped and replaced by another AED; however, the subjects´ participation in the study will continue.

If subjects in the Confirmatory Cohort receive <8 BRV doses, those subjects are allowed to continue study participation and complete study assessments per Table 5–2 with the exception of PK blood sampling. Those subjects should start the Down-Titration Period while completing the Evaluation Period in parallel for the full 96 hours.

After the enrollment of subjects, the weight of the subject will be measured and BRV will be given.

The following assessments will be performed after BRV administration:

- Vital signs (blood pressure, heart rate, respiratory rate [including apneas], oxygen saturation [pulse oximetry], and body temperature; at 0, 3, 6, 9, 12, 15, 18, 21, 24, 48, 72, and 96 hours)
- Physical and neurological examination (Sarnat scale for subjects with HIE; physical examination will include a check for the presence of skin rash and skin hypersensitivity [at 24, 48, 72, and 96 hours])
- Primary cause of seizure (HIE, hemorrhage, or infarction; CNS malformations; CNS infections; undetermined causes [at 96 hours])
- N-PASS and EEG parameters for the assessment of sedation (at 96 hours)
- Body weight (optional [at 24, 48, 72 and 96 hours]; dosage of BRV during the Evaluation Period will be based on the subject's weight measured prior to the start of the first BRV administration. However, dosage calculation can be adjusted to a more recent weight measurement, upon discretion of the Investigator, if weight is measured during the Evaluation Period)
- Video-EEG
- Heart rate monitoring
- Up to 6 PK samples (30 to 60 minutes, 2 to 4 hours, and 8 to 12 hours after the start of the most recent BRV infusion; the same timepoints apply to the first day and 1 of the 3 following days of the 96-hour Evaluation Period).
- Collection of AED PK sample 3 hours after the start of the initial BRV administration
- Safety laboratory assessments (hematology, biochemistry, liver enzymes, and endocrinology [at 24 and 96 hours])
- Thompson score (for subjects with HIE [at 96 hours])
- Mechanical ventilation

- Bayley-III (for subjects continuing into the long-term study only and only for subjects enrolled in countries where a validated translation is available)
- AEs as reported by the Investigator
- AEDs, concomitant medications, and medical procedures
- Infusion site reaction monitoring

8.2.3 BRV Extension Period

The BRV Extension Period is intended to bridge the period until subjects are old enough to participate in the long-term study. Subjects completing the Evaluation Period at a PNA of at least 28 days may directly roll over to the long-term study, if they meet the eligibility criteria. Those patients are not required to enter the BRV Extension Period.

At the end of the Evaluation Period, subjects who benefit from BRV treatment may enter the BRV Extension Period in accordance with the Investigator's opinion. Subjects participating in the BRV Extension Period will need to remain at the study site as long as BRV is administered iv. Only subjects able to swallow oral BRV should be allowed to be treated at home during the BRV Extension Period. If oral BRV administration is not possible, the subjects will be invited to return to the study site and receive iv BRV as indicated below. It will not be possible for subjects to receive iv BRV at any institutions other than the study site. All subjects who participate in the BRV Extension Period must be offered entry into the long-term study, if they meet the eligibility criteria. Subjects will participate in the BRV Extension Period until they reach a stable condition that will allow them to enter the long-term study, if epilepsy is confirmed. The maximum anticipated duration of the BRV Extension Period per subject is up to 90 days of PNA. For subjects entering the BRV Extension Period, study drug will be dispensed at the end of the Evaluation Period. Subjects not continuing the BRV treatment after they completed the Evaluation Period will not enter the BRV Extension Period but proceed immediately to the Down-Titration Period (see Section 8.2.4).

For subjects treated at home with oral BRV during the BRV Extension Period, a total of 2 on-site visits may take place (EPV1 and EPV2). Extension Period Visit 1 will be performed at 7±2 days after completion of the Evaluation Period (see Section 8.2.3.1). Extension Period Visit 2 will be performed on the same day when the subject enters the long-term study (see Section 8.2.3.2). If the long-term study is performed outside the N01349 hospital, an interval of up to 3 days between the N01349 EPV2 and long-term study Entry Visit is allowed. In addition, an Unscheduled Visit or Telephone Contact can be performed, as needed. For subjects treated during the BRV Extension Period at the study site with iv BRV, assessments will be performed at timepoints described for EPV1 and EPV2.

During the BRV Extension Period, subjects may continue receiving iv BRV but must switch to BRV oral solution before entering the long-term study. The timepoint of the switch from iv to oral solution will be at the discretion of the Investigator

Subjects who participate in the BRV Extension Period will continue to receive the same BRV dosage administered at the end of the Evaluation Period (ie, BRV 1mg/kg bid). The BRV dose should not be increased, but may be decreased at the discretion of the Investigator.

In the event that a long-term study is temporarily not available after the planned duration of the BRV Extension Period (28 [+7] days of PNA), subjects are allowed to remain in the BRV Extension Period until they reach a PNA of up to 90 days. For those subjects, the assessments planned for Unscheduled Visits (Section 8.2.3.3) will be conducted in intervals of approximately 30 days during the prolonged Extension Period.

8.2.3.1 Extension Period Visit 1

This visit will be performed at 7±2 days after completion of the Evaluation Period. The following assessments will be performed:

- BRV dispense
- AEs as reported by the Investigator
- AEDs, concomitant medications, and medical procedures
- Review of BRV dosing diary (only if oral BRV is administered at home)
- Infusion site reaction monitoring (for subjects treated with iv BRV)

For subjects unable to return to the hospital due to COVID-19, EPV1 can be performed remotely if BRV oral solution was dispensed at the time when the subject completed the Evaluation Period.

8.2.3.2 Extension Period Visit 2

This visit should be performed on the same day when the subject enters the long-term study. The following assessments will be performed:

- Vital signs (blood pressure, heart rate, respiratory rate [including apneas], oxygen saturation [pulse oximetry], and body temperature)
- Physical and neurological examination (Sarnat scale for subjects with HIE; physical examination will include a check for the presence of skin rash and skin hypersensitivity)
- BRV administration/dispense. If the subject enters the long-term study, no study drug from N01349 will be dispensed at EPV2. If the subject does not enter the long-term study, BRV from N01349 will be administered for down-titration (only applicable to subjects from the Confirmatory Cohorts).
- BRV return
- Safety laboratory assessments (hematology, biochemistry, liver enzymes, and endocrinology)
- Bayley-III (for subjects continuing into the long-term study only and only for subjects enrolled in countries where a validated translation is available)
- AEs as reported by the Investigator
- AEDs, concomitant medications, and medical procedures
- Review of BRV dosing diary (only if oral BRV is administered at home)
- Infusion site reaction monitoring (for subjects treated with iv BRV)
- Confirmation/diagnosis of epilepsy

- Medical History (for subjects entering the long-term study)

8.2.3.3 Unscheduled Visit

An Unscheduled Visit can take place at any time during the BRV Extension Period. The following assessments will be performed:

- Vital signs (blood pressure, heart rate, respiratory rate [including apneas], oxygen saturation [pulse oximetry], and body temperature)
- Physical and neurological examination (Sarnat scale for subjects with HIE; physical examination will include a check for the presence of skin rash and skin hypersensitivity)
- Safety laboratory assessments (hematology, biochemistry, liver enzymes, and endocrinology)
- AEs as reported by the Investigator
- AEDs, concomitant medications, and medical procedures
- Review of BRV dosing diary
- Infusion site reaction monitoring

For subjects who remain in the BRV Extension Period for a prolonged duration (ie, until they reach a PNA of 90 days), these assessments will be conducted at intervals of 30 (±3 days).

8.2.3.4 Telephone Contact

For subjects receiving oral BRV at home, a Telephone Contact can be performed at any time during the BRV Extension Period. The following information will be collected by the Investigator:

- AEs
- AEDs, concomitant medications, and medical procedures

8.2.4 Down-Titration Period

A Down-Titration Period of up to 1 week is recommended for subjects who complete the Evaluation Period, but do not enter the BRV Extension Period, discontinue BRV during the Evaluation Period, or start the BRV Extension Period but do not continue into the long-term study for any reason. The Down-Titration steps and duration may be adjusted at the Investigator's discretion.

The following assessments will be performed:

- Vital signs (blood pressure, heart rate, respiratory rate [including apneas], oxygen saturation [pulse oximetry], and body temperature)
- Physical and neurological examination (Sarnat scale for subjects with HIE; physical examination will include a check for the presence of skin rash and skin hypersensitivity; to be performed on the first day of the Down-Titration Period only)
- Primary cause of seizure (HIE, hemorrhage, or infarction; CNS malformations; CNS infections; undetermined causes; to be performed on the first day of the Down-Titration Period only)

- N-PASS
- BRV administration
- At least a 1-hour video-EEG on the final day of the Down-Titration Period (during the Down-Titration Period, additional VEEGs can be performed at the Investigator´s discretion)
- AEs as reported by the Investigator
- AEDs, concomitant medications, and medical procedures
- Infusion site reaction monitoring

8.2.5 Safety Follow-Up Period

Subjects will proceed to the Safety Follow-Up Period once they complete the Down-Titration Period. This visit will occur 30±3 days after the final administration of BRV. The following assessments will be performed:

- Vital signs (blood pressure, heart rate, respiratory rate [including apneas], oxygen saturation [pulse oximetry], and body temperature)
- Physical and neurological examination (Sarnat scale for subjects with HIE; physical examination will include a check for the presence of skin rash and skin hypersensitivity)
- Body weight and length and head circumference
- Confirmation of the primary cause of seizure (HIE, hemorrhage, or infarction; CNS malformations; CNS infections; undetermined causes)
- N-PASS
- Safety laboratory assessments (hematology, biochemistry, liver enzymes, and endocrinology)
- AEs as reported by the Investigator
- AEDs, concomitant medications, and medical procedures
- Medical History (for subjects not entering the long-term study)

For subjects unable to return to the hospital due to COVID-19, the Safety Follow-Up Visit can be performed remotely. In this case vital signs, the physical and neurological examination, biometric and psychometric parameters, and the laboratory assessment may not be performed.

9 ASSESSMENT OF PHARMACOKINETIC VARIABLES

9.1 Pharmacokinetic sampling and handling

For the determination of plasma concentrations of BRV and BRV metabolites, up to 6 blood microsamples (60µL/sample) will be collected per subject in the Exploratory (3 to 6 blood microsamples) and Confirmatory Cohorts (up to 6 blood microsamples) at 3 predetermined timepoints per day. An additional microsample (60µL) will be collected per subject for the determination of plasma concentrations of concomitant AEDs (PB and PHT).

Pharmacokinetic samples will be obtained either through a venous or arterial catheter or taken from routinely performed heel-pricks. Blood for PK samples should be drawn from a line different to that of the BRV infusion. Three BRV PK samples of blood will be collected at the

following predetermined timepoints at the first day of the Evaluation Period: 30 to 60 minutes, 2 to 4 hours, and 8 to 12 hours after the start of the most recent BRV infusion. For the Exploratory Cohort the same timepoints apply to the second day of the 48-hour Evaluation Period. For the Confirmatory Cohort(s), the second set of 3 BRV PK samples will be collected at the same timepoints on 1 of the other days of the 96-hour Evaluation Period. It will be acceptable if these samples are drawn on different days. The AED PK sample should be collected 3 hours after the start of the initial BRV administration. The timepoints for the collection of PK samples are described in Table 5–4 for the Exploratory Cohort and in Table 5–5 for the Confirmatory Cohorts.

Additional opportunistic blood samples for the PK analysis (Leroux et al, 2015) may be obtained at the Investigator's discretion at any time during the Evaluation Period. As opportunistic blood samples will be taken from routine laboratory blood samples, they are not considered an additional burden for the neonates. The plan for microsampling in N01349 is consistent with blood sampling schema in other neonatal studies (Allegaert and van den Anker, 2015; Jullien et al, 2015; O'Hara et al, 2015; Zhao and Jacqz-Aigrain, 2015; Zhao et al, 2014).

Exact dosing and sampling times will be recorded in the eCRF. Sampling times of pre-determined PK samples may be subject to change after analysis and review of data from the Exploratory Cohort to complete the PK profile.

The full set of a subject's PK plasma samples will be shipped for analyses after the subject has completed the Evaluation Period.

9.2 Pharmacokinetic sample shipment

Instructions on blood sample collection, processing, storage, and labeling/shipping will be provided in the laboratory manual for this study. On arrival, the samples will be stored at -20°C, until analysis.

Shipments due to arrive over the weekend or holidays must be avoided. For PK samples collected over a weekend in the site, these should be stored at -20°C and must be shipped under frozen conditions (packaged with dry ice) to the central laboratory on the following Monday. Prior to any shipment, an agreement must be made with the analytical laboratory for receipt of the samples.

10 ASSESSMENT OF EFFICACY

10.1 Assessment of the secondary efficacy variables (Confirmatory Cohort[s] only)

The main secondary efficacy variable is:

- Proportion of responders to BRV treatment from Baseline to 3 hours after the initial BRV dose

  A BRV responder is defined as a subject who achieved the following reduction in seizure burden (ENS in minutes per hour) without need for rescue medication, compared to the seizure burden measured during the Baseline Period immediately prior to BRV administration, evaluated for a 2-hour period starting 1 hour after the start of initial BRV treatment:

  – At least 80% reduction in nonsevere seizure burden

    (Nonsevere seizure burden is defined as ≤50% seizure activity on VEEG in all 30-minute timespans)

OR

  – At least 50% reduction in severe seizure burden

    A severe seizure burden is defined as >50% seizure activity on VEEG in any 30-minute timespan. Timespans of 30 minutes refer to the following intervals within the 2-hour period: 0 to ≤30 minutes, >30 to ≤60 minutes, >60 to ≤90 minutes, and >90 to ≤120 minutes

For this study, an ENS is defined as EEG seizure lasting for at least 10 seconds on VEEG. Baseline seizure burden is defined as seizure burden measured on the continuous VEEG (total ENS in minutes per hour) during a period of up to 1 hour immediately prior to the first administration of study drug.

For the analysis of the main secondary efficacy variable (Section 4.2.1), subjects who started another AED, increased the dose or frequency of administration of an AED ongoing at the time the first BRV infusion started, or are switched to another AED, or have been administered any rescue medication for the treatment of ENS during the first 3 hours after initiation of BRV treatment will be considered BRV nonresponders.

For the analysis of the following secondary efficacy variables, subjects who started another AED, increased the dose or frequency of administration of an AED ongoing at the time the first BRV infusion started, or are switched to another AED, or have been administered any rescue medication for the treatment of ENS following the first 3 hours after initiation of BRV treatment will be considered BRV responders:

- Proportion of subjects with at least 80% reduction in nonsevere seizure burden from Baseline to 3 hours after the initial BRV treatment
- Proportion of subjects with at least 50% reduction in severe seizure burden from Baseline to 3 hours after the initial BRV treatment
- Absolute reduction in average seizure burden measured by continuous VEEG from Baseline to the end of the 96-hour Evaluation Period
- Percent reduction in average seizure burden measured by continuous VEEG from Baseline to the end of the 96-hour Evaluation Period
- Proportion of BRV responders at the end of the 96-hour Evaluation Period
- Proportion of subjects who are seizure-free (100% reduction in seizure burden from Baseline) at 24 hours following the start of initial BRV treatment, categorized by subjects with nonsevere or severe seizure burden at Baseline
- Time to reduction in seizure burden for BRV responders (defined as the first timepoint when BRV responder criteria were met)
- Seizure freedom at the end of the Down-Titration Period
- Rate of at least 50% reduction in ENS frequency per hour from Baseline to the end of the 96-hour Evaluation Period
- Proportion of subjects who are seizure-free by time interval at 3 hours, at 3-hour intervals thereafter through 24 hours, and every 12 hours to 24 hours following the start of the initial BRV treatment
- Absolute difference in clinical seizures at the end of the 24-hour Evaluation Period from Baseline for neonates with motor seizures at the time of inclusion
- Percent difference in clinical seizures at the end of the 24-hour Evaluation Period from Baseline for neonates with motor seizures at the time of inclusion

10.2 Assessment of other efficacy variables

Other efficacy variables will include:

- Absolute and percentage reduction from Baseline in seizure burden at evaluation periods of 0 hours to 3 hours, >3 hours to 6 hours, >6 hours to 12 hours, >12 hours to 24 hours, >24 hours to 36 hours, >36 hours to 48 hours, >48 hours to 72 hours, and >72 hours to 96 hours after the start of initial BRV treatment
- Categorized percentage reduction from Baseline to the end of the 96-hour Evaluation Period in seizure burden (<-25% [worsening], -25% to <25% [no change], 25% to <50%, 50% to <80%, and ≥80%)

- Proportion of BRV responders by time interval at evaluation periods of 0 to 3 hours, >3 to 6 hours, >6 to 12 hours, >12 to 24 hours, >24 to 36 hours, >36 to 48 hours, >48 to 72 hours, and >72 to 96 hours after the start of initial BRV treatment
- Proportion of subjects who switch over from BRV to another AED during the 96-hour Evaluation Period
- Proportion of responders to other treatment during the 96-hour Evaluation Period (including at the end of the 96-hour Evaluation Period, and by time intervals: 0 hours to 3 hours, >3 hours to 6 hours, >6 hours to 12 hours, >12 hours to 24 hours, >24 hours to 36 hours, >36 hours to 48 hours, >48 hours to 72 hours, and >72 hours to 96 hours after the start of initial BRV treatment)

  (A responder to other treatment is defined as at least 80% reduction in nonsevere seizure burden from start of other treatment to end of other treatment or at least 50% reduction in severe seizure burden from the initiation of other treatment to end of other treatment during the 96-hour Evaluation Period).

To further evaluate BRV efficacy, a descriptive comparison will be conducted of the main efficacy variable data from N01349 with published responder rates for one or more AED treatments from literature (historical control group matched in age and condition) effective for the treatment of neonatal seizures in subjects of similar age (<29 days of PNA) and condition (neonatal seizures as noted in N01349 eligibility criteria). A recent study (Weeke et al, 2016) provides response rates for second line AED treatment of neonatal seizures in a similar population and with primary endpoints comparable to N01349. Results from this study, as well as results from other studies available in the literature at the time of N01349 completion and with populations and efficacy endpoints comparable to N01349, will be used for these comparisons.

10.3 Seizure burden

Seizure burden is defined as the total minutes of ENS per hour. Seizure burden information will be recorded for the Confirmatory Cohorts via a continuous VEEG. Seizure burden at Baseline will be evaluated over a period of at least 1 hour (subjects with intermittent seizures) or up to 30 minutes (subjects in status epilepticus).

Electroencephalographic neonatal seizures are defined as EEG seizures occurring for at least 10 seconds.

Seizure counts/seizure burden will be based on data collected using continuous VEEG. The VEEG recording will be evaluated by the local physician or central reader to evaluate eligibility of the subject. The VEEG recordings will subsequently be confirmed and quantified by the central reader at the end of the study.

11 ASSESSMENT OF SAFETY

11.1 Adverse events

11.1.1 Definitions

11.1.1.1 Adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with

this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the ICF), including any pretreatment and posttreatment periods required by the protocol, must be recorded even if no IMP was taken but specific study procedures were conducted. This includes all AEs not present prior to the signing of the ICF and all AEs that recurred or worsened after the signing of the ICF.

Signs or symptoms of the condition/disease for which the IMP is being studied should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the Investigator from the subject's history or based on assessments performed prior to the first administration of BRV.

11.1.1.2 Serious adverse event

Once it is determined that a subject experienced an AE, the seriousness of the AE must be determined. An SAE must meet 1 or more of the following criteria:

- Death
- Life-threatening

  (Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form).
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)
- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious

  (Important medical events may include, but are not limited to, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).
- Initial inpatient hospitalization or prolongation of hospitalization

  (A patient admitted to a hospital, even if he/she is released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for this criteria and, instead, should be evaluated for 1 of the other criteria in the definition of serious [eg, life-threatening adverse experience, important medical event].

  Hospitalizations for reasons not associated with the occurrence of an AE [eg, preplanned surgery or elective surgery for a pre-existing condition that has not worsened or manifested in an unusual or uncharacteristic manner] do not qualify for reporting. For example, if a subject has a condition recorded on his/her medical history and later has a preplanned surgery

for this condition, it is not appropriate to record the surgery or hospitalization as an SAE, since there is no AE upon which to assess the serious criteria. Please note that, if the pre-existing condition has worsened or manifested in an unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined).

11.1.1.2.1 Anticipated serious adverse events

The following list of anticipated SAEs has been identified, as these events are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure:

- Respiratory distress syndrome
- Convulsion

This original list will remain in effect for the duration of the protocol.

In addition, the following are anticipated SAEs in babies with HIE:

Acute

- Anuria/kidney failure
- Clotting aberrations up to disseminated intravascular coagulation
- Hypotonia
- Blood pressure instability
- Cardio-respiratory failure
- Multiorgan failure
- Severe encephalopathy with coma
- Status epilepticus
- Cerebral oedema
- Death

Chronic

- Cerebral palsy
- Visual Impairment
- Epilepsy
- Learning Difficulties
- Behavioural Difficulties

These lists do not change the Investigator's obligation to report all SAEs (including anticipated SAEs) as detailed in Section 11.1.2.3.

11.1.1.3 Adverse events of special interest

An AE of special interest is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound.

The following will be considered AEs of special interest for the study population:

- Autoimmune nephritis
- Nephritis
- Nephritis allergic
- Tubulointerstitial nephritis
- Tubulointerstitial nephritis and uveitis syndrome
- Potential drug-induced liver injury as indicated by:
  - Direct (conjugated) bilirubin >2mg/dL
  - Condition requiring phototherapy or exchange transfusion due to elevation total of bilirubin values
  - AST, ALT or ALP values ≥3x ULN according to the subject's GA and the site's normal values for that GA, with the following exception:

    For subjects with perinatal asphyxia, if initial and peak LFT elevation occurs within 5 days after birth, and if the time course of the elevation of LFT is compatible with hepatic injury due to perinatal asphyxia (ie, peak LFT elevation within few days after birth, and subsequent normalization until up to day 14 after birth) only AST, ALT or ALP elevation ≥5x ULN must be reported as an AE of special interest.

11.1.2 Procedures for reporting and recording adverse events

The subject's parent(s) or legal representative(s) will be given the opportunity to report AEs spontaneously. A general prompt will also be given at each study visit to detect AEs. For example:

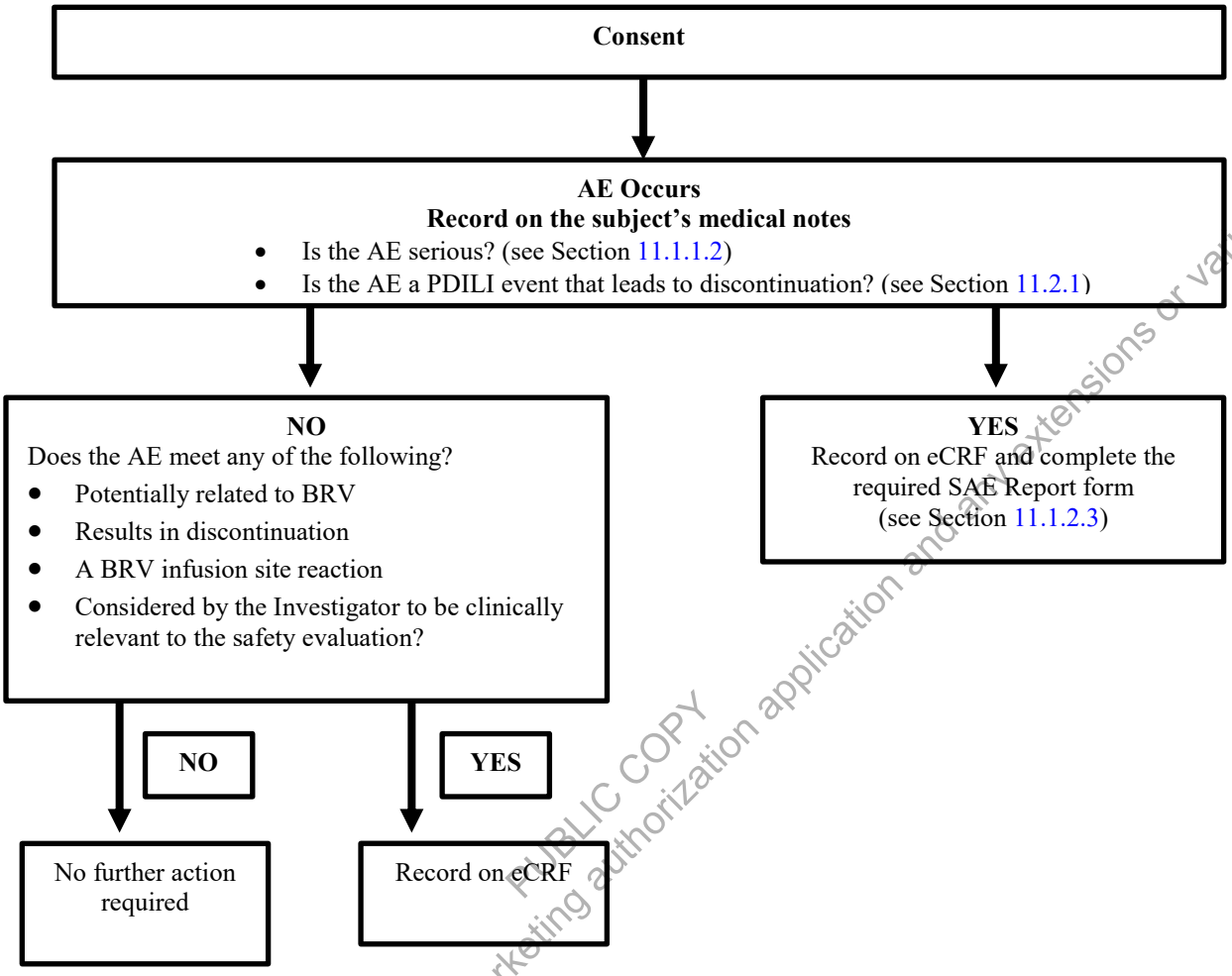
> "Did you notice anything unusual about your child's health (since your last visit)?"

The requirements for recording AEs are detailed in Articles 16 and 17 of the Clinical Trials Directive (CTD) 2001/20/EC1 published in 2001, which establishes specific provisions regarding the conduct of clinical trials, in particular relating to the implementation of GCP. Articles 16 and 17 of the CTD outline the legal obligations for both the Investigator and Sponsor for the recording and reporting of all AEs and reactions.

In line with GCP, from the signing of the ICF, the Investigator will evaluate the subject for occurrence of any AEs based on continued observation and medical notes throughout the study. Serious AEs, AEs that are considered related to the medicinal (investigational) product, AEs leading to discontinuation, BRV infusion site reactions, or AEs considered by the Investigator to be critical to the safety evaluation of the protocol will also be recorded on the Adverse Event eCRF. Further guidance on the reporting requirements for AEs is provided in Figure 11–1. The

predicted and expected AEs for BRV are also provided in Section 11.1.1.2.1, and reporting requirements for serious AEs are detailed in Section 11.1.2.3 .

Figure 11–1: Adverse event reporting flowchart



AE=adverse event; BRV=brivaracetam; eCRF=electronic case report form; SAE=serious adverse event

This AE reporting flowchart details the decision-making process for recording AEs in the eCRF. Serious AEs and nonserious AEs (that are potentially related to the study drug, result in discontinuation, are considered BRV infusion site reactions, or are considered by the Investigator to be critical to the safety evaluation) are to be recorded in the eCRF. All AEs will be recorded in the subject's medical notes.

Examples of AEs critical to the safety evaluation of the protocol include:

- AEs that might alter the current benefit-risk assessment of BRV use in neonatal seizures
- AEs that would be sufficient to consider changes in the study protocol
- AEs that would be sufficient to consider changes in the overall conduct of the study

11.1.2.1 Description of adverse events

When recording an AE, the Investigator should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The eCRF and source documents should be consistent. Any discrepancies between the Investigator's records and the corresponding medical terminology should be clarified in the source documentation.

Details for completion of the Adverse Event eCRF (including judgment of relationship to IMP) are described in the eCRF Completion Guidelines.

11.1.2.2 Rule of repetition of an adverse event

An increase in the intensity of an AE should lead to the repetition of the AE being reported with:

- The outcome date of the first AE that is not related to the natural course of the disease being the same as the start date of the repeated AE, and the outcome of "worsening"
- The AE verbatim term being the same for the first and repeated AE, so that the repeated AE can be easily identified as the worsening of the first one

11.1.2.3 Additional procedures for reporting serious adverse events

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact information for SAE reporting listed in the Serious Adverse Event Reporting section at the front of the protocol). The Investigator must forward to UCB (or its representative) a duly completed "Investigator SAE Report Form for Development Drug" (SAE Report form) provided by UCB, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the global safety database.

An Investigator SAE Report form will be provided to the Investigator. The Investigator SAE Report form must be completed in English.

It is important for the Investigator, when completing the SAE Report form, to include the assessment as to a causal relationship between the SAE and the IMP administration. This insight from the Investigator is very important for UCB to consider in assessing the safety of the IMP and in determining whether the SAE requires reporting to the regulatory authorities in an expedited manner.

Additional information (eg, autopsy or laboratory reports) received by the Investigator must be provided within 24 hours. All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in the Investigator SAE Report form.

The Investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the Investigator is certain that they are in no way associated with the IMP), up to 30 days from the end of the study for each subject, and to also inform participating subjects parent(s) or legal representative(s) of the need to inform the Investigator of any SAE within this period. Serious AEs that the Investigator thinks may be associated with the IMP must be reported to UCB regardless of the time between the event and the end of the study.

Upon receipt of the SAE Report form, UCB will perform an assessment of expectedness of the reported SAE. The assessment of the expectedness of the SAE is based on the IB.

11.1.2.4 Immediate reporting of adverse events

The following AEs must be reported immediately (see Section 11.1.2.3):

- Serious adverse event (see Section 11.1.1.2):
  - Adverse event that the Investigator classifies as serious by the above definitions regardless of causality
  - New onset or worsening of status epilepticus after the administration of BRV
- Suspected transmission of an infectious agent via a medicinal product (see Section 11.1.4)
- Adverse event of special interest (see Section 11.1.1.3)

11.1.3 Follow-up of adverse events

An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow-up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest; further details regarding follow-up of PDILI events are provided in Section 11.2.1.4.

If an AE is ongoing at the end of the study for a subject, follow-up should be provided until resolution/stable level of sequelae is achieved, or until the Investigator no longer deems that it is clinically significant, or until the subject is lost to follow-up. If no follow-up is provided, the Investigator must provide a justification. The follow-up will usually be continued for 30 days after the subject has discontinued his/her IMP.

Information on SAEs obtained after clinical database lock will be captured through the Patient Safety (PS) database without limitation of time.

11.1.4 Suspected transmission of an infectious agent

A suspected transmission of infectious agent is defined as any infection that is temporally related to the administration of the medicinal product with no other likely cause. The Medical Monitor should be contacted immediately. No further medicinal product from that specific batch should be administered. Infections should be treated according to normal clinical practice.

For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product should be considered as an SAE; such cases must be reported immediately, recorded in the AE module of the eCRF, and followed as any other SAE. Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

11.1.5 Overdose of investigational medicinal product

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the eCRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. These events are only considered AEs or SAEs if there are associated clinical signs and symptoms.

11.1.6 Safety signal detection

Selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to BRV so that Investigators, parent(s) or legal representative(s) of the clinical study subject, regulatory authorities, and IECs will be informed appropriately and as early as possible.

The Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the PS representative.

No formal interim analysis is planned for this study; however, PK and safety data will be presented to and reviewed by a DMC. It was originally planned that the DMC would convene to review the PK and safety data every 6 months; however, due to the low enrollment rate, the interval between DMC meetings may exceed 6-month intervals, at the discretion of the DMC. The DMC will oversee the safety of the study by convening to review the PK and safety data after the 6 subjects from the Exploratory Cohort have completed or withdrawn from the study. The PK and safety data will again be reviewed after each of the 3 Confirmatory Cohorts (12 subjects each) have completed or withdrawn from the study.

The DMC will consist of 3 voting members, none of whom will be involved in the conduct of the study, either by management or participation. As appropriate for the stage of development and accumulated experience with BRV, medically qualified personnel at UCB may identify additional safety measures (eg, AEs, vital signs, laboratory or heart rate results) for which data will be periodically reviewed during the course of the study.

Serious adverse events and AEs of special interest will be monitored and will be triaged by the Study Physician and UCB PS in real time. After this triage, events will be passed on to the DMC as appropriate. The DMC or Sponsor can convene an ad hoc DMC meeting to review the data and make recommendations on the continuation or modification of the study. The objectives and procedures for the DMC will be detailed in the DMC Charter.

A DMC will be in place for the duration of this study (see Section 13.8.3).

11.2 Laboratory measurements

Safety laboratory assessments will be performed as shown in Table 5–1, Table 5–2, and Table 5-3. Blood samples will be collected in line with Section 13.2 of the "Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population" (European Union Commission ad hoc group, 2008). If clinically significant abnormalities are observed, the laboratory measurements may be performed more frequently at the Investigator's discretion.

Laboratory measurements, including laboratory assessments for PDILI, will be performed by local laboratories unless historical data is available. Historical safety laboratory assessments, previously collected as standard of care, may be accepted from referring hospitals as Baseline measurement if performed 36 hours prior to the Evaluation Period.

As part of routine assessments performed by local laboratories, the parameters shown in Table 11–1 and Table 11–2 will be measured.

Table 11–1: Mandatory laboratory measurements

Hematology	Biochemistry
Basophils	Calcium
Eosinophils	Chloride
Lymphocytes	Potassium
Atypical lymphocytes	Sodium
Monocytes	Glucose
Neutrophils	Urea/BUN[a]
Hematocrit	Creatinine[b]
Hemoglobin	Creatine kinase
MCH	AST
MCHC	ALT
MCV	ALP
Platelet count	GGT
RBC count	LDH
WBC count	Total bilirubin
	Direct (conjugated) bilirubin

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=gamma-glutamyltransferase; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; WBC=white blood cell

[a] Urea or BUN to be tested depending on the local lab´s standard panel for neonates.

[b] During the first days of life, creatinine will only be collected if the site assesses this parameter per standard of care.

Table 11–2: Optional laboratory measurements

Biochemistry	Urinalysis[b]	Endocrinology[c]
Total cholesterol[a]	Protein	TSH
	Bacteria	T_4
	Glucose	
	pH	
	RBC	
	WBC	

RBC=red blood cell; T_4=thyroxine; TSH=thyroid-stimulating hormone; WBC=white blood cell

[a] Total cholesterol to be measured if this is part of the local lab´s standard panel for neonates.

[b] Urinalysis to be performed only if a urine sample was obtained for clinical purposes. A urine dipstick is acceptable.

[c] TSH and T_4 to be recorded for the study only if measured for neonatal screening of congenital hypothyroidism prior to or during study participation.

11.2.1 Evaluation of PDILI

The PDILI IMP discontinuation criteria (Food and Drug Administration [FDA], Guidance for Industry, Drug-induced liver injury, 2009) for this study are provided in Section 6.3.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and Sponsor within 24 hours of learning of their occurrence. Any PDILI event that leads to discontinuation must be reported as an AE of special interest (see Section 11.1.1.3) and must also be reported as an SAE see Section 11.1.1.2).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 11–3 specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 11.2.1.1). Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 11.2.1.4).

The results of all monitoring, including laboratory testing and other testing, should be made available to the study site and Sponsor.

All initial tests resulting in abnormal hepatic laboratory values need to be repeated, but appropriate medical action must not be delayed while waiting for the repeat result.

Table 11–3 summarizes the required investigations and follow-up for PDILI.

Table 11–3: Required investigations and follow-up for PDILI

Patient population	Laboratory value		Immediate		Follow-Up	
	ALT/ AST/ALP	Direct (conjugated) bilirubin[a]	Consultation requirements	Actions	Testing	Evaluation
Subjects **without** perinatal asphyxia	≥3xULN according to the subject's GA and site's normal value	NA	Hepatology consultation (see Section 11.2.1); Medical Monitor must be notified within 24 hours (eg, laboratory alert) and subject discussed with Medical Monitor ASAP[b]	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 11.2.1.1); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values.
Subjects **with** perinatal asphyxia[c]	≥5xULN according to the subject's GA and site's normal value	NA				
All subjects	NA	≥2mg/dL				

ASAP=as soon as possible; GA=gestational age; HCP=healthcare practitioner; IMP=investigational medicinal product; NA=not applicable; PDILI=potential drug-induced liver injury; ULN=upper limit of normal

[a] Any requirement for phototherapy or exchange transfusion due to elevated bilirubin necessitates withdrawal regardless of laboratory values.

[b] Details provided in Section 11.2.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

[c] For subjects with perinatal asphyxia, if initial and peak LFT elevation occurs within 5 days after birth, and if the time course of LFT elevation is compatible with hepatic injury due to perinatal asphyxia (ie, peak LFT elevation within few days after birth, and subsequent normalization until up to day 14 after birth): in case AST, ALT or ALP elevation ≥5x ULN occurs within 5 days after birth in patients with perinatal asphyxia and suspected hepatic hypoxic injury, study drug must be discontinued and LFTs retested within 24 hours. If AST, ALT and ALP values confirmed <5x ULN, the subject may restart study drug after consultation with and approval by the Medical Monitor.

11.2.1.1 Consultation with Medical Monitor and local hepatologist

Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours, and the subject must be discussed with the Medical Monitor as soon as possible. If applicable, the subject may also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist or neonatologist with relevant expertise. If determined necessary, this discussion should be followed by a full assessment (see Section 11.2.1.3) and SAE report (if applicable).

11.2.1.2 Immediate action: determination of IMP discontinuation

All PDILI events require immediate action, testing, and monitoring.

The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of IMP (followed by immediate investigation) to immediate and permanent discontinuation (see Section 6.3.1 and Table 11–3 for details).

When IMP is discontinued, all concomitant medications that are not medically necessary should also be discontinued. The Investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

11.2.1.3 Testing: identification/exclusion of alternative etiology

The measurements and additional information recommended for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are detailed in Table 11–4 (laboratory measurements) and Table 11–5 (additional information). Recommended testing is at the discretion of the Investigator and should be individualized appropriately based on clinical situation.

Results of the laboratory measurements and information collected are to be submitted to the Sponsor on the corresponding eCRF. If the medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable.

All blood samples will be tested locally.

Table 11–4 shows the PDILI laboratory measurements recommended to be assessed.

Table 11–4: Recommended PDILI laboratory measurements[a]

Virology-related (virology tests dependent on local vaccination schedule)	HSV blood PCR (or other testing: HSV IgM, viral culture of blood or CSF, CSF PCR)
	Enterovirus blood PCR (or other testing)
	Hepatitis A IgM antibody[b]
	Hepatitis E IgM antibody[b]
	Hepatitis C IgM[b]
	HBsAg[b]
	Cytomegalovirus testing (culture or polymerase chain reaction) of saliva/urine
	Epstein-Barr viral capsid antigen IgM antibody
Hematology	Eosinophil count
Urinalysis	Toxicology screen
Chemistry	Amylase
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
	Lactate, pyruvate (mitochondrial screen)
	Plasma acylcarnitine profile (fatty acid oxidation defects)
	Ferritin (screen for gestational alloimmune liver disease [neonatal hemochromatosis])
	Confirm newborn screening results (galactosemia and tyrosinemia)
	Serum amino acid profile (urea cycle and metabolic)
Additional	Prothrombin time/INR

CPK=creatine phosphokinase; CSF=cerebrospinal fluid; HBsAg=hepatitis B virus surface antigen; HSV=herpes simplex virus; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PCR=polymerase chain reaction; PDILI=potential drug-induced liver injury

[a] Recommended testing is at the discretion of the Investigator and should be individualized appropriately based on clinical situation

[b] Maternal viral hepatitis status may be considered

Table 11–5 shows the additional PDILI information to be collected:

Table 11–5: PDILI information to be collected

New or updated information
Concomitant medications prescription with dosages and dates should be included.
Pertinent medical history, including the following: • Adverse reactions to drugs • Allergies • Relevant family history or inheritable disorders (eg, Gilbert's syndrome, alpha-1 antitrypsin deficiency)
The appearance or worsening of clinical symptoms of hepatitis or hypersensitivity
Recent clinically significant hypotension or hypoxemia with compromised cardiopulmonary function
Results of liver imaging or liver biopsy, if done
Results of any specialist or hepatology consult, if done
Results of Echocardiogram (for evaluation of potential cardiac dysfunction) and abdominal ultrasound with Doppler (vascular and anatomic), if done
Any postmortem/pathology reports

PDILI=potential drug-induced liver injury

11.2.1.4 Follow-up evaluation

Potential drug-induced liver injury events require follow-up monitoring as described in Table 11–5. Monitoring should continue until liver chemistry values normalize, stabilize, or return to Baseline. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

11.3 Other safety measurements

11.3.1 Physical and neurological examinations

Physical and neurological examinations will be performed at study timepoints described in Table 5–1 and Table 5–2 for the Exploratory and Confirmatory Cohorts, respectively; and in Table 5-3 during the BRV Extension Period and Safety Follow-Up Period for both the Exploratory and Confirmatory Cohorts. Physical and neurological examinations will be performed by a medically qualified clinician. The physical examinations will include a check for the presence of skin rash and skin hypersensitivity.

Physical and neurological assessments for subjects with HIE will also include the Sarnat scale, a classification scale for HIE with grading based on clinical presentation, EEG findings, the presence of seizures, and the duration of illness. The Sarnat grading scale comprises 6 components: alertness, muscle tone, seizures, pupils, respiration, and duration assessed together to provide 3 stages (Grade I [mild]; Grade II [moderate]; Grade III [severe]) of HIE (Sarnat and Sarnat, 1976).

Clinically significant new or worsened abnormalities must be reported as AEs.

11.3.2 Medical history including Apgar score

The Apgar score describes the condition of the newborn infant immediately after birth (Papile, 2001) and, when properly applied, is a tool for standardized assessment. It also provides a mechanism to record fetal-to-neonatal transition. Apgar score is collected routinely at birth and the data will be used as part of the medical history for the subject.

The Apgar score comprises 5 components: heart rate, respiratory effort, muscle tone, reflex irritability, and color, each of which is given a score of 0, 1, or 2. The score is reported at 1 and 5 minutes after birth. The Apgar score continues to provide convenient shorthand for reporting the status of the newborn infant and the response to resuscitation (Committee on Obstetric Practice, ACOG; American Academy of Pediatrics; Committee on Fetus and Newborn, ACOG, 2006).

11.3.3 Vital signs

Vital sign measurements, including systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate (including apneas), oxygen saturation (pulse oximetry), and body temperature, should be measured at the study timepoints as described in Table 5–1 and Table 5–2 for the Exploratory and Confirmatory Cohorts, respectively; and in Table 5-3 during the BRV Extension Period and Safety Follow-Up Period for both the Exploratory and Confirmatory Cohorts.

11.3.4 Biometric parameters

Biometric parameters, including length, body weight and head circumference, will be measured at the study timepoints as described in Table 5–1 and Table 5–2 for the Exploratory and Confirmatory Cohorts, respectively; and in Table 5-3 during the Safety Follow-Up Period for both the Exploratory and Confirmatory Cohorts. Head circumference Baseline measurement should be taken within 7 days prior to drug administration, or at birth for subjects ≤7 days old.

11.3.5 N-PASS

The psychometric parameters, including N-PASS, will be measured at the study timepoints as described in Table 5–1 and Table 5–2 for the Exploratory and Confirmatory Cohorts, respectively; and in Table 5-3 during the BRV Extension Period and Safety Follow-Up Period for both the Exploratory and Confirmatory Cohorts.

The N-PASS was developed as a clinically relevant tool to assess ongoing or acute pain in neonates and infants, as well as sedation levels. The 5 indicators are: (1) crying/irritability (silent cry observed in the intubated infant is scored as a cry), (2) behavior/state, (3) facial expression, (4) extremities/tone, and (5) vital signs. Points are added to the preterm infant's pain score to approximate the normal response of a full-term infant. These points were derived from the Premature Infant Pain Profile pain assessment tool (Stevens et al, 1996).

Gestational age groups are <28 weeks (3 points), 28 to 31 weeks (2 points), 32 to 35 weeks (1 point), and >35 weeks (0 points). Scores range from 0 to 13. Behavioral state as a modifier was not included in the development of N-PASS, as it was designed initially for ongoing pain assessment (Hummel et al, 2010).

11.3.6 Video-EEG Parameters

Video-EEG monitoring performed during the Evaluation Period will be assessed for the subject's reactivity, in addition to the interpretation of the N-PASS in terms of sedation status.

11.3.7 HIE (Thompson score)

The Thompson score will be used to measure the severity of HIE for subjects with HIE at the timepoints described in Table 5–1 and Table 5–2 for the Exploratory and Confirmatory Cohorts, respectively.

The Thompson score is derived from 9 aspects of the neurological examination of infants with HIE: the total score ranges from 0 to 22 and the kappa coefficient is 0.87 (Thompson et al, 1997). This score allows a more precise description of infants than "mild", "moderate" or "severe" and recognizes the prognostic significance of mixed signs within these 3 categories. In normothermic infants, a maximum score >10 during the first 7 days of life predicts an abnormal outcome with 100% sensitivity and 61% specificity (Thompson et al, 1997).

11.3.8 Withdrawal and rebound phenomena

Withdrawal and rebound phenomena will be assessed by observing any AEs experienced by subjects following the cessation of BRV administration. These AEs will be reported by the Investigators, and any AEs relating to BRV withdrawal will be used for the analysis of withdrawal and rebound phenomena. Withdrawal and rebound phenomena, if any, will be captured from data collected at the end of BRV exposure for subjects in both the Exploratory and Confirmatory Cohorts.

11.3.9 Mechanical ventilation

Numbers and percentage of subjects requiring mechanical ventilation will be recorded from Baseline through the 48-hour Evaluation Period for the Exploratory Cohort and the 96-hour Evaluation Period for the Confirmatory Cohort.

Duration of mechanical ventilation will be recorded over the Evaluation Period.

11.3.10 Bayley Scales of Infant and Toddler Development, Third Edition

The Bayley-III scales will be used in this study. The data collected will not be used for analysis, but as the Baseline for subjects who are entering the long-term study.

The Bayley-III scales are recognized internationally as one of the most comprehensive developmental assessment instruments (Sattler and Hoge, 2006) used to examine the major facets of a young child's development (Bayley, 2006). The Bayley-III scales are a standardized, individually administered adaptive assessment that measures the developmental functioning of infants and young children from 1 month to 42 months of age (Bayley, 2006). The Bayley-III scales measure cognitive, language, motor, social-emotional, and adaptive.

The Bayley-III scales are an individually administered adaptive assessment that presents children with situations and tasks designed to produce an observable set of behavioral responses. They consist of a cognitive scale, a language composite scale with receptive and expressive language subscales, a motor composite scale with fine and gross motor subscales to be completed by the Investigator or designee, a social-emotional scale, comprising social-emotional competence, and sensory processing, and an adaptive behavior scale, which assesses the attainment of skills necessary for the development of independence, to be completed by the neonate's parent(s) or caregiver.

The Bayley-III scales will be completed before the subject enters the long-term study (at EPV 2) and again in the long-term study for subjects enrolled in countries where a validated translation of the scale is available in the local language.

12 STUDY MANAGEMENT AND ADMINISTRATION

12.1 Adherence to protocol

The Investigator should not deviate from the protocol. However, the Investigator should take any measure necessary in deviation from or not defined by the protocol to protect clinical study subjects from any immediate hazard to their health and safety. In this case, this action should be taken immediately, without prior notification of the regulatory authority, IEC, or Sponsor.

After implementation of such a measure, the Investigator must notify the Clinical Project Manager of the Sponsor within 24 hours and follow any local regulatory requirements.

12.2 Monitoring

Monitoring of the study will be delegated by UCB to a CRO. The CRO will monitor the study to meet the CRO's monitoring Standard Operating Procedures (SOPs), ICH-GCP guideline, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate.

The Investigator and his/her staff are expected to cooperate with UCB (or designee) and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information. The Investigator(s)/institution(s) will permit direct access to source data/documents for study-related monitoring, audits, IEC review, and regulatory inspection(s).

The Investigator will allow UCB (or designee) to periodically review the eCRF entries against the corresponding source documents (eg, hospital and laboratory records for each study participant). Monitoring visits will provide UCB (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of eCRFs, ensure that all protocol requirements, applicable authorities' regulations, and Investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

12.2.1 Definition of source data

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes). Printouts of eCRF screens are not considered acceptable source documents.

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records or other printouts, completed scales, quality of life questionnaires, or video, for example. Source documents should be kept in a secure, limited access area.

Apart from the VEEG, other source documents that may be computer generated and stored electronically must be printed for review by the monitor. Once printed, these copies should be signed and dated by the Investigator and become a permanent part of the subject's source

documents. The Investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

12.2.2 Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, subject files, recordings from automated instruments, tracings [VEEG], laboratory notes). All data reported on the eCRF should be supported by source documents, unless otherwise specified in Section 12.2.1.

12.3 Data handling

12.3.1 Case Report form completion

The Investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRFs and in all required reports.

Any change or correction to the eCRF after saving must be accompanied by a reason for the change.

Corrections made after the Investigator's review and approval (by means of a password/electronic signature) will be reapproved by the Investigator.

The Investigator should maintain a list of personnel authorized to enter data into the electronic eCRF.

Detailed instructions will be provided in the eCRF Completion Guidelines.

12.3.2 Database entry and reconciliation

Case Report forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. This study will be performed using remote data capture. The data are entered into the eCRFs once and are subsequently verified if the study is performed using electronic data capture.

An electronic audit trail system will be maintained within the CDMS to track all data changes in the database once the data have been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

12.3.3 Subject Screening and Enrollment log/Subject Identification Code list

The subject's screening and enrollment will be recorded in the Subject Screening and Enrollment Log.

The Investigator will keep a Subject Identification Code list. This list remains with the Investigator and is used for unambiguous identification of each subject.

The subject's consent and enrollment in the study must be recorded in the subject's medical record. These data should identify the study and document the dates of the subject's participation.

12.4 Termination of the study

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the Investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IEC should also be informed and provided with reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of all unused BRV and other material in accordance with UCB procedures for the study.

12.5 Archiving and data retention

The Investigator will maintain adequate records for the study, including eCRFs, medical records, laboratory results, Informed Consent documents, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

All essential documents are to be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (Committee for Proprietary Medicinal Products [CPMP]/ICH/135/95, 2002 [Section 4.9.5]). The Investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The Investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's trial master file.

12.6 Audit and inspection

The Investigator will permit study-related audits mandated by UCB, after reasonable notice, and inspections by domestic or foreign regulatory authorities.

The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects enrolled have been protected, that enrolled subjects (ie, signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the IMP have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, and IEC SOPs, ICH-GCP, and applicable regulatory requirements.

The Investigator will provide direct access to all study documents, source records, and source data. If an inspection by a regulatory authority is announced, the Investigator will immediately inform UCB (or designee).

12.7 Good Clinical Practice

Noncompliance with the protocol, ICH-GCP, or local regulatory requirements by the Investigator, institution, institution staff, or designees of the Sponsor will lead to prompt action

by UCB to secure compliance. Continued noncompliance may result in the termination of the site's involvement in the study.

13 STATISTICS

A description of statistical methods follows and will be given in more detail in the Statistical Analysis Plan (SAP). In general, descriptive summaries will be used to present the study results overall and by cohorts (Exploratory Cohort and each individual Confirmatory Cohort).

13.1 Definition of analysis sets

Analysis sets will be defined as follows:

- The Pharmacokinetic Per-Protocol Set will consist of all subjects who provide at least 1 measurable plasma sample (with recorded sampling time) on at least 1 post-Baseline visit with documented study drug intake times. This analysis set will be used for the Exploratory Cohort and the Confirmatory Cohort(s).
- The SS will consist of all enrolled subjects who take at least 1 dose of BRV. All safety analyses will be performed on the SS for the Exploratory Cohort and the Confirmatory Cohort(s).
- The Full Analysis Set will be used for the analysis of seizure data (efficacy) and will consist of all subjects in the SS who have a minimum of 2 hours of interpretable VEEG data from both the Baseline period and the first 3 hours of the post-Baseline period after initial BRV treatment.

13.2 General statistical considerations

Descriptive statistics, such as the mean, standard deviation, median, 25th percentile, 75th percentile, minimum value, and maximum value will be provided for quantitative variables. Counts and percentages will be provided for categorical variables. Confidence intervals (CIs) (95%) will be provided for efficacy variables, which will be described in the SAP. Key supporting data will be provided in data listings.

13.3 Pharmacokinetic variable analysis

The PK data, along with the safety data collected from the Exploratory Cohort and the 3 Confirmatory Cohorts, will be reviewed by the DMC. In addition, plasma concentrations of BRV and its metabolites will be monitored and subjected to interpretation on an ongoing basis. The analysis of the PK parameters for the Exploratory and Confirmatory Cohorts will include a sub-analysis for any concomitant use of hypothermia.

13.3.1 Exploratory Cohort

Based on the plasma samples collected for the Exploratory Cohort, relevant PK parameters including AUC, C_{max}, volume of distribution, and clearance, will be estimated using noncompartmental methods, with sub-analysis by concomitant use of hypothermia. Clinical interpretation of the tolerability of BRV, as well as plasma concentration data from the Exploratory Cohort, will be used to confirm, or adjust as needed, the maximum recommended dose for the Confirmatory Cohorts.

13.3.2 Confirmatory Cohorts

Plasma concentrations of BRV will be used as described for the PK Exploratory Cohort together with demographic and other variables, to build a population PK model by nonlinear mixed effects modeling. The model will be used for simulating various dosing regimens to establish dosing recommendations as a function of developmental variables. Details of the population PK modeling procedures will be described in a separate Data Analysis Plan.

13.4 Safety analyses

All safety analyses will be presented for the SS. Descriptive summaries will be presented by cohort for AEs, SAEs, physical and neurological examination assessments, laboratory results, heart rate, vital signs, body weight, and head circumference. Subject characteristics related to safety, such as cooling status variables (target low body temperature, age since birth when cooling began, duration of cooling [date and start and stop time of cooling], and timing of cooling in relation to first dose of BRV), rewarming status variables (duration of rewarming [date and start and stop time of rewarming] and timing of rewarming in relation to first dose of BRV), the mother's use of AEDs (including BZD and opiates) at childbirth, N-PASS score, and Thompson score will also be summarized descriptively. The primary cause of seizure (eg, HIE, hemorrhage, or infarction; CNS malformations; CNS infections; undetermined causes) may also be used to categorize the safety review. EEG parameters for the assessment of sedation will also be summarized.

13.5 Planned efficacy analyses

All efficacy parameters will be summarized descriptively.

Video-EEGs will be assessed locally by the Investigator for any medical decisions or medical interventions. Video-EEGs may also be assessed by a blinded, central reader to support Investigators if needed. The final analysis of VEEG outputs will be based solely on the assessment of a central reader. Efficacy parameters will be summarized descriptively (overall [with CIs]) by cohort. All efficacy variables will be analyzed by the primary cause of seizure (HIE, hemorrhage, or infarction; CNS malformations; CNS infections; undetermined causes) and concomitant use of hypothermia, and reported for each subject using data listings.

13.5.1 Analysis of the secondary efficacy variables

The main secondary efficacy variable is as follows:

- Proportion of responders to BRV treatment from Baseline to 3 hours after the initial BRV dose.

  A BRV responder is defined as a subject who achieves the following reduction in seizure burden (ENS in minutes per hour) without need for rescue medication, compared to the seizure burden measured during the Baseline Period immediately prior to BRV administration, evaluated for a 2-hour period starting 1 hour after the start of initial BRV treatment:

– At least 80% reduction in nonsevere seizure burden

(Nonsevere seizure burden is defined as ≤50% seizure activity on VEEG in all 30-minute timespans)

OR

– At least 50% reduction in severe seizure burden

(Severe seizure burden is defined as >50% seizure activity on VEEG in any 30-minute timespan). Timespans of 30 minutes refer to the following intervals within the 2-hour period: 0 to ≤30 minutes, >30 to ≤60 minutes, >60 to ≤90 minutes, and >90 to ≤120 minutes.

For this study, an ENS is defined as an EEG seizure lasting for at least 10 seconds on VEEG. Baseline seizure burden is defined as seizure burden measured on the continuous VEEG (total ENS in minutes per hour) during a period of up to 1 hour immediately prior to the first administration of study drug.

For the Confirmatory Cohorts this means:

- For the analysis of the main secondary efficacy variable, subjects must not have used any rescue medication for the treatment of ENS during the first 3 hours after initiation of BRV treatment to be considered BRV responders.
- For the analysis of the secondary efficacy variables (other than the main secondary efficacy variable) and other efficacy variables, subjects must not have used any rescue medication for the treatment of ENS following the first 3 hours after initiation of BRV treatment to be considered BRV responders.

Additional details will be provided in the SAP.

Descriptive statistics will be presented for the following secondary efficacy variables:

- Proportion of subjects with at least 80% reduction in nonsevere seizure burden from Baseline to 3 hours after the initial BRV treatment
- Proportion of subjects with at least 50% reduction in severe seizure burden from Baseline to 3 hours after the initial BRV treatment
- Absolute reduction in average seizure burden measured by continuous VEEG from Baseline to the end of the 96-hour Evaluation Period
- Percent reduction in average seizure burden measured by continuous VEEG from Baseline to the end of the 96-hour Evaluation Period
- Proportion of BRV responders at the end of the 96-hour Evaluation Period
- Proportion of subjects who are seizure-free (100% reduction in seizure burden from Baseline) at 24 hours following the start of initial BRV treatment, categorized by subjects with nonsevere or severe seizure burden at Baseline
- Time to reduction in seizure burden for BRV responders (defined as the first timepoint when BRV responder criteria are met)
- Seizure freedom at the end of the Down-Titration Period (Confirmatory Cohorts only)

- Rate of at least 50% reduction in ENS frequency per hour from Baseline to the end of the 96-hour Evaluation Period
- Proportion of subjects who are seizure-free by time interval at 3 hours, at 3-hour intervals thereafter through 24 hours, and every 12 hours to 24 hours following the start of the initial BRV treatment
- Absolute difference in clinical seizures at the end of the 24-hour Evaluation Period from Baseline for neonates with motor seizures at the time of inclusion
- Percent difference in clinical seizures at the end of the 24-hour Evaluation Period from Baseline for neonates with motor seizures at the time of inclusion

Historical controls will be matched by age and condition, using comparable standard of care and diagnostic methods. The efficacy of BRV will be evaluated for the main efficacy variable by comparing the 95% CI of the BRV responder rate (with all Confirmatory Cohorts combined) to responder rates for the referenced historical control group. If the BRV lower 95% CI limit is higher than the historical control group responder rate, then BRV would be considered efficacious compared to the historical control group. If the BRV upper 95% CI limit is lower than the historical control group responder rate, then BRV will not be considered efficacious compared to the historical control group. If the BRV 95% CI limits contain the historical control group responder rates, then the results will be considered inconclusive.

13.5.2 Analysis of the other efficacy variables

Descriptive statistics will be presented for the other efficacy variables:

- Absolute reduction from Baseline in seizure burden at evaluation periods of 0 hours to 3 hours, >3 hours to 6 hours, >6 hours to 12 hours, >12 hours to 24 hours, >24 hours to 36 hours, >36 hours to 48 hours, >48 hours to 72 hours, and >72 hours to 96 hours after the start of initial BRV treatment
- Percentage reduction from Baseline in seizure burden at evaluation periods of 0 hours to 3 hours, >3 hours to 6 hours, >6 hours to 12 hours, >12 hours to 24 hours, >24 hours to 36 hours, >36 hours to 48 hours, >48 hours to 72 hours, and >72 hours to 96 hours after the start of initial BRV treatment
- Categorized percentage reduction from Baseline to the end of the 96-hour Evaluation Period in seizure burden (<-25% [worsening], -25% to <25% [no change], 25% to <50%, 50% to <80%, and ≥80%)
- Proportion of BRV responders by time interval at evaluation periods of 0 hours to 3 hours, >3 hours to 6 hours, >6 hours to 12 hours, >12 hours to 24 hours, >24 hours to 36 hours, >36 hours to 48 hours, >48 hours to 72 hours, and >72 hours to 96 hours after the start of initial BRV treatment
- Proportion of subjects who are switched over from BRV to another AED during the 96-hour Evaluation Period
- Proportion of responders to other treatment during the 96-hour Evaluation Period (including at the end of the 96-hour Evaluation Period, and by time intervals: 0 hours to 3 hours, >3 hours to 6 hours, >6 hours to 12 hours, >12 hours to 24 hours, >24 hours to 36 hours,

>36 hours to 48 hours, >48 hours to 72 hours, and >72 hours to 96 hours after the start of initial BRV treatment

(A responder to other treatment is defined as at least 80% reduction in nonsevere seizure burden from start of other treatment to end of other treatment or at least 50% reduction in severe seizure burden from the initiation of other treatment to end of other treatment during the 96-hour Evaluation Period).

13.6 Handling of protocol deviations

Important protocol deviations are deviations from the protocol that could potentially have a meaningful impact on key PK, efficacy, or safety outcomes for an individual subject. The criteria for identifying important protocol deviations and the classification of important protocol deviations will be documented in a protocol-defined specification document. To the extent feasible, rules for identifying important protocol deviations will be defined without review of the data and without consideration of the frequency of occurrence of such deviations. Whenever possible, criteria for identifying important protocol deviations will be implemented algorithmically to ensure consistency in the classification of important protocol deviations across all subjects.

Important protocol deviations will be reviewed as part of the ongoing data cleaning process prior to database lock to confirm exclusion from analysis sets.

13.7 Handling of dropouts or missing data

For subjects who dropped out during the Evaluation Period, the number of hours from the start of the Evaluation Period to the time of withdrawal (in hours) will be considered for analysis. Subjects in the Confirmatory Cohorts who started another AED, increased the dose or frequency of administration of an AED ongoing at the time the first BRV infusion started, or are switched to another AED, or have been administered any rescue medication for the treatment of ENS during the first 3 hours after initiation of BRV treatment will be considered BRV nonresponders.

The impact of missing data on the assessment of the main secondary efficacy variable will be evaluated with sensitivity analyses with further details to be included in the SAP.

No imputation of missing values associated with an individual date or visit is planned for the safety analysis, with the exception of partial date information for AEs and concomitant medications, in order to determine whether they are treatment emergent.

13.8 Planned PK data review and safety data monitoring

13.8.1 Exploratory Cohort

Upon the completion of the Exploratory Cohort, the DMC will be provided with the summaries and the listings of PK and safety data for review to make recommendations concerning the dosing of BRV in the Confirmatory Cohorts (see Section 13.8.3). During the DMC review of PK and safety data, the enrollment of subjects will be on hold.

13.8.2 Confirmatory Cohorts

At least 36 subjects will be enrolled in 3 consecutive Confirmatory Cohorts, each consisting of 12 subjects. A PK and safety data review will be performed after completion each of the cohorts. Both PK and safety summaries and data listings will be generated first for the DMC to review. In

addition, plasma concentrations of BRV and its metabolites will be monitored and subjected to interpretation on an ongoing basis.

During the DMC review of the PK and safety data, the recruitment of subjects for the subsequent Confirmatory Cohorts will continue. The DMC may give a recommendation to stop the study after reviewing the PK and safety data.

13.8.3 DMC and stopping rules

The DMC will consist of 3 voting members, none of whom will be involved in the conduct of the study, either by management or participation.

The DMC will oversee the PK and safety of the study by reviewing the PK and safety data periodically, in order to evaluate the risk-benefit profile in relation to the overall progress of the study. The DMC will make recommendations regarding subject safety and continuance of the study based on the observed risk-benefit of the emerging data; however, no formal statistical stopping rules will be defined. Details will be provided in a DMC charter.

13.9 Determination of sample size

At least 42 evaluable subjects will be enrolled in this study. At least 6 subjects will be enrolled in the Exploratory Cohort and at least 36 subjects will be enrolled in 3 successive Confirmatory Cohorts, each consisting of 12 subjects. At least 2 subjects undergoing hypothermia treatment will be included in the Exploratory Cohort and each of the 3 Confirmatory Cohorts.

Subjects in the Exploratory Cohort might be replaced due to lack of data, as deemed necessary following the review of PK and safety data by the DMC.

No formal sample size calculation has been performed as a single treatment BRV arm is planned for descriptive summary of results and for comparison with the 6 subjects from the Exploratory Cohort. The total number of at least 36 subjects in the Confirmatory Cohorts is expected to provide sufficient evidence of tolerability, safety, and efficacy, as well as good precision for the PK profile of BRV in neonates.

Subjects who drop out or are withdrawn from study participation will not be replaced.

14 ETHICS AND REGULATORY REQUIREMENTS

14.1 Informed consent

The informed consent of the parent(s) or legal representative(s) for the subject must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

When a neonate with repeated EEG seizures is identified, the parent(s) or legal representative(s) will be approached and given written information about the underlying disease and a basic description of the study. This information will be discussed with the parent(s) or legal representative(s). If the parent(s) or legal representative(s) of the subject are interested in study participation, the approved ICF will be provided to them, and they will be given time to read the document. Prior to obtaining informed consent, information should be given in both oral and written form in a language and at a level of complexity understandable to the subject's parent(s) or legal representative(s), by the Investigator (or designee). The parent(s) or legal

representative(s) of each subject will have the opportunity to discuss the study and its alternatives with the Investigator.

Prior to participation in the study, the ICF must be signed and personally dated by the subject's parent(s) or legal representative(s), and by the person who conducted the informed consent discussion (Investigator or designee). The subject's parent(s) or legal representative(s) must receive a copy of the signed and dated ICF. As part of the consent process, the parent(s) or legal representative(s) of each subject must consent to direct access to the subject's medical records for study-related monitoring, auditing, IEC review, and regulatory inspection. An informed consenting process managed via telephone is allowed where applicable per local regulations.

During the Screening, Baseline, Evaluation, and BRV Extension Periods, continuous consent will be ensured by meetings between the Investigator and/or designee and the parent(s) or legal representative(s). The purpose of these meetings will be to discuss the ongoing care of the subject, as well as their continued participation in the study. Parent(s) or legal representative(s) will be informed again that they can withdraw the subject from the study at any time and that the decision will not influence the care of the subject. Continuous consent will be documented in the subjects' medical charts and eCRF. Comprehension of the study and its potential risks is enhanced by this continuous process (Allmark and Mason, 2006) and, thus, a more informed consent is obtained.

If the ICF is amended during the study, the Investigator (or the Sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended ICF by the IEC and use of the amended form.

14.2 Subject identification cards

Upon signing the ICF, the subject's parent(s) or legal representative(s) will be provided with a subject identification card of his/her neonate in the language of the subject's parent(s) or legal representative(s). The Investigator will fill in the subject identifying information and medical emergency contact information. The Investigator will instruct the subject's parent(s) or legal representative(s) to keep the card with him/her at all times.

14.3 Independent Ethics Committees

The study will be conducted under the auspices of an IEC, as defined in local regulations, ICH-GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator/UCB will ensure that an appropriately constituted IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the Investigator/UCB will forward copies of the protocol, ICF, IB, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other subject-related documents to be used for the study to the IEC for its review and approval.

Before initiating the study, the Investigator will have written and dated full approval from the IEC responsible for the protocol.

The Investigator will also promptly report to the IEC all changes in the study, all unanticipated problems involving risks to human subjects or others, and any protocol deviations, to eliminate immediate hazards to subjects.

The Investigator will not make any changes in the study or study conduct without IEC approval, except where necessary to eliminate apparent immediate hazards to the subjects. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the Investigator to obtain an expedited review by the IEC as allowed.

As part of the IEC requirements for continuing review of approved studies, the Investigator will be responsible for submitting periodic progress reports to the IEC (based on IEC requirements), at intervals appropriate to the degree of subject risk involved, but no less than once per year. The Investigator should provide a final report to the IEC following study completion.

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities and all active Investigators in accordance with applicable regulatory requirements. The appropriate IEC will also be informed by the Investigator or the Sponsor, as specified by the applicable regulatory requirements in each concerned country. Where applicable, Investigators are to provide the Sponsor (or its representative) with evidence of such IEC notification.

14.4 Subject privacy

UCB staff (or designee) will affirm and uphold the subject's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the subject number assigned at Screening.

The Investigator agrees that representatives of UCB, its designee, representatives of the relevant IEC, or representatives of regulatory authorities will be allowed to review that portion of the subject's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports for deaths occurring during the study).

14.5 Protocol amendments

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective.

Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by UCB, the IEC, and the regulatory authorities (if required), prior to being implemented.

15 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

Finance, insurance, and publication rights are addressed in the Investigator and/or CRO agreements, as applicable.

16 REFERENCES

Allegaert K, van den Anker J. Neonatal drug therapy: the first frontier of therapeutics for children. Clin Pharmacol Ther. 2015;98:288-97.

Allmark P, Mason S. Should desperate volunteers be included in randomised controlled trials? J Med Ethics. 2006;32:548-53.

Bayley N. Bayley Scales of Infant and Toddler Development. 3rd ed. San Antonio: Pearson Education Inc; 2006.

Boylan GB, Rennie JM, Chorley G, Pressler RM, Fox GF, Farrer K et al. Second-line anticonvulsant treatment of neonatal seizures: a video-EEG monitoring study. Neurology. 2004;62:486-8.

Boylan GB, Rennie JM, Pressler RM, Wilson G, Morton M, Binnie CD. Phenobarbitone, neonatal seizures, and video-EEG. Arch Dis Child Fetal Neonatal Ed. 2002;86:F165-70.

Castro Conde JR, Hernández Borges AA, Doménech Martínez E, González Campo C, Perera Soler R. Midazolam in neonatal seizures with no response to phenobarbital. Neurology. 2005;64:876-9.

Clancy RR, Legido A, Lewis D. Occult neonatal seizures. Epilepsia. 1988;29:256-61.

Committee on Obstetric Practice, ACOG; American Academy of Pediatrics; Committee on Fetus and Newborn, ACOG. ACOG Committee Opinion. Number 333, May 2006 (replaces No. 174, July 1996): The Agpar score. Obstet Gynecol. 2006;107:1209-12.

CPMP/ICH/135/95 Note for guidance on Good Clinical Practice (EMEA) Jul 2002.

European Union Commission ad hoc group. Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use. Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population. 2008; 13.2. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/ethical_considerations_en.pdf.

Food and Drug Administration. Guidance for Industry. Drug-induced liver injury: premarketing clinical evaluation. US Dept of Health and Human Services, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, 07/2009.

Glass HC, Kan J, Bonifacio SL, Ferriero DM. Neonatal seizures: treatment practices among term and preterm infants. Pediatr Neurol. 2012;46:111-5.

Hummel P, Lawlor-Klean P, Weiss MG. Validity and reliability of the N-PASS assessment tool with acute pain. J Perinatol. 2010;30:474-8.

Jullien V, Pressler RM, Boylan G, Blennow M, Marlow N, Chiron C, et al. Pilot evaluation of the population pharmacokinetics of bumetanide in term newborn infants with seizures. J Clin Pharmacol. 2015;56:284-90

Leroux S, Turner MA, Barin-Le Guellec C, Hills H, van den Ankers JN, Kearns GL, et al. Pharmacokinetic Studies in Neonates: The Utility of an Opportunistic Sampling Design. Clin Pharmacokinet. 2015;54:1273–85.

Mizrahi E, Kellaway P. Characterization and classification of neonatal seizures. Neurology. 1987;37:1837-44.

O'Hara K, Wright IM, Schneider JJ, Jones AL, Martin JH. Pharmacokinetics in neonatal prescribing: evidence base, paradigms and the future. 2015;80:1281-8.

Painter MJ, Scher MS, Stein AD, Armatti S, Wang Z, Gardiner JC, et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. N Engl J Med. 1999;341:485-9.

Papile LA. The Apgar score in the 21st century. N Engl J Med. 2001;344:519-20.

Pressler RM, Mangum B. Newly emerging therapies for neonatal seizures. Semin Fetal Neonatal Med. 2013;18:216-23

Pressler RM, Boylan GB, Marlow N, Blennow M, Chiron C, Cross JH. Bumetanide for the treatment of seizures in newborn babies with hypoxic ischaemic encephalopathy (NEMO): an open-label, dose finding, and feasibility phase 1/2 trial. Lancet Neurol. 2015;14:469-77.

Ronen GM, Penney S, Andrews W. The epidemiology of clinical neonatal seizures in Newfoundland: a population-based study. J Pediatr. 1999;134:71-5.

Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. Arch Neurol. 1976;33:696-705.

Sattler JM, Hoge RD. Assessment of children: behavioral, social, and clinical foundations. Fifth ed. La Mesa: Jerome M Sattler; 2006.

Scher MS, Alvin J, Gaus L, Minnigh B, Painter MJ. Uncoupling of EEG-clinical neonatal seizures after antiepileptic drug use. Pediatr Neurol. 2003;28:277-80.

Slaughter L, Patel AD, Slaughter JL. Pharmacological treatment of neonatal seizures: a systematic review. J Child Neurol. 2013;28:351-64.

Stevens B, Johnston C, Petryshen P, Taddio A. Premature Infant Pain Profile: development and initial validation. Clin J Pain. 1996;12:13-22.

Thompson CM, Puterman AS, Linley LL, Hann FM, van der Elst CW, Molteno CD, et al. The value of a scoring system for hypoxic ischaemic encephalopathy in predicting neurodevelopmental outcome. Acta Paediatr. 1997;86:757-61.

Tulloch JK, Carr RR, Ensom MA. A systematic review of the pharmacokinetics of antiepileptic drugs in neonates with refractory seizures. J Pediatr Pharmacol Ther. 2012;17:31-44.

van Rooij LG, van den Broek MP, Rademaker CM, de Vries LS. Clinical Management of Seizures in Newborns: diagnosis and management. Paediatr Drugs. 2013a;15:9-18.

van Rooij LG, Hellström-Westas L, de Vries LS. Treatment of neonatal seizures. Semin Fetal Neonatal Med. 2013b;18:209-15.

Volpe J. Neurology of the newborn. Fifth ed. Philadelphia: Saunders Elsevier; 2008.

Weeke LC, Toet MC, van Rooij LG, Groenendaal F, Boylan GB, Pressler RM, et al. Lidocaine response rate in aEEG-confirmed neonatal seizures: Retrospective study of 413 full-term and preterm infants. Epilepsia. 2016;57(2):233-42.

Zhao W, Hill H, Le Guellec C, Neal T, Mahoney S, Paulus S, et al. Population pharmacokinetics of ciprofloxacin in neonates and young infants less than three months of age. Antimicrob Agents Chemother. 2014;58(11):6572-80.

Zhao W, Jacqz-Aigrain E. Author's reply to Standing et al. Pharmacokinetic studies in neonates: the utility of an opportunistic sampling design. Clin Pharmacokinet. 2015;54:1289-91.

17 APPENDICES

17.1 Protocol Amendment 1

Rationale for the amendment

The primary purpose of this non-substantial amendment is to make LFT ranges specified in the exclusion and withdrawal criteria, as well as the PDILI criteria, required investigations and laboratory measurements more age specific and appropriate for the target patient population. Changes were also made to take into account feedback from investigators on the practical aspects of conducting a clinical study in the neonatal population. In addition, editorial changes were made to the text in order to clarify different aspects of the study design. Administrative changes may not be included in the summary table of changes since they are considered minor.

Modifications and changes

Global changes

- Duration of BRV infusion was specified
- Condition under which BRV treatment should be stopped after a subject completed the Evaluation Period was clarified.
- The Schedule of Assessment was adapted to reflect protocol changes
- Drug dosing diary was introduced for subjects treated with oral BRV at home during the BRV Extension
- Duration of VEEGs performed during the Down-Titration Period was specified
- Exclusion criterion #7 was modified: AST, ALT and ALP values were specified for subjects with perinatal asphyxia
- Numbering of "may" withdrawal criteria" was changed to a consecutive numbering throughout section 6.3
- Withdrawal criterion #6 was modified: AST, ALT and ALP values were specified for subjects with perinatal asphyxia
- Withdrawal criterion #9a was modified (former "may" withdrawal criterion #3): AST, ALT and ALP values were specified for subjects with perinatal asphyxia
- PDILI criterion was aligned with updated exclusion criterion#7, withdrawal criterion #6 and withdrawal criterion #9a (former "may" withdrawal criterion #3)
- Type of syringes used to administer oral BRV during the BRV Extension Period was aligned with those used in Follow-up study N01266
- Timepoint of EPV2 was specified
- Method of PK blood sample collection was specified
- Description of AESI associated with PDILI was aligned with the updated PDILI criterion
- Reporting requirements for PDILI were clarified
- Number of DMC voting members was increased from 3 to 4 members

- Consultation with local hepatologists was modified in case of PDILI
- Description of the testing, laboratory measurements, information to be collected, and investigation of PDILI was modified
- PDILI laboratory measurements were added to cover additional potential causes of PDILI in neonates

Specific changes

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Sections 2.3, 5.1.1, 5.4.2, 7.2 and 8.1.3	Intravenously administered BRV is bioequivalent to the same dosage given orally in healthy adults when given as a bolus or as a 15-minute infusion	Intravenously administered BRV is bioequivalent to the same dosage given orally in healthy adults when given as a bolus or as an approximately 15-minute infusion	Based on Investigators´ feedback, the duration of infusions was adapted to clinical needs.
Sections 5.1.2, 8.2.3 and Footnote to Table 5-2	If subjects continue to have seizures after 96 hours of BRV administration, BRV administration will be stopped and replaced by another AED.	If subjects do not benefit from BRV treatment after 96 hours of BRV administration, BRV administration will be stopped and replaced by another AED	Condition clarified under which BRV treatment should be stopped after a subject completed the Evaluation Period.
Table 5-1	MDZ infusion	Removed	MDZ treatment removed as it is not considered a study specific assessment but standard of care.
Tables 5-1 and 5-2	Not applicable	Dispense BRV dosing diary	Dosing diary added to allow parents to document the dosing of BRV during the BRV Extension Period, if oral BRV is administered at home.
Footnote to Table 5-1	Not applicable	The BRV dosing diary will be dispensed only if the subject enters the BRV Extension Period	Index j added for clarification of the newly inserted item “Dispense BRV dosing diary”.
Footnote to Table 5-2	Not applicable	The BRV dosing diary will be dispensed only if the subject enters the BRV Extension Period	Index l added for clarification of the newly inserted item “Dispense BRV dosing diary”.
Table 5-3	Not applicable	Review BRV dosing diary	Task added, which is part of the Investigators´ drug accountability.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Table 5-3	VEEG	1-hour VEEG	The duration of video-EEGs recorded during Down-Titration was specified to clearly separate this assessment from the 24-hour continuous video-EEG performed during the Evaluation Period.
Footnote to Table 5-3	Video-EEG will only apply to subjects of the Confirmatory Cohorts who complete the study after the Evaluation Period.	Video-EEG will only apply to subjects of the Confirmatory Cohorts who complete the study after the Evaluation Period. The video-EEG will be recorded for at least 1 hour on the final day of the Down-Titration Period. Additional video-EEGs can be performed at any time during the Down-Titration Period at the investigator´s discretion.	Description of the video-EEG that will be recorded at the end of the Down-Titration Period was specified to clearly separate this assessment from the 24-hour continuous video-EEG performed during the Evaluation Period. Also, adding clarification that the protocol allows other video-EEGs to be performed during the Down-Titration Period at the discretion of the Investigator.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 6.2	7. Subject has 2x upper limit of normal (ULN) of any of the following: aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP), according to the subject's GA and the site's normal range values for the respective GA.	7a. Subject has 2x upper limit of normal (ULN) of any of the following: aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP), with the following exception: For subjects with perinatal asphyxia, elevation of AST, ALT or ALP <5x ULN is acceptable, if initial and peak elevation of liver function tests (LFTs) occurs within 5 days after birth, and the time course of LFT elevation is compatible with hepatic injury due to perinatal asphyxia. The determination of ULN will be based on the subject's GA and the site's normal range values for the respective GA.	Based on Investigators' feedback, LFT values specified were modified to make them more age and indication specific. These changes are also intended to ensure a balanced enrollment of subjects, regardless of the cause/underlying disease of ENS.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 6.3	6. Subject has 3x ULN of any of the following: AST, ALT, and ALP, according to the subject's GA and the site's normal range values for the respective GA.	6a. Subject has AST, ALT or ALP values 3x ULN, with the following exception: For subjects with perinatal asphyxia, elevation of AST, ALT or ALP <5x ULN is acceptable for continuation in the study, if initial and peak elevation of LFTs occurs within 5 days after birth, and if the time course of LFT elevation is compatible with hepatic injury due to perinatal asphyxia (ie, peak LFT elevation within a few days after birth, and subsequent normalization until up to day 14 after birth). In case AST, ALT or ALP elevation ≥5x ULN occurs within 5 days after birth, study drug must be discontinued and LFTs retested within 24 hours. If AST, ALT and ALP are confirmed to be <5x ULN, the subject may restart study drug after consultation with and approval by the Medical Monitor. The determination of ULN will be based on the subject's GA and the site's normal range values for the respective GA.	Based on Investigators' feedback, LFT values specified in withdrawal criterion #6 were adapted in accordance with exclusion criteria changes (see Section 6.2).

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 6.3	1. Subject experiences prolongation of seizure duration, a worsening of seizure burden, or emergence of new seizure type or illness considered by the investigator to require intervention.	7a. Subject experiences prolongation of seizure duration, a worsening of seizure burden, or emergence of new seizure type considered by the investigator to require intervention.	Modified to delete redundant information which is covered by withdrawal criterion #8. Numbering changed to a consecutive numbering throughout section 6.3.
Section 6.3	2. Investigator may withdraw subject due to any medical condition, based on clinical judgment and discretion.	8. Investigator may withdraw subject due to any medical condition, based on clinical judgment and discretion.	Numbering changed to a consecutive numbering throughout section 6.3.
Section 6.3	3. The Investigator may withdraw the subject if AST/ ALT/ ALP levels are between >2x and 3x ULN, according to the subject's GA and the site's normal range values for the respective GA.	9a. Subject has AST, ALT or ALP values between >2x and ≤3x ULN, with the following exception: For subjects with perinatal asphyxia, elevation of AST, ALT or ALP <5x ULN is acceptable for continuation in the study, if initial and peak LFT elevation occurs within 5 days after birth, and if the time course of LFT elevation is compatible with hepatic injury due to perinatal asphyxia (ie, peak LFT elevation within a few days after birth, and subsequent normalization until up to day 14 after birth). The determinations of ULN will be based on the subject's GA and the site's normal range values for the respective GA.	Aligned with changes to exclusion criterion #7 and withdrawal criterion #6. Numbering changed to a consecutive numbering throughout section 6.3.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 6.3	4. Subject has rapidly increasing total bilirubin without requiring or being expected to require phototherapy or exchange transfusion; the subject's withdrawal will be at the discretion of the Investigator.	10. Subject has rapidly increasing total bilirubin without requiring or being expected to require phototherapy or exchange transfusion; the subject's withdrawal will be at the discretion of the Investigator.	Numbering changed to a consecutive numbering throughout section 6.3.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 6.3.1	Subject has AST/ALT/ALP values >3x ULN according to the subject's GA and the site's normal values for that GA.	Subject has AST, ALT or ALP values >3x ULN, with the following exception: For subjects with perinatal asphyxia, elevation of AST, ALT or ALP <5x ULN is acceptable for continuation in the study, if initial and peak LFT elevation occurs within 5 days after birth, and if the time course of LFT elevation is compatible with hepatic injury due to perinatal asphyxia (ie, peak LFT elevation within few days after birth, and subsequent normalization until up to day 14 after birth). In case AST, ALT or ALP elevation ≥5x ULN occurs within 5 days after birth, study drug must be discontinued and LFTs retested within 24 hours. If AST, ALT and ALP are confirmed to be <5x ULN, the subject may restart study drug after consultation with and approval by the Medical Monitor. The determination of ULN will be based on the subject's GA and the site's normal range values for the respective GA.	The PDILI criterion was aligned with changes to exclusion criterion #7, withdrawal criterion#6 and withdrawal criterion #9a (former "may" withdrawal criterion #3).

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 7.2	For subjects who are switched to BRV oral solution, the dose will be measured using the appropriate syringes (1mL and 5mL) with an adaptor able to fit all the bottle sizes.	For subjects who are switched to BRV oral solution, the dose will be measured using the appropriate syringes (1mL, 3mL or 10mL) with an adaptor able to fit all the bottle sizes.	To avoid confusion and the risk of dosing errors in subjects transitioning to Follow-up study N01266, syringes used for the administration of oral BRV were aligned with those used in study N01266.
Section 7.3	Brivaracetam 10mg/mL oral solution will be packaged in 300mL type-III amber glass bottles with child-resistant tamper evident polypropylene screw closures. Syringes of 1mL and 5mL will be provided with an adaptor able to fit all the bottle sizes.	Brivaracetam 10mg/mL oral solution will be packaged in 300mL type-III amber glass bottles with child-resistant tamper evident polypropylene screw closures. Syringes of 1mL, 3mL or 10mL will be provided with an adaptor able to fit all the bottle sizes.	To avoid confusion and the risk of dosing errors in subjects transitioning to Follow-up study N01266, syringes used for the administration of oral BRV were aligned with those used in study N01266.
Sections 7.7 and 8.1.4	Not applicable	Hand out and return of a dosing diary and documentation of drug use during home administration of oral BRV added to the description of the BRV Extension Period (EPV1, EPV2)	Introduction of a dosing diary to facilitate parents´ recording of BRV oral solution administered at home during the BRV Extension Period. Diaries will be returned to the site and reviewed by the site personnel to ensure correct use/dosing of BRV.
Section 7.8.2	For the Exploratory Cohort, with the exception of MDZ as scheduled in the Protocol, if other BZDs are given prior to the first BRV administration, the subjects will be considered BRV nonresponders.	Removed	The Exploratory Cohort will not be analyzed for efficacy. For this reason it is unreasonable to classify subjects as “BRV nonresponders”.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 7.8.3	For the analysis of the key efficacy variables, subjects must not have used >1 dose of rescue medication following the first 3 hours after initiation of BRV treatment to be considered BRV responders.	For the analysis of the key efficacy variables (other than the main efficacy variable) and other efficacy variables, subjects must not have used >1 dose of rescue medication following the first 3 hours after initiation of BRV treatment to be considered BRV responders.	Modified to clarify what is meant by the term "key efficacy variables".
Section 8.1.4	Not applicable	In this case the parent(s) or legal representative(s) will receive a dosing diary to record the home administration of oral BRV.	Introduction of a dosing diary to facilitate parents´ recording of BRV oral solution administered at home during the BRV Extension Period. Diaries will be returned to the site and reviewed by the site personnel to ensure correct use/dosing of BRV.
Sections 8.1.4 and 8.2.4	Extension Period Visit 2 will be performed when the subject enters the long-term study (see Section 8.1.4.2).	Extension Period Visit 2 will be performed on the same day when the subject enters the long-term study (see Section 8.1.4.2).	Modified to clarify that EPV2 will not only be performed if a subject transitions to the Follow-up study N01266 but <u>on that</u> particular day.
Sections 8.1.4.1, 8.1.4.2, 8.2.4.1 and 8.2.4.2	Not applicable	Review of BRV dosing diary (only if oral BRV is administered at home)	Introduction of a dosing diary to facilitate parents´ recording of BRV oral solution administered at home during the BRV Extension Period. Diaries will be returned to the site and reviewed by the site personnel to ensure correct use/dosing of BRV.
Sections 8.1.4.3 and 8.2.4.3	Not applicable	Review of BRV dosing diary	Introduction of a dosing diary to facilitate parents´ recording of BRV oral solution administered at home during the BRV Extension Period.. Diaries will be returned to the site and reviewed by the site personnel to ensure correct use/dosing of BRV.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Sections 8.1.4.4 and 8.2.4.4	Not applicable	Discussion of BRV dosing diary	Introduction of a dosing diary to facilitate parents´ recording of BRV oral solution administered at home during the BRV Extension Period. Diaries will be discussed over the phone to ensure correct use/dosing of BRV.
Sections 8.1.4.2 and 8.2.4.2	The EPV2 will be performed when the subject enters the long-term study.	The EPV2 will be performed on the same day when the subject enters the long-term study.	Modified to clarify that EPV2 will not only be performed if a subject transitions to the Follow-up study N01266 but on that particular day.
Section 8.2.5	Video-EEG	At least a 1-hour video-EEG on the final day of the Down-Titration Period (during the Down-Titration Period, additional video-EEGs can be performed at the investigator´s discretion)	Description of the video-EEG that will be recorded at the end of the Down-Titration Period was specified to clearly separate this assessment from the 24-hour continuous video-EEG performed during the Evaluation Period. Also, adding clarification that the protocol allows other video-EEGs to be performed in the Down-Titration Period at the discretion of the Investigator.
Section 9.1	Pharmacokinetic samples will be obtained either through an existing central line or taken from routinely performed heel-pricks.	Pharmacokinetic samples will be obtained either through a venous or arterial catheter or taken from routinely performed heel-pricks.	Description of the method of blood drawing for the PK analysis was specified based on feedback received from investigators. The former term “existing central line” was too specific to cover all the different possible routes of drawing blood from individual patients.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 11.1.1.3	AST/ALT/ALP >3x ULN according to the subject's GA and the site's normal values for that GA	AST, ALT or ALP values ≥3x ULN according to the subject's GA and the site's normal values for that GA, with the following exception: For subjects with perinatal asphyxia, if initial and peak LFT elevation occurs within 5 days after birth, and if the time course of the elevation of LFT is compatible with hepatic injury due to perinatal asphyxia (ie, peak LFT elevation within few days after birth, and subsequent normalization until up to day 14 after birth) only AST, ALT or ALP elevation ≥5x ULN must be reported as an AE of special interest.	The description of AESI associated with PDILI was aligned with the PDILI criterion specified in section 6.3.1.
Figure 11-1	Not applicable	Is the AE a PDILI event that leads to discontinuation? (see Section 11.2.1)	Information added for consistency with the change made to section 11.1.1.3 (description of AESI associated with PDILI)
Sections 11.1.6 and 13.8.3	The DMC will consist of 3 voting members, none of whom will be involved in the conduct of the study, either by management or participation	The DMC will consist of **4** voting members, none of whom will be involved in the conduct of the study, either by management or participation.	The number of voting DMC members was increased to cover the medical expertise needed to assess PK and safety data for the evaluation of the risk-benefit profile in relation to the overall progress of the study.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 11.2.1.1	Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours, and the subject must be discussed with the Medical Monitor as soon as possible. If applicable, the subject must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 11.2.1.3) and SAE report (if applicable).	Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours, and the subject must be discussed with the Medical Monitor as soon as possible. If applicable, the subject may also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist or neonatologist with relevant expertise. If determined necessary, this discussion should be followed by a full assessment (see Section 11.2.1.3) and SAE report (if applicable).	Modified based on feedback received from Investigators to better reflect the qualification of medical personnel needed and available on a local level to discuss cases of PDILI.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 11.2.1.3	The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are detailed in Table 11-3 (laboratory measurements) and Table 11-4 (additional information). Results of the laboratory measurements and information collected are to be submitted to the Sponsor on the corresponding eCRF. If the medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable. All blood samples will be tested locally. Table 11-3 shows the PDILI laboratory measurements to be assessed.	The measurements and additional information recommended for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are detailed in Table 11-3 (laboratory measurements) and Table 11-4 (additional information). Results of the laboratory measurements and information collected are to be submitted to the Sponsor on the corresponding eCRF. If the medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable. All blood samples will be tested locally. Table 11-3 shows the PDILI laboratory measurements recommended to be assessed.	Additional laboratory tests were included which cover causes of PDILI in neonates. In order to limit the extent of laboratory and other examinations to a minimum, these tests are considered as recommendations and leave it at the Investigator´s discretion to decide which tests/measurements are appropriate within the given situation, taking into consideration the clinical status and medical history of subjects and their mothers.
Section 11.3.6	Video-EEG monitoring will be assessed for the subject's reactivity, in addition to the interpretation of the N-PASS in terms of sedation status.	Video-EEG monitoring performed during the Evaluation Period will be assessed for the subject's reactivity, in addition to the interpretation of the N-PASS in terms of sedation status.	Description of the video-EEG assessed for the subject´s reactivity was specified to clearly separate it from the 1-hour video-EEG recorded on the final day of the Down-Titration Period.

In addition, the following intext tables were modified:

Table 11-2: Required investigations and follow-up for PDILI

Laboratory value		Immediate		Follow-Up	
ALT/ AST/ALP	**Conjugated bilirubin[a]**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN according to the subject's GA and site's normal value	NA	Hepatology consultation. Medical Monitor must be notified within 24 hours (eg, laboratory alert) and subject discussed with Medical Monitor ASAP[b]	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 11.2.1.1); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values.
≥2x and ≤3xULN according to the subject's GA and site's normal value	≥2mg/dL				
NA	≥2mg/dL				

ASAP=as soon as possible; GA=gestational age; HCP=healthcare practitioner; IMP=investigational medicinal product; NA=not applicable; PDILI=potential drug-induced liver injury; ULN=upper limit of normal

a Any requirement for phototherapy or exchange transfusion due to elevated bilirubin necessitates withdrawal regardless of laboratory values.

[b] Details provided in Section 11.2.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

To align the investigations and follow-up for PDILI with the updated exclusion criterion #7, withdrawal criterion #6 and PDILI criterion, Table 11-2 was changed to:

Table 11-2: Required investigations and follow-up for PDILI

Patient population	Laboratory value		Immediate		Follow-Up	
	ALT/ AST/ALP	Conjugated bilirubin[a]	Consultation requirements	Actions	Testing	Evaluation
Subjects without perinatal asphyxia	≥3xULN according to the subject's GA and site's normal value	NA	Hepatology consultation (see Section 11.2.1). Medical Monitor must be notified within 24 hours (eg, laboratory alert) and subject discussed with Medical Monitor ASAP[b]	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 11.2.1.1); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values.
Subjects with perinatal asphyxia[c]	≥5xULN according to the subject's GA and site's normal value	NA				
All subjects	NA	≥2mg/dL				

ASAP=as soon as possible; GA=gestational age; HCP=healthcare practitioner; IMP=investigational medicinal product; NA=not applicable; PDILI=potential drug-induced liver injury; ULN=upper limit of normal

a Any requirement for phototherapy or exchange transfusion due to elevated bilirubin necessitates withdrawal regardless of laboratory values.

[b] Details provided in Section 11.2.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

[c] For subjects with perinatal asphyxia, if initial and peak LFT elevation occurs within 5 days after birth, and if the time course of LFT elevation is compatible with hepatic injury due to perinatal asphyxia (ie, peak LFT elevation within few days after birth, and subsequent normalization until up to day 14 after birth): in case AST, ALT or ALP elevation ≥5x ULN occurs within 5 days after birth in patients with perinatal asphyxia and suspected hepatic hypoxic injury, study drug must be discontinued and LFTs retested within 24 hours. If AST, ALT and ALP values confirmed <5x ULN, the subject may restart study medication after consultation with and approval by the Medical Monitor

Table 11-3: PDILI laboratory measurements

Virology-related (virology tests dependent on local vaccination schedule)	Hepatitis A IgM antibody
	Hepatitis E IgM antibody
	Hepatitis C IgM
	HBsAg
	Cytomegalovirus testing (culture or polymerase chain reaction) of saliva/urine
	Epstein-Barr viral capsid antigen IgM antibody
Hematology	Eosinophil count
Urinalysis	Toxicology screen
Chemistry	Amylase
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
Additional	Prothrombin time/INR

CPK=creatine phosphokinase; HBsAg=hepatitis B virus surface antigen; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PDILI=potential drug-induced liver injury

To include additional laboratory tests which cover causes of PDILI in neonates and to limit the extent of laboratory and other examinations to a minimum, these tests are considered as recommendations and leave it at the Investigator´s discretion to decide which tests/measurements are appropriate within the given situation, taking into consideration the clinical status and medical history of the subject and its mother, Table 11-3 was changed to:

Table 11-3: Recommended PDILI laboratory measurements[a]

Virology-related (virology tests dependent on local vaccination schedule)	HSV blood PCR (or other testing: HSV IgM, viral culture of blood or CSF, CSF PCR)
	Enterovirus blood PCR (or other testing)
	Hepatitis A IgM antibody[b]
	Hepatitis E IgM antibody[b]
	Hepatitis C IgM[b]
	HBsAg[b]
	Cytomegalovirus testing (culture or polymerase chain reaction) of saliva/urine
	Epstein-Barr viral capsid antigen IgM antibody
Hematology	Eosinophil count
Urinalysis	Toxicology screen
Chemistry	Amylase
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
	Lactate, pyruvate (mitochondrial screen)
	Plasma acylcarnitine profile (fatty acid oxidation defects)
	Ferritin (screen for gestational alloimmune liver disease [neonatal hemochromatosis])
	Confirm newborn screening results (galactosemia and tyrosinemia)
	Serum amino acid profile (urea cycle and metabolic)
Additional	Prothrombin time/INR

Table 11-3: Recommended PDILI laboratory measurements[a]

CPK=creatine phosphokinase; CSF=cerebrospinal fluid; HBsAg=hepatitis B virus surface antigen; HSV=herpes simplex virus; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PCR=polymerase chain reaction; PDILI=potential drug-induced liver injury

[a] Recommended testing is at the discretion of the Investigator and should be individualized appropriately based on clinical situation
[b] Maternal viral hepatitis status may be considered

Table 11-4: PDILI information to be collected

New or updated information
Concomitant medications prescription with dosages and dates should be included.
Pertinent medical history, including the following: • Adverse reactions to drugs • Allergies • Relevant family history or inheritable disorders (eg, Gilbert's syndrome, alpha-1 antitrypsin deficiency)
The appearance or worsening of clinical symptoms of hepatitis or hypersensitivity
Recent clinically significant hypotension or hypoxemia with compromised cardiopulmonary function
Results of liver imaging or liver biopsy, if done
Results of any specialist or hepatology consult, if done
Any postmortem/pathology reports

PDILI=potential drug-induced liver injury

For the evaluation of potential cardiac dysfunction in case of PDILI, Table 11-4 was changed to

Table 11-4: PDILI information to be collected

New or updated information
Concomitant medications prescription with dosages and dates should be included.
Pertinent medical history, including the following: • Adverse reactions to drugs • Allergies • Relevant family history or inheritable disorders (eg, Gilbert's syndrome, alpha-1 antitrypsin deficiency)
The appearance or worsening of clinical symptoms of hepatitis or hypersensitivity
Recent clinically significant hypotension or hypoxemia with compromised cardiopulmonary function
Results of liver imaging or liver biopsy, if done
Results of any specialist or hepatology consult, if done
Results of Echocardiogram (for evaluation of potential cardiac dysfunction) and abdominal ultrasound with Doppler (vascular and anatomic), if done
Any postmortem/pathology reports

PDILI=potential drug-induced liver injury

17.2 Protocol Amendment 2

Rationale for the amendment

The primary purpose of this non-substantial amendment is to adapt the definition of the subjects´ age at enrollment based on a request from the European Medicines Agency´s (EMA) Paediatric Committee (PDCO). In addition, editorial changes were made to clarify different aspects of the study design. Administrative and stylistic changes may not be included in the summary table of specific changes since they are considered minor.

Modifications and changes

Global changes

- The definition of the subjects´ age at enrollment was adapted to a request from PDCO
- MDZ treatment in the Exploratory Cohort during the 3-hour interval prior to start of BRV treatment was clarified
- Timepoints for the dispense of BRV for subjects entering the BRV Extension Period were added
- Timepoints for the collection of PK samples were specified
- Number of DMC voting members was decreased from 4 to 3 members
- Sections referring to Monitoring and Source Data were aligned with the updated UCB protocol template
- Sections referring to the treatment with Permitted/Prohibited Concomitant Medication and Rescue Medication were edited for clarification

Specific changes

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Sections 1, 2.3, 5.4.1, 6.1	Subject is male or female, with an age at birth of at least 34 weeks of GA and up to 28 days of postnatal age at the time of enrollment.	Subject is male or female, with an age at birth of 34 weeks to less than 42 weeks of GA and up to 28 days of postnatal age at the time of enrollment.	The definition of the subject age at enrollment was adapted based on a request from PDCO.
Sections 1, 5.1, 7.2	For the Exploratory Cohort (first step), enrolled subjects will receive a therapeutic dose of MDZ (dose of MDZ is at the discretion of the Investigator) prior to receiving BRV.	For the Exploratory Cohort (first step), enrolled subjects will receive one or multiple therapeutic doses of MDZ (dose of MDZ is at the discretion of the Investigator) prior to receiving BRV.	Edited to clarify that MDZ treatment in the Exploratory Cohort during the 3 hours prior to the start of BRV treatment is not limited to a single MDZ dose.
Section 5.1.1	Evaluation Period (in total, 51 hours: 3 hours for the evaluation of MDZ and 48 hours for the evaluation of BRV): Subjects will receive iv MDZ at a therapeutic dose (MDZ dose is at the discretion of the Investigator).	Evaluation Period (in total, 51 hours: 3 hours for the evaluation of MDZ and 48 hours for the evaluation of BRV): Subjects will receive iv MDZ (one or multiple therapeutic doses; MDZ dose is at the discretion of the Investigator).	Aligned with the change described above.
Section 4.2.1	The use of rescue medication will affect the analysis of the key efficacy variables in the different study Cohorts (see Section 7.8.3).	The use of rescue medication will affect the analysis of the key efficacy variables in the different study Cohorts (see Section 13.5.1).	Reference to section 7.8.3 adjusted to the shift of text.
Table 5-1	Not applicable	Dispense BRV for the BRV Extension Period[k]	Row added to indicate BRV dispense at the end of the Evaluation Period (after 48 hours).

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Table 5-1	Not applicable	[k] Dispensing of BRV is only applicable if the subject enters the BRV Extension Period	Footnote k added to further explain the addition of BRV dispensing at the end of the Evaluation Period.
Table 5-2	Not applicable	Dispense BRV for the BRV Extension Period[m]	Row added to indicate BRV is dispensed at the end of the Evaluation Period (after 96 hours).
Table 5-2	Not applicable	[m] Dispensing of BRV is only applicable if the subject enters the BRV Extension Period	Footnote m added to further explain the addition of BRV dispensing at the end of the Evaluation Period.
Table 5-2	[b] If subjects do not benefit from BRV treatment after 96 hours of BRV administration, BRV administration will be stopped and replaced by another AED; however, the subject's participation in the Evaluation Period will continue.	[b] If subjects do not benefit from BRV treatment after 96 hours of BRV administration, BRV administration will be stopped and replaced by another AED; however, the subject's participation in the study will continue.	In the Confirmatory Cohort all subjects will complete the Evaluation Period after 96 hours. Subjects who do not benefit from BRV at this point will enter the Down-Titration and Safety Follow-up Period. The subject´s participation in the "study" will hence continue.
Table 5-3	[g] If the subject enters the long-term study, no medication from N01349 will be dispensed in EPV2. If the subject does not enter the long-term study, BRV from N01349 will be administered for down-titration	[g] If the subject enters the long-term study, no study drug from N01349 will be dispensed in EPV2. If the subject does not enter the long-term study, BRV from N01349 will be administered for down-titration (only applicable to subjects from the Confirmatory Cohorts).	Footnote g aligned with modifications to sections 8.1.4.2 and 8.2.4.2.
Figure 5-4	[a] Switching to another AED or addition of rescue medication is	[a] Switching to another AED or addition of rescue medication	Footnote a aligned with modifications to section 7.8.3.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	only permitted 3 hours after the first BRV administration.	should only occur following 3 hours after the first BRV administration.	
Section 7.8.1	Prior to BRV administration, the following AEDs are permitted during the study: • PB • MDZ (Exploratory Cohort only) For the Exploratory Cohort, subjects will be permitted to receive any concomitant medications at any time during the study after BRV administration as deemed necessary by the Investigator. For the Confirmatory Cohorts, subjects will be permitted to receive AEDs only 3 hours following the first BRV administration. Other concomitant medications will be permitted as deemed necessary by the Investigator.	Concomitant treatment with non-AEDs is permitted for the Exploratory and Confirmatory Cohort(s) at any time throughout the study. Concomitant treatment with AEDs is permitted as follows: **Prior** to first BRV administration: • PB • MDZ (Exploratory Cohort only) **After** first BRV administration: • Any AEDs (including MDZ) – Exploratory Cohort: from first BRV administration – Confirmatory Cohorts: from 3 hours following first BRV administration	Simplified to clarify 1) the concomitant treatment with non-AEDs and AEDs and 2) the treatment of concomitant AEDs relative to the first administration of BRV.
Section 7.8.2	For the Confirmatory Cohorts only, subjects will not be permitted to receive treatments for neonatal seizures (other than the specified PB doses) prior to and for the first 3	For the Exploratory Cohort, subjects will not be permitted to receive treatments for neonatal seizures (other than the specified PB doses and MDZ) prior to the first BRV administration.	Description of prohibited concomitant treatment in the Exploratory Cohort added for clarification.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	hours after the first BRV administration.	For the Confirmatory Cohorts, subjects will not be permitted to receive treatments for neonatal seizures (other than the specified PB doses) prior to and for the first 3 hours after the first BRV administration.	
Section 7.8.3	Rescue medication can be given at any time if considered necessary by the Investigator. **However,** it is prohibited for subjects to receive rescue medication prior to BRV dosing for the Exploratory Cohort (except for MDZ as scheduled in the Protocol) and during the 3 hours after the initial dose of BRV for the Confirmatory Cohorts. If this occurs, subjects will be considered BRV nonresponders. For the Confirmatory Cohorts this means: • For the analysis of the main efficacy variable, subjects must not have used any rescue medication (including BZDs) during the first 3 hours after initiation of BRV treatment to be considered BRV responders.	Rescue medication in this study is considered as any treatment with AEDs. Rescue medication can be given at any time if considered necessary by the Investigator. **However,** during the Evaluation Period rescue medication should not be administered – if possible – in the following time frames: • Prior to BRV dosing for the Exploratory Cohort (except for MDZ as scheduled in the Protocol). • During the first 3 hours after the initial dose of BRV for the Confirmatory Cohorts. If this occurs, subjects will be considered BRV nonresponders.	Edited for clarification. Text about the analysis of the main efficacy variable and key efficacy variables was moved to section 13.5.1 (Analysis of the key efficacy variables).

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	• For the analysis of the key efficacy variables (other than the main efficacy variable) and other efficacy variables, subjects must not have used >1 dose of rescue medication following the first 3 hours after initiation of BRV treatment to be considered BRV responders. A single dose of short-acting BZD as rescue medication is allowed, but only after 3 hours subsequent to the initiation of treatment with BRV.		
Sections 8.1.4 and 8.2.4	Not applicable	For subjects entering the BRV Extension Period, study drug will be dispensed at the end of the Evaluation Period.	Added in conjunction with above described changes to Tables 5-1 and 5-2.
Sections 8.1.4.2 and 8.2.4.2	• BRV administration/dispense (If the subject enters the long-term study, no medication from N01349 will be dispensed in EPV2. If the subject does not enter the long-term study, BRV from N01349 will be administered for down-titration).	• BRV administration/dispense. If the subject enters the long-term study, no study drug from N01349 will be dispensed at EPV2. If the subject does not enter the long-term study, BRV from N01349 will be administered for down-titration (only applicable to subjects from the Confirmatory Cohorts).	Edited for clarification.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 9.1	For the determination of plasma concentrations of BRV, BRV metabolites, and plasma concentrations of concomitant AEDs (PB and PHT), up to 6 blood microsamples (65µL/sample) will be collected per subject in the Exploratory (3 to 6 blood microsamples) and Confirmatory Cohorts (up to 6 blood microsamples) at 3 predetermined timepoints per day. Pharmacokinetic samples will be obtained either through a venous or arterial catheter or taken from routinely performed heel-pricks. Blood for PK samples should be drawn from a line different to that of the BRV infusion. Three PK samples of blood will be collected at the following predetermined timepoints at the first day of the Evaluation Period: 30 to 60 minutes, 2 to 4 hours, and 8 to 12 hours after the start of the most recent BRV infusion. For the Exploratory Cohort the same timepoints apply to the second day of the 48-hour Evaluation Period. For the Confirmatory Cohort(s), the second	For the determination of plasma concentrations of BRV and BRV metabolites, up to 6 blood microsamples (65µL/sample) will be collected per subject in the Exploratory (3 to 6 blood microsamples) and Confirmatory Cohorts (up to 6 blood microsamples) at 3 predetermined timepoints per day. An additional microsample (65µL) will be collected per subject for the determination of plasma concentrations of concomitant AEDs (PB and PHT). Pharmacokinetic samples will be obtained either through a venous or arterial catheter or taken from routinely performed heel-pricks. Blood for PK samples should be drawn from a line different to that of the BRV infusion. Three BRV PK samples of blood will be collected at the following predetermined timepoints at the first day of the Evaluation Period: 30 to 60 minutes, 2 to 4 hours, and 8 to 12 hours after the start of the most recent BRV infusion. For the Exploratory Cohort the same timepoints apply to the second day of the 48-hour Evaluation	Edited for clarification.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	set of 3 PK samples will be collected at the same timepoints on 1 of the other days of the 96-hour Evaluation Period. It will be acceptable if these samples are drawn on different days. The timepoints for the collection of PK samples are described in Table 5–4 for the Exploratory Cohort and in Table 5–5 for the Confirmatory Cohorts. An additional microsample (65µL) will be collected for the determination of plasma concentrations of concomitant AEDs (PB and PHT). The AED PK sample should be collected 3 hours after the start of the initial BRV administration.	Period. For the Confirmatory Cohort(s), the second set of 3 BRV PK samples will be collected at the same timepoints on 1 of the other days of the 96-hour Evaluation Period. It will be acceptable if these samples are drawn on different days. The AED PK sample should be collected 3 hours after the start of the initial BRV administration. The timepoints for the collection of PK samples are described in Table 5–4 for the Exploratory Cohort and in Table 5–5 for the Confirmatory Cohorts.	
Section 11.1.1.2.1	In addition, the following are expected SAEs in babies with HIE:	In addition, the following are anticipated SAEs in babies with HIE:	The term describing SAEs was clarified since SAEs listed are anticipated to occur in babies with HIE independent of exposure to BRV.
Sections 11.1.6 and 13.8.3	The DMC will consist of 4 voting members, none of whom will be involved in the conduct of the study, either by management or participation.	The DMC will consist of 3 voting members, none of whom will be involved in the conduct of the study, either by management or participation.	The Biostatistician initially counted as 1 of the 4 voting DMC members will be supporting the DMC as a subject matter expert but not act as *voting* DMC member. Hence, the number of *voting* DMC members was corrected. Since the 3 voting DMC members are health professionals, the medical expertise covered by the DMC remains unchanged.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 12.2	UCB (or designee) will monitor the study to meet the Sponsor's monitoring SOPs, ICH-GCP guideline, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate. Monitoring of the study may be delegated by UCB to a contract research organization (CRO) or a contract monitor.	Monitoring of the study will be delegated by UCB to a CRO. The CRO will monitor the study to meet the CRO's monitoring Standard Operating Procedures (SOPs), ICH-GCP guideline, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate.	Aligned with the updated UCB protocol template.
Section 12.2.1	Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records or other printouts, completed scales, or quality of life questionnaires, for example. Source documents should be kept in a secure, limited access area.	Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records or other printouts, completed scales, quality of life questionnaires, or video, for example. Source documents should be kept in a secure, limited access area.	Aligned with the updated UCB protocol template.
Section 13.5.1	Not applicable	For the Confirmatory Cohorts this means: • For the analysis of the main efficacy variable, subjects must not have used any rescue medication (including BZDs)	Moved from section 7.8.3.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
		during the first 3 hours after initiation of BRV treatment to be considered BRV responders. • For the analysis of the key efficacy variables (other than the main efficacy variable) and other efficacy variables, subjects must not have used >1 dose of rescue medication following the first 3 hours after initiation of BRV treatment to be considered BRV responders. A single dose of short-acting BZD as rescue medication is allowed, but only after 3 hours subsequent to the initiation of treatment with BRV.	
Figure 11-1	Does the AE meet any of the following? • Potentially related to BRV (see Section 11.1.1.2.1)	Does the AE meet any of the following? • Potentially related to BRV	Reference deleted since AEs described in section 11.1.1.2.1 are observed in babies and in babies with HIE regardless of study drug exposure.

Table 5-4: Schedule for PK Sampling (Exploratory Cohort)Table

Assessment	MDZ	48-hour Evaluation Period					
		Time relative to the start of the latest BRV infusion given per day					
		Day 1[a]			Day 2[ab]		
		30-60min[c]	2-4h	8-12h	30-60min	2-4h	8-12h
BRV PK samples[d]		X	X	X	X	X	X
AED PK sample			X[e]				

AED=antiepileptic drug; BRV=brivaracetam; h=hours; MDZ=midazolam; min=minutes; PK=pharmacokinetic(s)
Note: Blood for PK samples should be drawn from a line different to that of the BRV infusion.
[a] Blood sample collection 8-12 hours is relative to BRV dosing only if BRV is administered once per day. In case of a second BRV dose on the same day, the third blood sample should be collected 30 to 60 minutes after the start of the second BRV infusion.
[b] Blood sampling is only needed on Day 2 if subjects are dosed with BRV on Day 2.
[c] The PK sample should be collected 30 to 60 minutes after the start of the BRV infusion.
[d] The PK sampling timepoints for the first 3 samples of the Exploratory Cohorts are as follows: 30 to 60 minutes, 2 to 4 hours, and 8 to 12 hours after the start of the most recent BRV infusion. The second set of 3 samples will be collected at the same timepoints on the second day of the 48-hour Evaluation Period.
[e] The AED PK sample should be collected 3 hours after the start of the initial BRV administration.

For clarification of timepoints at which PK blood samples will be collected in the Exploratory Cohort, Table 5-4 was changed to

Table 5-4: Schedule for PK Sampling (Exploratory Cohort)

Assessment	48-hour Evaluation Period					
	Time relative to the start of the most recent BRV infusion					
	Day 1			Day 2[a]		
	30-60min[b]	2-4h	8-12h	30-60min	2-4h	8-12h
BRV PK samples[c]	X	X	X	X	X	X
AED PK sample		X[d]				

AED=antiepileptic drug; BRV=brivaracetam; h=hours; MDZ=midazolam; min=minutes; PK=pharmacokinetic(s)
Note: Blood for PK samples should be drawn from a line different to that of the BRV infusion.
[a] Blood sampling is only needed on Day 2 if subjects are dosed with BRV on Day 2.
[b] The first PK sample should be collected 30 to 60 minutes after the start of the BRV infusion.
[c] The BRV PK sampling timepoints for the first 3 samples of the Exploratory Cohorts are as follows: 30 to 60 minutes, 2 to 4 hours, and 8 to 12 hours after the start of the most recent BRV infusion. The second set of 3 samples will be collected at the same timepoints on the second day of the 48-hour Evaluation Period.
[d] The AED PK sample should be collected 3 hours after the start of the initial BRV administration.

Table 5-5: Schedule for PK Sampling (Confirmatory Cohorts)

Assessment	96-hour Evaluation Period											
	Time relative to the start of the latest BRV infusion given per day											
	Day 1[a]			Day 2[a]			Day 3[a]			Day 4[a]		
	30-60min[c]	2-4 h	8-12 h	30-60min	2-4 h	8-12 h	30-60min	2-4 h	8-12 h	30-60min	2-4 h	8-12 h
BRV PK samples[b]	X	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
AED PK sample		X[d]										

AED=antiepileptic drug; BRV=brivaracetam; h=hours; PK=pharmacokinetic(s); min=minutes; (X)=optional for that day

Note: Blood for PK samples should be drawn from a line different to that of the BRV infusion.

[a] Blood sample collection 8-12 hours is relative to BRV dosing only if BRV is administered once per day. In case of a second BRV dose on the same day, the third blood sample should be collected 30 to 60 minutes after the start of the second BRV infusion.

[b] The PK sampling timepoints for the first 3 samples of the Confirmatory Cohorts are as follows: 30 to 60 minutes, 2 to 4 hours, and 8 to 12 hours after the start of the most recent BRV infusion. The second set of 3 PK samples will be collected within the same timeframes as the first set on one of the following days: either Day 2 (post-24 hours), OR Day 3 (post-48 hours) OR Day 4 (post-72hours). It is acceptable if these samples are drawn on different days.

[c] The first PK sample will be collected 30 to 60 minutes after the start of the BRV infusion.

[d] The AED PK sample should be collected 3 hours after the start of the initial BRV administration.

For clarification of timepoints at which PK blood samples should be collected in the Confirmatory Cohorts, Table 5-5 was changed to

Table 5-5: Schedule for PK Sampling (Confirmatory Cohorts)

Assessment	96-hour Evaluation Period											
	Time relative to the start of the most recent BRV infusion											
	Day 1			Day 2			Day 3			Day 4		
	30-60min[a]	2-4 h	8-12 h	30-60min	2-4 h	8-12 h	30-60min	2-4 h	8-12 h	30-60min	2-4 h	8-12 h
BRV PK samples[b]	X	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
AED PK sample		X[c]										

AED=antiepileptic drug; BRV=brivaracetam; h=hours; PK=pharmacokinetic(s); min=minutes; (X)=optional for that day

Note: Blood for PK samples should be drawn from a line different to that of the BRV infusion.

[a] The first PK sample will be collected 30 to 60 minutes after the start of the BRV infusion.

[b] The BRV PK sampling timepoints for the first 3 samples of the Confirmatory Cohorts are as follows: 30 to 60 minutes, 2 to 4 hours, and 8 to 12 hours after the start of the most recent BRV infusion. The second set of 3 PK samples will be collected within the same timeframes as the first set on one of the following days: either Day 2 (post-24 hours), OR Day 3 (post-48 hours) OR Day 4 (post-72hours). It is acceptable if these samples are drawn on different days.

[c] The AED PK sample should be collected 3 hours after the start of the initial BRV administration.

17.3 Protocol Amendment 3

Rationale for the amendment

The primary purpose of this non-substantial amendment is to incorporate feedback and clarification based on IEC and Investigator requests. Administrative and stylistic changes may not be included in the summary table of specific changes since they are considered minor.

Modifications and changes

Global changes

- Modification of safety lab panel
- Alignment of language presented in the Pediatric Investigation Plan
- Safety labs from third parties considered as medical history
- Clarification of timepoints for weight measurements
- Alignment of ALP measurement
- Definition of BRV nonresponders
- Use of VEEG traces recorded before parents consented for the determination of the Baseline VEEG
- Continuous VEEG to be allowed interruption
- PB treatment permitted to start prior to the subject's admission into the study site, as well as allowed to be administered in 3 separate doses
- Recommendations for subjects discontinuing BRV treatment
- Blood sampling guidance
- Adverse event recording clarification
- Allowance of telephone consenting process
- Clarification about the transition from N01349 to follow-up study N01266
- Change in serious adverse event contact information
- Dosing and data modeling clarification

Specific changes

Section Impacted	Key components of previous text	Key components of amended text	Rationale
STUDY CONTACT INFORMATION	[redacted], [redacted] 8010 Arco Corporate Drive, [redacted] [redacted] Raleigh, NC 27617 [redacted] [redacted]	[redacted] UCB BioSciences, Inc. 8010 Arco Corporate Drive, [redacted] Raleigh, NC 27617 [redacted] [redacted]	The clinical trial biostatistician has changed.
STUDY CONTACT INFORMATION	[redacted] Neonatal Neurologist	[redacted] Pediatric Neonatologist	A member of the DMC has changed.
SERIOUS ADVERSE EVENT REPORTING	Europe: +32 2 386 24 21 DS_ICT@ucb.com	Europe: +32 238 66561 PSRapidalert@ucb.com	Change in serious adverse event contact information.
Section 1	As the patient population of neonates with electroencephalographic neonatal seizures (ENS) is limited, N01349 is designed with a 2-step approach to allow for confirmation (or adjustment) of dosing based on results from the first step (Exploratory Cohort) and evaluation of BRV efficacy in the second step (Confirmatory Cohorts).	As the patient population of neonates with electroencephalographic neonatal seizures (ENS) is limited, N01349 is designed with a 2-step approach to allow for confirmation (or adjustment) of BRV dosing based on results from the first step (Exploratory Cohort) and evaluation of BRV efficacy in the second step (Confirmatory Cohorts).	Specification of drug dosing.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 1	Subjects will first receive 1 or 2 doses of phenobarbital (PB) (total therapeutic administered dose of 20 to 40mg/kg; dosing regimen at the Investigator's discretion).	Subjects will first receive 1 to 3 doses of phenobarbital (PB) (total therapeutic administered dose of 20 to 40mg/kg; dosing regimen at the Investigator's discretion).	Based on Investigator feedback, the total PB dose of 20 to 40mg/kg may be administered over 3 separate doses.
Section 1	For the Exploratory Cohort (first step), enrolled subjects will receive one or multiple doses of a therapeutic dose of midazolam (MDZ) (dose of MDZ is at the discretion of the Investigator) prior to receiving BRV.	For the Exploratory Cohort (first step), enrolled subjects will receive one or multiple doses or continuous infusion of a therapeutic dose of midazolam (MDZ) (dose and dosing frequency of MDZ are at the discretion of the Investigator) prior to receiving BRV.	Dose frequency and continuous infusion are also at the discretion of the Investigator.
Section 1	This treatment represents the first use of BRV in neonates (0.5mg/kg bid), which is 4-fold less than the highest dosage of 4mg/kg/day that has been used previously in study N01263 (subjects ≥1 month old to <16 years of age; Section 2.2).	This treatment represents the first use of BRV in neonates (0.5mg/kg bid), which is 4-fold less than the highest dosage of 4mg/kg/day that has been used previously in study N01263 (Section 2.2). In BRV PK modeling studies CL0187 and N01331, PK profiles were extrapolated allometrically to the neonatal age group from the pediatric data collected in N01263 (age range of ≥1 month to <16 years). A total of 600 samples from 96 subjects were used for this modeling. The results of this modeling suggest that a dosing	Age specification not needed. Data modeling details added.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
		regimen of 2mg/kg bid in pediatric subjects ≥1 month to <16 years of age with a maximum of 100mg bid would result in plasma concentration profiles similar to those attained in older children and adults who received therapeutic doses of BRV (up to 100mg bid). Since extrapolation of data from subjects ≥1 month to subjects ≤2 weeks may be imprecise due to variability in ontogeny in the metabolic and excretory functions in neonates, actual PK measurements conducted in the Exploratory Cohort of N01349 will be used to confirm the relationship between dose and plasma concentration in neonates.	
Section 1	The iv dose and dosing frequency of BRV selected for the Confirmatory Cohorts will be determined by the evaluation of BRV plasma concentrations from the Exploratory Cohort to be within the range of plasma concentrations observed in children ≥1 month old who received BRV 4mg/kg/day.	The iv dose and dosing frequency of BRV selected for the Confirmatory Cohorts will be determined by the evaluation of BRV plasma concentrations from the Exploratory Cohort, as well as by the PK modeling of N01263 data described above, to be within the range of plasma concentrations observed in children ≥1 month old who received BRV 4mg/kg/day.	Per agency recommendation, clarification that BRV dose and dosing frequency is also determined by previous PK modeling of N01263 data.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Sections 1, 5.1, 5.4.2	Not applicable	The recommendation to confirm or adjust the originally calculated BRV dose of the Confirmatory Cohorts of study N01349 will be given by the DMC after review of PK and safety data of the Exploratory Cohort.	Clarification of DMC participation in determination of Confirmatory Cohort dosage.
Sections 1, 4.2.1, 10.1, 13.5.1	Not applicable	Timespans of 30 minutes refer to the following intervals within the 2-hour period: 0 to ≤30 minutes, >30 to ≤60 minutes, >60 to ≤90 minutes, and >90 to ≤120 minutes.	Clarification of 30-minute time intervals.
Section 4.2.1	• Absolute reduction and proportion of clinical seizures correlated with continuous VEEG from Baseline to the end of the 96-hour Evaluation Period, and each of the 3-hour intervals	• Absolute and percent difference in clinical seizures at the end of the 24-hour Evaluation Period from Baseline for neonates with motor seizures at the time of inclusion	Alignment of language presented in the Pediatric Investigation Plan.
Section 4.3	• Mechanical ventilation: – Number and percentage of subjects requiring ventilation during treatment with BRV over the Evaluation Period – Number and percentage of subjects requiring ventilation during treatment with other	• Mechanical ventilation: – Number and percentage of subjects requiring mechanical ventilation during the Evaluation Period – Duration of mechanical ventilation during the Evaluation Period	Alignment of language presented in the Pediatric Investigation Plan.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	AEDs over the Evaluation Period – Absolute and relative duration of ventilation during the treatment with BRV – Absolute and relative duration of ventilation during the treatment with other AEDs		
Section 5.1	For the Exploratory Cohort (first step), enrolled subjects will receive one or multiple therapeutic doses of MDZ (dose of MDZ is at the discretion of the Investigator) prior to receiving BRV.	For the Exploratory Cohort (first step), enrolled subjects will receive one or multiple therapeutic doses or continuous infusion of MDZ (dose and dosing frequency of MDZ are at the discretion of the Investigator) prior to receiving BRV.	Dose frequency and continuous infusion are also at the discretion of the Investigator.
Section 5.1	The iv dose of BRV selected for the Confirmatory Cohorts will be determined by the evaluation of BRV plasma concentrations from the Exploratory Cohort to be within the range of plasma concentrations observed in children ≥1 month old who received 4mg/kg/day.	The iv dose of BRV selected for the Confirmatory Cohorts will be determined by the evaluation of BRV plasma concentrations from the Exploratory Cohort, as well as by previous PK modeling of N01263 data, to be within the range of plasma concentrations observed in children ≥1 month old who received 4mg/kg/day.	Per agency recommendation, clarification that BRV dose and dosing frequency is also determined by previous PK modeling of N01263 data.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 5.1	Not applicable	The recommendation to confirm or adjust the originally calculated BRV dose of the Confirmatory Cohorts of study N01349 will be given by the DMC after review of PK and safety data of the Exploratory Cohort.	Clarification of DMC participation in determination of Confirmatory Cohort dosage.
Section 5.1	Not applicable	Blood samples for routine assay of hematology, biochemistry, liver enzymes, and endocrinology will be collected in line with Section 13.2 of the "Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population" (European Union Commission ad hoc group, 2008), and according to the schedule of study assessments in Table 5-1 (Exploratory Cohort) and Table 5-2 (Confirmatory Cohorts). The local laboratories will perform the routine analysis of blood samples. For Screening and determination of eligibility, use of laboratory data acquired prior to Screening per standard of care inside or outside the study site within 36 hours prior to the start of the Evaluation Period is allowed.	Movement of text from Section 5.1.2 to Section 5.1, since information applied to both cohorts. Blood sampling guidance. Laboratory assessments are allowed to be administered at a separate site. Allowance of use of standard of care laboratory data.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 5.1	Not applicable	Paragraphs 17 to 21 were moved from Section 5.1.2 to Section 5.1.	Text was moved to Section 5.1 since information applied to both cohorts.
Section 5.1	The independent central reader will be blinded from concomitant AED treatment that the subject has received.	The independent central reader will be blinded from site-specific information and the subject's medical history.	Blinding clarification.
Section 5.1	Not applicable	Interruption of the VEEG is allowed up to 30 minutes per day. Depending on medical needs related to standard of care (eg, MRIs to be performed), interruptions longer than this are acceptable. However, every effort should be made to avoid VEEG interruption of the 2-hour Baseline VEEG and during the first 3 hours after the start of the initial BRV administration for the Confirmatory Cohorts.	Based on Investigator feedback, neonates with hypoxic ischemic encephalopathy may disconnect from the EEG for other assessments, therefore interruptions exist and are allowed.
Section 5.1.1	For the Exploratory Cohort, at least 6 subjects who do not have adequate seizure control after receiving 1 or 2 doses of PB (total therapeutic administered dose of 20 to 40mg/kg; dosing regimen at the Investigator's discretion) will be enrolled and dosed with one or multiple therapeutic doses of MDZ (dose of MDZ is at the discretion of the	For the Exploratory Cohort, at least 6 subjects who do not have adequate seizure control after receiving 1 to 3 doses of PB (PB treatment may have started prior to the subject's admission into the study site; total therapeutic administered dose of 20 to 40mg/kg; dosing regimen at the Investigator's discretion) will be enrolled and dosed with one or	Dose frequency and continuous infusion are also at the discretion of the Investigator. Based on Investigator feedback, the total PB dose of 20 to 40mg/kg may be administered over 3 separate doses. PB treatment is permitted to start prior to subject's admission into the study.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	Investigator). Phenobarbital treatment must be discontinued prior to entering the Evaluation Period. Approximately 3 hours after the MDZ dosing, an initial low dose of BRV (0.5mg/kg [bid]) will be administered according to the standard of care.	multiple therapeutic doses of MDZ (dose and dosing frequency of MDZ are at the discretion of the Investigator). Phenobarbital treatment must be discontinued prior to entering the Evaluation Period. Approximately 3 hours after the initiation of MDZ dosing, an initial low dose of BRV (0.5mg/kg [bid]) will be administered according to the standard of care.	
Section 5.1.1	The first iv dose of PB (standard of care) can be administered between 36 hours and 2 hours prior to the first administration of MDZ (depending on the number of PB doses and time between PB doses and the interval between PB treatment and first administration of MDZ). The initial PB treatment may have been administered prior to the subject's enrollment in the study.	The Screening Period is up to 36 hours prior to the first administration of MDZ (depending on the number of PB doses and time between PB doses and the interval between PB treatment and first administration of MDZ). The PB treatment may have been administered prior to the subject's enrollment in the study and/or at a location other than the study site.	PB treatment is permitted to start prior to subject's admission into the study, as well as allowed to be administered at a separate site prior to the study admittance.
Section 5.1.1	Baseline Period (included in the Screening Period): 2 hours immediately prior to the start of MDZ infusion. The occurrence of ENS during the 2-hour period must be confirmed either by the local or	Baseline Period (included in the Screening Period): 2 hours immediately prior to the start of MDZ infusion. The occurrence of ENS during the 2-hour Baseline Period must be confirmed either by the local or central VEEG reader prior to drug	Permitted use of EEG traces recorded before parents consented for the determination of the Baseline EEG.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	central VEEG reader prior to the start of MDZ treatment.	administration. Preferably, the central VEEG reader should confirm the required ENS. Video-EEGs that are acquired per standard of care prior to consenting and meet study-specific technical and quality requirements (eg, ability for immediate cloud-based central review) can be used as part of the Baseline assessment VEEG.	
Sections 5.1.1, 8.1.3	Not applicable	The first MDZ infusion marks the starting point of the Evaluation Period.	Clarification of the initiation of the Evaluation Period.
Section 5.1.1	Subjects will receive iv MDZ (one or multiple therapeutic doses; MDZ dose is at the discretion of the Investigator).	Subjects will receive iv MDZ (one or multiple therapeutic doses or continuous infusion; MDZ dose and dosing frequency are at the discretion of the Investigator).	Dose frequency and continuous infusion are also at the discretion of the Investigator.
Section 5.1.1	Following the first BRV infusion, 3 to 6 PK blood microsamples (65µL/sample) will be collected during the 48-hour Evaluation Period from each subject for the determination of plasma concentrations of BRV and its metabolites, as described in Table 5-4.	Following the first BRV infusion, 3 to 6 PK blood microsamples (60µL/sample) will be collected during the 48-hour Evaluation Period from each subject for the determination of plasma concentrations of BRV and its metabolites, as described in Table 5-4.	Volume of microsample tubes is 60 µL.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 5.1.2	For the Confirmatory Cohorts, enrollment will only start after the dosing of BRV is determined based on the PK findings of the Exploratory Cohort. A total of at least 36 subjects without adequate seizure control after receiving 1 or 2 doses of PB (total therapeutic administered dose of 20 to 40mg/kg; dosing regimen at the Investigator's discretion) will enter the Confirmatory Cohorts.	For the Confirmatory Cohorts, enrollment will only start after the dosing of BRV is determined based on the PK findings of the Exploratory Cohort and an existing PK model from N01263. A total of at least 36 subjects without adequate seizure control after receiving 1 to 3 doses of PB (PB treatment may have started prior to the subject's admission into the study site; total therapeutic administered dose of 20 to 40mg/kg; dosing regimen at the Investigator's discretion) will enter the Confirmatory Cohorts.	Based on Investigator feedback, the total PB dose of 20 to 40mg/kg may be administered over 3 separate doses. Dosing frequency is also at the discretion of the Investigator. Per agency recommendation, clarification that BRV dose and dosing frequency is also determined by previous PK modeling of N01263 data.
Section 5.1.2	The first iv dose of PB (standard of care) can be administered between 36 hours and 2 hours prior to the first administration of MDZ (depending on the number of PB doses and time between PB doses and the interval between PB treatment and first administration of MDZ). The initial PB treatment may have been administered prior to the subject's enrollment in the study.	The Screening Period is up to 36 hours prior to the first administration of BRV (depending on the number of PB doses and time between PB doses and the interval between PB treatment and first administration of BRV). The PB treatment may have been administered prior to the subject's enrollment in the study and/or at a location other than the study site.	PB treatment is permitted to start prior to subject's admission into the study, as well as allowed to be administered at a separate site prior to the study admittance.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 5.1.2	– Baseline Period (included in the Screening Period): 2 hours immediately prior to the start of BRV infusion. The occurrence of ENS during this 2 hour period must be confirmed either by the local or central VEEG reader prior to the start of MDZ treatment.	– Baseline Period (included in the Screening Period): 2 hours immediately prior to the start of BRV infusion. The occurrence of ENS during the 2-hour Baseline Period must be confirmed either by the local or central VEEG reader prior to drug administration. Preferably, the central VEEG reader should confirm the required ENS. Video-EEGs that are acquired per standard of care prior to consenting and meet study-specific technical and quality requirements (eg, ability for immediate cloud-based central review) can be used as part of the Baseline assessment VEEG.	Permitted use of EEG traces recorded before parents consented for the determination of the Baseline EEG.
Sections 5.1.2, 8.2.3	Not applicable	The first administration of BRV marks the starting point of the Evaluation Period.	Clarification of the initiation of the Evaluation Period.
Section 5.1.2	The BRV dose for subjects in the Confirmatory Cohorts will be determined based on the results of the PK analysis of the Exploratory Cohort (predicted to be	The BRV dose for subjects in the Confirmatory Cohorts will be determined based on the results of the PK analysis of the Exploratory Cohort (predicted to be approximately the	Per agency recommendation, clarification that BRV dose and dosing frequency is also determined by previous PK modeling of N01263 data.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	approximately the BRV plasma concentrations in the same range as those observed at the highest recommended dose in older children and adults who receive BRV 200mg/day).	BRV plasma concentrations in the same range as those observed at the highest recommended dose in older children and adults who receive BRV 200mg/day), as well as based on an existing PK model from N01263.	
Section 5.1.2	Following the first BRV infusion, 6 PK blood microsamples (65µL/sample) will be collected during the 96-hour Evaluation Period for each subject for the determination of plasma concentrations of BRV and its metabolites, as described in Table 5-5.	Following the first BRV infusion, 6 PK blood microsamples (60µL/sample) will be collected during the 96-hour Evaluation Period for each subject for the determination of plasma concentrations of BRV and its metabolites, as described in Table 5-5.	Volume of microsample tubes is 60 µL.
Section 5.1.2	• Down-Titration Period (up to 1 week): A Down-Titration Period of up to 1 week is recommended for subjects in the Confirmatory Cohorts who do not proceed to the BRV Extension Period, or start the BRV Extension Period but do not enter the long-term study.	• Down-Titration Period (up to 1 week): A Down-Titration Period of up to 1 week is recommended for subjects in the Confirmatory Cohorts who discontinue BRV treatment prior to completion of the Evaluation Period, who do not proceed to the BRV Extension Period, or start the BRV Extension Period but do not enter the long-term study.	Recommendations for subjects discontinuing BRV treatment.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 5.1.2, Table 5-2 footnote b	Not applicable	Subjects discontinuing BRV treatment during the Evaluation Period should start the Down-Titration Period while completing the Evaluation Period in parallel for the full 96 hours.	Recommendations for subjects discontinuing BRV treatment.
Table 5-1 footnote c, Table 5-2 footnote d	[c] The occurrence of ENS during the 2-hour period must be confirmed either by the local or central VEEG reader, prior to the start of MDZ treatment.	[c] The occurrence of ENS during the 2-hour Baseline Period must be confirmed either by the local or central VEEG reader prior to drug administration. Preferably, the central VEEG reader should confirm the required ENS.	Permitted use of EEG traces recorded before parents consented for the determination of the Baseline EEG.
Table 5-1 footnote d	Not applicable	[d] Measurement of body weight is optional at 24 and 48 hours. Dosage of BRV during the Evaluation Period will be based on the subject's weight measured prior to the start of the first BRV administration. However, dosage calculation can be adjusted to a more recent weight measurement, upon discretion of the Investigator, if weight is measured during the Evaluation Period.	Clarification of timepoints for weight measurements.
Table 5-1 footnote f, Table 5-2 footnote h	Not applicable	[f] Video-EEGs that are acquired per standard of care prior to consenting and meet study-specific technical and quality requirements can be used as	Permitted use of EEG traces recorded before parents consented for the determination of the Baseline EEG.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
		part of the Baseline assessment VEEG.	
Table 5-1 footnote g	[g] Following the first BRV infusion, 3 to 6 blood microsamples (65µL/sample) will be collected from each subject in the Exploratory Cohort.	[g] Following the first BRV infusion, 3 to 6 blood microsamples (60µL/sample) will be collected from each subject in the Exploratory Cohort.	Volume of microsample tubes is 60 µL.
Table 5-1 footnote i, Table 5-2 footnote k	Not applicable	i For Screening and determination of eligibility, use of laboratory data acquired prior to Screening per standard of care inside or outside the study site within 36 hours prior to the start of the Evaluation Period is allowed.	Allowance of use of standard of care laboratory data.
Table 5-2 footnote e	Not applicable	[e] Measurement of body weight is optional at 24, 48, 72, and 96 hours. Dosage of BRV during the Evaluation Period will be based on the subject's weight measured prior to the start of the first BRV administration. However, dosage calculation can be adjusted to a more recent weight measurement, upon discretion of the Investigator, if weight is measured during the Evaluation Period.	Clarification of timepoints for weight measurements.
Table 5-2 footnote i	i Following the first BRV infusion, 6 blood microsamples (65µL/sample) will be collected	[i] Following the first BRV infusion, 6 blood microsamples (60µL/sample)	Volume of microsample tubes is 60 µL.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	during the Evaluation Period from each subject.	will be collected during the Evaluation Period from each subject.	
Table 5-3 footnote a	a i For Screening and determination of eligibility, use of laboratory data acquired prior to Screening per standard of care inside or outside the study site within 36 hours prior to the start of the Evaluation Period is allowed. A Down-Titration Period of up to 1 week applies only to subjects in the Confirmatory Cohorts. The Down-Titration Period is recommended for subjects who do not proceed to the BRV Extension Period, or start the BRV Extension Period but do not enter the long-term study.	a A Down-Titration Period of up to 1 week applies only to subjects in the Confirmatory Cohorts. The Down-Titration Period is recommended for subjects who discontinue BRV treatment prior to completion of the Evaluation Period, who do not proceed to the BRV Extension Period, or start the BRV Extension Period but do not enter the long-term study. Subjects discontinuing BRV treatment during the Evaluation Period can continue assessments pertaining to the Evaluation Period, except the collection of blood microsamples for the determination of BRV plasma concentrations. Those subjects should start the Down-Titration Period in parallel to completing the Evaluation Period.	Recommendations for subjects discontinuing BRV treatment.
Section 5.4.2	The doses planned to be applied in this study are based on the available data in 96 pediatric subjects (overall, 1 month to 17 years of age with the following number of subjects per pediatric age group: 1 month to <2 years of age, 29 subjects; 2 years	The doses planned to be applied in this study are based on pediatric data collected in N01263 subjects (overall 96 subjects in the age range of 1 month to 17 years with the following number of subjects per pediatric age group: 1 month to <2 years of age,	Clarification of dosage selection.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	to <6 years of age, 26 subjects; 6 years to <12 years of age, 24 subjects; 12 years to <16 years of age, 17 subjects).	29 subjects; 2 years to <6 years of age, 26 subjects; 6 years to <12 years of age, 24 subjects; 12 years to <16 years of age, 17 subjects).	
Section 5.4.2	The dose of BRV to be administered in the Confirmatory Cohorts will be determined by the evaluation of plasma samples collected in the Exploratory Cohort and should not exceed the range of plasma concentrations observed in children ≥1 month old who received BRV 4mg/kg/day.	The dose of BRV to be administered in the Confirmatory Cohorts will be determined by the evaluation of plasma samples collected in the Exploratory Cohort, as well as by the PK modeling of N01263 data described above, and should not exceed the range of plasma concentrations observed in children ≥1 month old who received BRV 4mg/kg/day. The plasma concentration of BRV 4mg/kg/day for neonates is predicted to be approximately equivalent to the plasma concentrations observed in adults who receive BRV 200mg/day. The dose in neonates to reach the same plasma concentrations will be confirmed or adapted upon completion of enrollment and analysis of PK and safety data from the Exploratory Cohort involving the DMC. The BRV dose used in the Confirmatory Cohorts will be based	Per agency recommendation, clarification that BRV dose and dosing frequency is also determined by previous PK modeling of N01263 data. Clarification of DMC participation in determination of Confirmatory Cohort dosage.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
		on recommendations made by the DMC.	
Section 6.1	2.Confirmation on VEEG of ≥2 minutes of cumulative ENS or ≥3 identifiable ENS within the 2 hours prior to entering the Evaluation Period (ENS is defined as a seizure lasting for at least 10 seconds on VEEG), despite receiving PB (total therapeutic administered dose of 20 to 40mg/kg) for the treatment of repeated seizures.	2a. Confirmation on VEEG of ≥2 minutes of cumulative ENS or ≥3 identifiable ENS within the 2 hours prior to entering the Evaluation Period (ENS is defined as a seizure lasting for at least 10 seconds on VEEG), despite receiving PB (total therapeutic administered dose of 20 to 40mg/kg) for the treatment of repeated seizures. The occurrence of ENS during the 2-hour Baseline Period must be confirmed either by the local or central VEEG reader prior to drug administration. Preferably, the central VEEG reader should confirm the required ENS.	Local and central reader preference clarification.
Section 6.2	1. Subject received AED treatment (other than the required 1 or 2 doses of PB [total therapeutic administered dose of 20 to 40mg/kg] for the treatment of repeated seizures) prior to entering the Evaluation Period.	1a. Subject received AED treatment (other than the required 1 to 3 doses of PB [total therapeutic administered dose of 20 to 40mg/kg] for the treatment of repeated seizures) prior to entering the Evaluation Period.	Based on Investigator feedback, the total PB dose of 20 to 40mg/kg may be administered over 3 separate doses.
Section 6.2	8. Subject has conjugated bilirubin levels >2mg/dL.	8a. Subject has direct (conjugated) bilirubin levels >2mg/dL.	Language correction.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 6.3	4. Subject has conjugated bilirubin levels >2mg/dL.	4a. Subject has direct (conjugated) bilirubin levels >2mg/dL.	Language correction.
Section 6.3.1	• Subject has conjugated bilirubin >2mg/dL.	• Subject has direct (conjugated) bilirubin >2mg/dL.	Language correction.
Section 7.2	Subjects in the Exploratory Cohort will be dosed with iv MDZ (dosing of MDZ is at the discretion of the Investigator).	Subjects in the Exploratory Cohort will be dosed with iv MDZ (dosing and dosing frequency of MDZ are at the discretion of the Investigator).	Dose frequency and continuous infusion are also at the discretion of the Investigator.
Section 8.1.1	The first iv dose of PB (standard of care) can be administered between 36 hours and 2 hours prior to the first administration of MDZ (depending on the number of PB doses and time between PB doses and the interval between PB treatment and first administration of MDZ).	The Screening Period is up to 36 hours prior to the first administration of MDZ (depending on the number of PB doses and time between PB doses and the interval between PB treatment and first administration of MDZ).	PB treatment is permitted to start prior to subject's admission into the study, as well as allowed to be administered at a separate site prior to the study admittance.
Sections 8.1.1, 8.2.1	The initial PB treatment may have started prior to the subject's admission to the study.	The PB treatment may have started prior to the subject's admission to the study and/or at a location other than the study site but should be completed prior to the 2-hour Baseline Period.	PB treatment is permitted to start prior to subject's admission into the study, as well as allowed to be administered at a separate site prior to the study admittance.
Section 8.1.2	Not applicable	Video-EEGs that are acquired per standard of care prior to consenting and meet study-specific requirements (eg, ability for immediate cloud-based	Permitted use of EEG traces recorded before parents consented for the determination of the Baseline EEG.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
		central review) can be used as part of the Baseline assessment VEEG.	
Section 8.1.2	The occurrence of ENS during this 2-hour period must be confirmed either by the local or central VEEG reader prior to the start of MDZ treatment.	The occurrence of ENS during the 2-hour Baseline Period must be confirmed either by the local or central VEEG reader prior to drug administration. Preferably, the central VEEG reader should confirm the required ENS.	Permitted use of EEG traces recorded before parents consented for the determination of the Baseline EEG.
Section 8.1.2, 8.2.2	Verification of inclusion/exclusion criteria. Confirmation on VEEG of ≥2 minutes of cumulative ENS or ≥3 identifiable ENS within the 2 hours prior to entering the Evaluation Period (ENS is defined as a seizure lasting for at least 10 seconds on VEEG), despite PB treatment	Verification of inclusion/exclusion criteria. Confirmation on VEEG of ≥2 minutes of cumulative ENS or ≥3 identifiable ENS within the 2 hours prior to entering the Evaluation Period (ENS is defined as a seizure lasting for at least 10 seconds on VEEG), despite PB treatment prior to Baseline	PB treatment is permitted to start prior to subject's admission into the study, as well as allowed to be administered at a separate site prior to the study admittance.
Section 8.1.2	Not applicable	Baseline laboratory measurements will be performed by local laboratories unless historical data is available. Historical safety laboratory assessments, previously collected as standard of care, may be accepted from referring hospitals as Baseline measurement if performed 36 hours prior to the start of the Evaluation Period. In this case, test results will be	Allowance of use of standard of care laboratory data.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
		considered medical history. Prior laboratory assessment results should already be available at Baseline and verified prior to initiation of the MDZ infusion.	
Section 8.1.3	• Body weight (24 and 48 hours)	• Body weight (optional [at 24 and 48 hours]; dosage of BRV during the Evaluation Period will be based on the subject's weight measured prior to the start of the first BRV administration. However, dosage calculation can be adjusted to a more recent weight measurement, upon discretion of the Investigator, if weight is measured during the Evaluation Period)	Clarification of timepoints for weight measurements.
Sections 8.1.4, 8.2.4	Extension Period Visit 2 will be performed on the same day when the subject enters the long-term study (see Section 8.1.3.2).	Extension Period Visit 2 will be performed on the same day when the subject enters the long-term study N01266 (see Section 8.1.3.2). If study N01266 is performed outside the N01349 hospital, an interval of up to 3 days between the N01349 EPV2 and N01266 Entry Visit is allowed.	Clarification of visit intervals.
Section 8.2.1	The Screening Period (up to 36 hours) will be from the signing and dating of the written ICF by the	The Screening Period will be from the signing and dating of the written ICF by the parent(s) or legal	Elimination of repetition.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	parent(s) or legal representative(s) of the subject to the end of the Baseline Period.	representative(s) of the subject to the end of the Baseline Period.	
Section 8.2.1	The first iv dose of PB (standard of care) can be administered between 36 hours and 2 hours prior to the first administration of BRV (depending on the number of PB doses and time between PB doses and the interval between PB treatment and first administration of BRV).	The Screening Period is up to 36 hours prior to the first administration of BRV (depending on the number of PB doses and time between PB doses and the interval between PB treatment and first administration of BRV).	PB treatment is permitted to start prior to subject's admission into the study, as well as allowed to be administered at a separate site prior to the study admittance.
Section 8.2.2	The occurrence of ENS during this 2-hour period must be confirmed either by the local or central VEEG reader prior to the start of BRV treatment.	The occurrence of ENS during the 2-hour Baseline Period must be confirmed either by the local or central VEEG reader prior to drug administration. Preferably, the central VEEG reader should confirm the required ENS. Video-EEGs that are acquired per standard of care prior to consenting and meet study-specific technical and quality requirements (eg, ability for immediate cloud-based central review) can be used as part of the Baseline assessment VEEG.	Permitted use of EEG traces recorded before parents consented for the determination of the Baseline EEG.
Section 8.2.2	Not applicable	Baseline laboratory measurements will be performed by local laboratories unless historical data is available. Historical safety laboratory	Allowance of use of standard of care laboratory data.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
		assessments, previously collected as standard of care, may be accepted from referring hospitals as Baseline measurement if performed 36 hours prior to the start of the Evaluation Period. In this case, test results will be considered medical history. Prior laboratory assessment results should already be available at Baseline and verified prior to initiation of BRV administration.	
Section 8.2.3	Not applicable	If subjects in the Confirmatory Cohort receive <8 BRV doses, those subjects are allowed to continue study participation and complete study assessments per Table 17-2, with the exception of PK blood sampling. Those subjects should start the Down-Titration Period while completing the Evaluation Period in parallel for the full 96 hours.	Recommendations for subjects discontinuing BRV treatment.
Section 8.2.3	• Body weight (at 24, 48, 72 and 96 hours).	• Body weight (optional [at 24, 48, 72 and 96 hours]; dosage of BRV during the Evaluation Period will be based on the subject's weight measured prior to the start of the first BRV administration. However, dosage calculation can be adjusted to a more recent	Clarification of timepoints for weight measurements.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
		weight measurement, upon discretion of the Investigator, if weight is measured during the Evaluation Period)	
Section 8.2.5	A Down-Titration Period of up to 1 week is recommended for subjects who complete the Evaluation Period, but do not enter the BRV Extension Period, or start the BRV Extension Period but do not continue into the long-term study for any reason.	A Down-Titration Period of up to 1 week is recommended for subjects who complete the Evaluation Period, but do not enter the BRV Extension Period, discontinue BRV during the Evaluation Period, or start the BRV Extension Period but do not continue into the long-term study for any reason.	Recommendations for subjects discontinuing BRV treatment.
Section 9.1	For the determination of plasma concentrations of BRV and BRV metabolites, up to 6 blood microsamples (65µL/sample) will be collected per subject in the Exploratory (3 to 6 blood microsamples) and Confirmatory Cohorts (up to 6 blood microsamples) at 3 predetermined timepoints per day. An additional microsample (65µL) will be collected per subject for the determination of plasma concentrations of concomitant AEDs (PB and PHT).	For the determination of plasma concentrations of BRV and BRV metabolites, up to 6 blood microsamples (60µL/sample) will be collected per subject in the Exploratory (3 to 6 blood microsamples) and Confirmatory Cohorts (up to 6 blood microsamples) at 3 predetermined timepoints per day. An additional microsample (60µL) will be collected per subject for the determination of plasma concentrations of concomitant AEDs (PB and PHT).	Volume of microsample tubes is 60 µL.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Sections 10.1, 13.5.1	• Absolute reduction and proportion of clinical seizures correlated with continuous VEEG from Baseline to the end of the 96-hour Evaluation Period, and at each of the 3-hour intervals	• Absolute and percent difference in clinical seizures at the end of the 24-hour Evaluation Period from Baseline for neonates with motor seizures at the time of inclusion	Alignment of language presented in the Pediatric Investigation Plan.
Section 11.1.1	• Potential drug-induced liver injury as indicated by: – Conjugated bilirubin >2mg/dL	• Potential drug-induced liver injury as indicated by: – Direct (conjugated) bilirubin >2mg/dL	Language correction.
Section 11.1.2	In line with GCP, from the signing of the ICF, the Investigator will record any AEs that occur to the subject, and will keep detailed records of all AEs that occur. All AEs will be recorded daily in each subject's medical notes. Serious AEs, AEs that are considered related to the medicinal (investigational) product, AEs leading to discontinuation, infusion site reactions, or AEs considered by the Investigator to be critical to the safety evaluation of the protocol will also be recorded on the Adverse Event eCRF.	In line with GCP, from the signing of the ICF, the Investigator will evaluate the subject for occurrence of any AEs based on continued observation and medical notes throughout the study. Serious AEs, AEs that are considered related to the medicinal (investigational) product, AEs leading to discontinuation, BRV infusion site reactions, or AEs considered by the Investigator to be critical to the safety evaluation of the protocol will also be recorded on the Adverse Event eCRF.	Adverse event recording clarification.

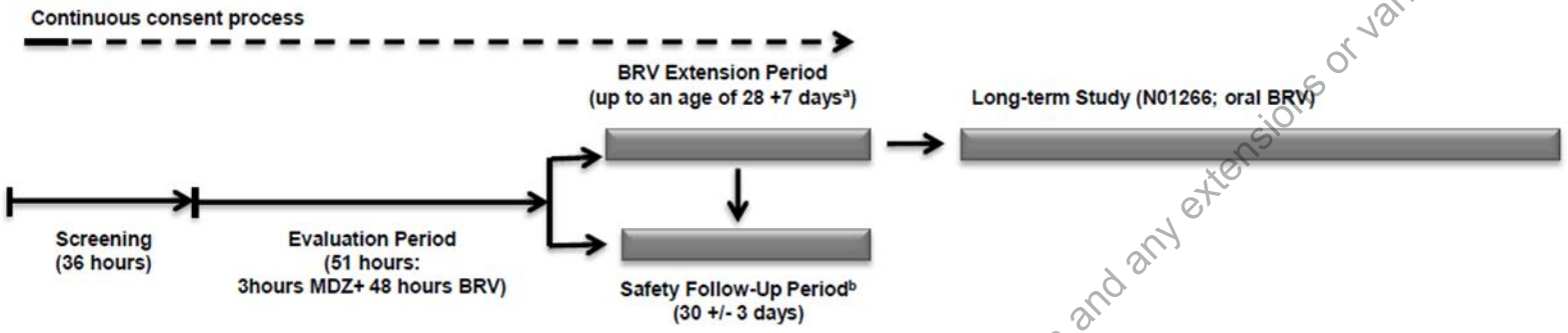
Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 11.2	Not applicable	Blood samples will be collected in line with Section 13.2 of the "Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population" (European Union Commission ad hoc group, 2008).	Recommendations for subjects discontinuing BRV treatment.
Section 11.2	All laboratory measurements, including laboratory assessments for PDILI, will be performed by local laboratories.	Laboratory measurements, including laboratory assessments for PDILI, will be performed by local laboratories unless historical data is available. Historical safety laboratory assessments, previously collected as standard of care, may be accepted from referring hospitals as Baseline measurement if performed 36 hours prior to the Evaluation Period.	Allowance of use of standard of care laboratory data.
Section 11.2	As part of routine assessments performed by local laboratories, the parameters shown in Table 11-1 will be measured.	As part of routine assessments performed by local laboratories, the parameters shown in Table 11-1 and Table 11-2 will be measured.	Table addition.
Table 11-3	Conjugated bilirubin	Direct (conjugate) bilirubin	Language correction.
Section 11.2.1.3	Not applicable	Recommended testing is at the discretion of the Investigator and should be individualized	Testing recommendation clarification.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
		appropriately based on clinical situation.	
Section 11.3.8	Not applicable	Withdrawal and rebound phenomena, if any, will be captured from data collected at the end of BRV exposure for subjects in both the Exploratory and Confirmatory Cohorts	Text was relocated.
Section 11.3.9	Numbers and percentage of subjects requiring mechanical ventilation at the time they are treated with BRV will be recorded from Baseline through the 48-hour Evaluation Period for the Exploratory Cohort and the 96-hour Evaluation Period for the Confirmatory Cohorts and compared between subjects that required BRV only and subjects treated with BRV and receiving rescue medication or other AEDs. Absolute and relative duration of ventilation at the time subjects are treated with BRV will be recorded over the Evaluation Period and compared between subjects treated with BRV only and subjects treated with BRV and receiving rescue medication or other AEDs.	Numbers and percentage of subjects requiring mechanical ventilation will be recorded from Baseline through the 48-hour Evaluation Period for the Exploratory Cohort and the 96-hour Evaluation Period for the Confirmatory Cohort. Duration of mechanical ventilation will be recorded over the Evaluation Period.	Alignment of language presented in the Pediatric Investigation Plan.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 13.3	Not applicable	The analysis of the PK parameters for the Exploratory and Confirmatory Cohorts will include a sub-analysis for any concomitant use of hypothermia.	Content consistency. Text was relocated.
Section 13.4	The primary cause of seizure (HIE, hemorrhage, or infarction; CNS malformations; CNS infections; undetermined causes) may also be used to categorize the safety review.	The primary cause of seizure (eg, HIE, hemorrhage, or infarction; CNS malformations; CNS infections; undetermined causes) may also be used to categorize the safety review.	Typographical change.
Section 13.7	Subjects in the Confirmatory Cohorts are withdrawn, are switched over to another AED treatment, prior to the Evaluation Period or are administered >1 dose of rescue medication (including BZDs) following the first 3 hours after initial BRV treatment started will be considered BRV nonresponders.	Subjects in the Confirmatory Cohorts who drop out due to lack of BRV efficacy, are switched over to another AED treatment, or are administered >1 dose of rescue medication (including BZDs) following the first 3 hours after initial BRV treatment started will be considered BRV nonresponders.	Recommendations for subjects discontinuing BRV treatment.
Section 13.8.1	Upon the completion of the Exploratory Cohort, the DMC will be provided with the summaries and the listings of PK and safety data for review (see Section 13.8.3).	Upon the completion of the Exploratory Cohort, the DMC will be provided with the summaries and the listings of PK and safety data for review to make recommendations concerning the dosing of BRV in the Confirmatory Cohorts (see Section 13.8.3).	Clarification of DMC participation in determination of Confirmatory Cohort dosage.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 14.1	Not applicable	An informed consenting process managed via telephone is allowed where applicable per local regulations.	Allowance of telephone consenting process.
References	Not applicable	European Union Commission ad hoc group. Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use. Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population. 2008; 13.2. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/ethical_considerations_en.pdf.	Reference addition.

Figure 5-1: Schematic overview of the study for the Exploratory Cohort



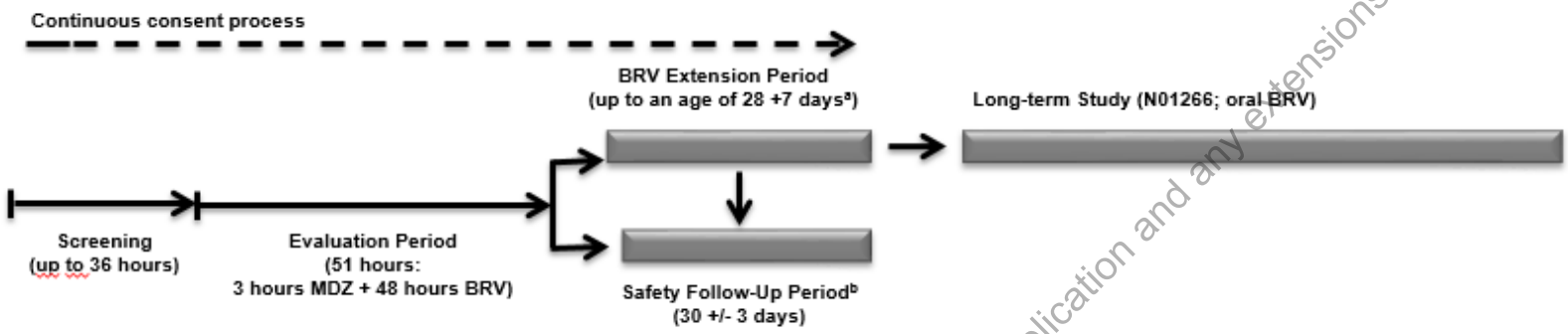
BRV=brivaracetam; ICF=informed consent form; MDZ=midazolam; VEEG=(multichannel) video-electroencephalography
Note: A continuous consent process will be followed. Parent(s) or legal representative(s) will be informed about the study as early as possible and asked to sign the ICF after the occurrence of seizures has been confirmed by VEEG. During the course of the study, parent(s) or legal representative(s) will be updated about the care of their neonate, and continuous consent will be ensured by meetings between the Investigator (or designee) and the subject's parent(s) or legal representative(s).

[a] The anticipated duration of the BRV Extension Period is up to 28 days of postnatal age (+7 days).

[b] Subjects in the Exploratory Cohort will enter the Safety Follow-Up Period, if they complete the Evaluation Period or are discontinued from the BRV Extension Period.

For adjustment of dosing and time intervals, Figure 5-1 was changed to:

Figure 5-1: Schematic overview of the study for the Exploratory Cohort

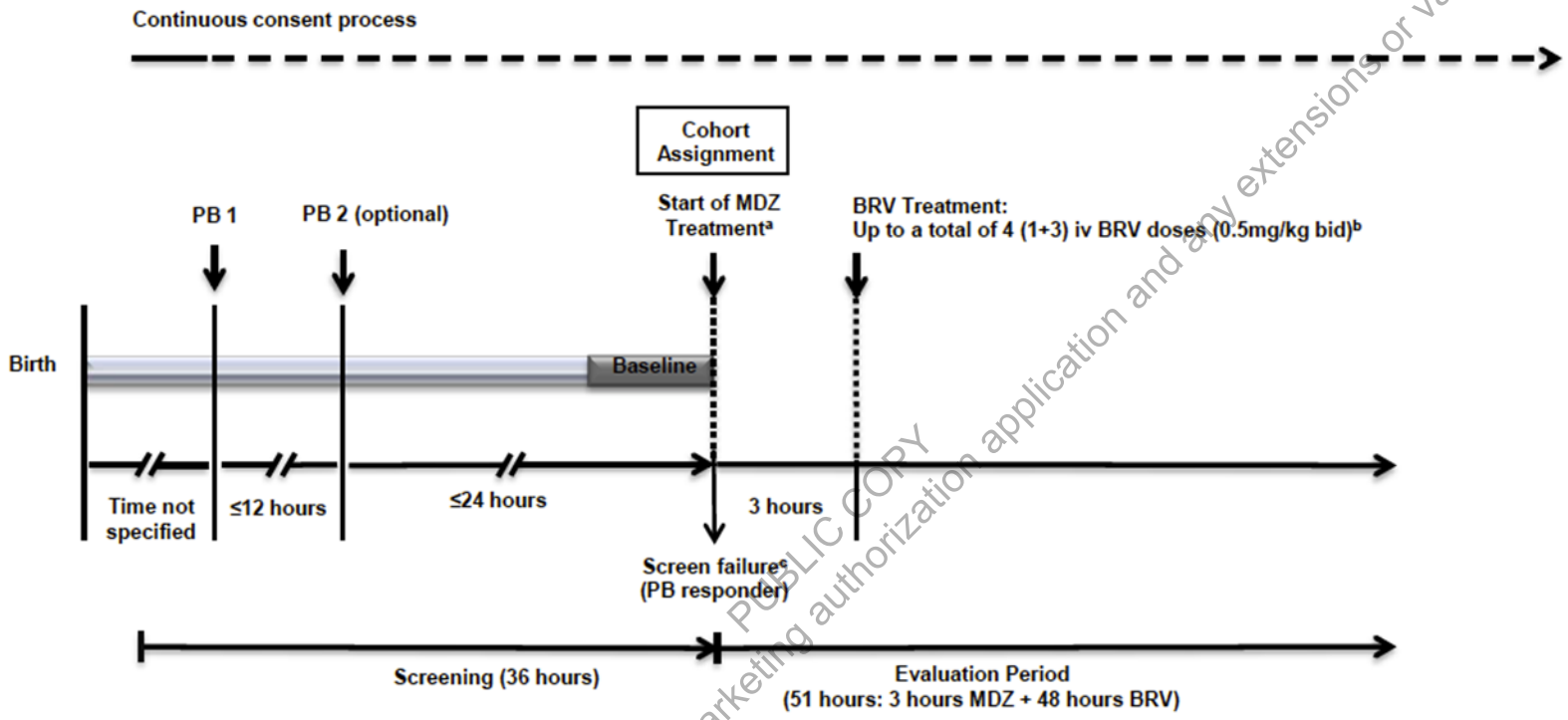


BRV=brivaracetam; ICF=Informed Consent form; MDZ=midazolam; VEEG=(multichannel) video-electroencephalography
Note: A continuous consent process will be followed. Parent(s) or legal representative(s) will be informed about the study as early as possible and asked to sign the ICF after the occurrence of seizures has been confirmed by VEEG. During the course of the study, parent(s) or legal representative(s) will be updated about the care of their neonate, and continuous consent will be ensured by meetings between the Investigator (or designee) and the subject's parent(s) or legal representative(s).

[a] The anticipated duration of the BRV Extension Period is up to 28 days of postnatal age (+7 days).

[b] Subjects in the Exploratory Cohort will enter the Safety Follow-Up Period, if they complete the Evaluation Period or are discontinued from the BRV Extension Period.

Figure 5-2: Screening and Evaluation Periods (Exploratory Cohort)



BRV=brivaracetam; ICF=informed consent form; MDZ=midazolam; PB=phenobarbital

Note: The Screening Period is from signing and dating of the written ICF up to Cohort Assignment. The first iv dose of PB (standard of care) can be administered between 36 hours and 2 hours prior to the first administration of MDZ (depending on the number of PB doses and time between PB doses and the interval between PB treatment and first administration of MDZ). The PB treatment may have been administered prior to the subject's enrollment in the study and/or at a location other than the designated site.

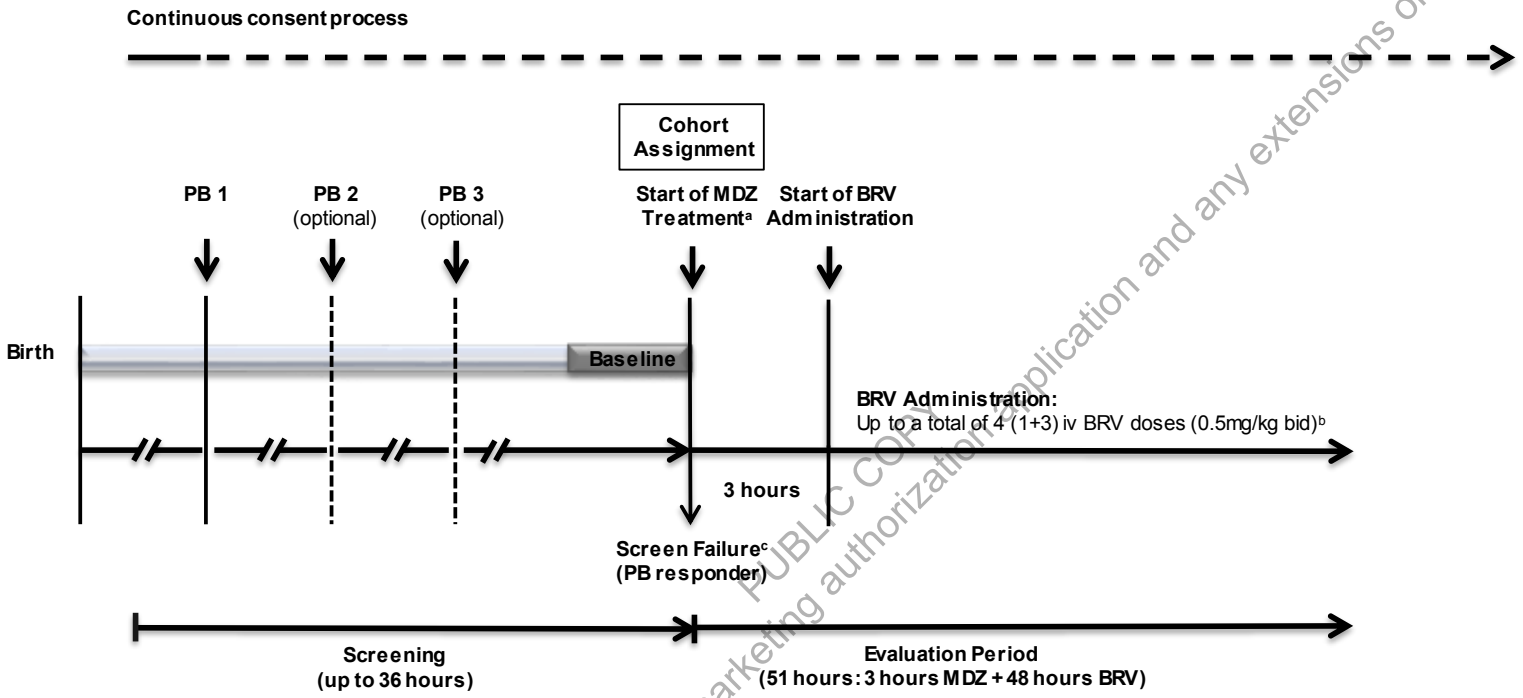
[a] Treatment with MDZ will continue in parallel with BRV.

[b] Subjects enrolled in the Exploratory Cohort will receive a therapeutic dose of MDZ (dose and dosing frequency of MDZ are at the discretion of the Investigator) prior to receiving BRV. Subsequently, an initial low dose of iv BRV will be administered. At the discretion of the Investigator, 3 additional iv BRV doses can be administered, up to a total of 4 iv BRV doses (0.5mg/kg twice daily [bid]), during the 48-hour Evaluation Period.

[c] If seizures are adequately controlled with previous AED treatment per SOC, subjects will be considered screen failures and will not be permitted to enter the Evaluation Period.

For adjustment of dosing and time intervals, Figure 5-2 was changed to:

Figure 5-2: Screening and Evaluation Periods (Exploratory Cohort)



BRV=brivaracetam; ICF=Informed Consent form; MDZ=midazolam; PB=phenobarbital

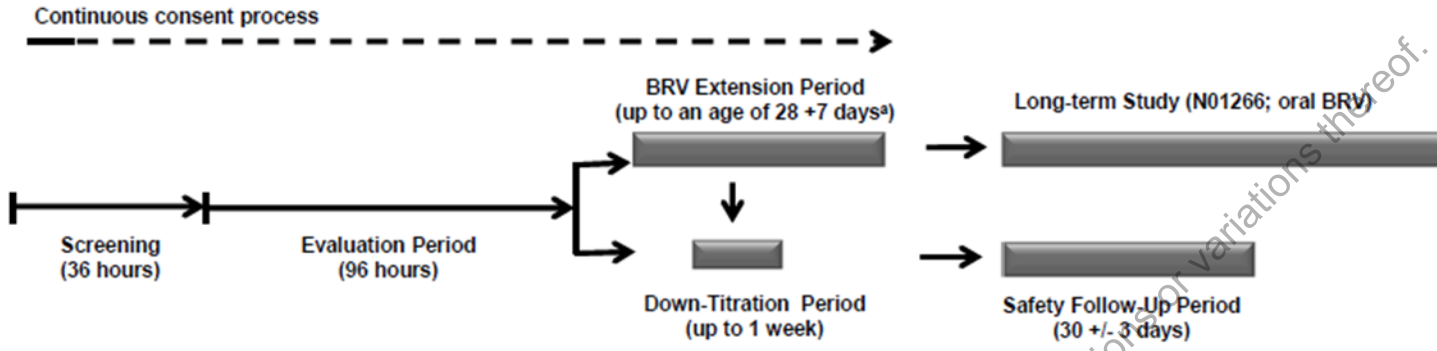
Note: The Screening Period is from signing and dating of the written ICF up to Cohort Assignment. The Screening Period is up to 36 hours prior to the first administration of MDZ (depending on the number of PB doses and time between PB doses and the interval between PB treatment and first administration of MDZ). The PB treatment may have been administered prior to the subject's enrollment in the study and/or at a location other than the study site.

[a] Treatment with MDZ will continue in parallel with BRV.

[b] Subjects enrolled in the Exploratory Cohort will receive one or multiple therapeutic doses or continuous infusion of MDZ (dose and dose frequency of MDZ are at the discretion of the Investigator) prior to receiving BRV. Subsequently, an initial low dose of iv BRV will be administered. At the discretion of the Investigator, 3 additional iv BRV doses can be administered, up to a total of 4 iv BRV doses (0.5mg/kg twice daily [bid]), during the 48-hour Evaluation Period.

[c] If seizures are adequately controlled with previous AED treatment per SOC, subjects will be considered screen failures and will not be permitted to enter the Evaluation Period.

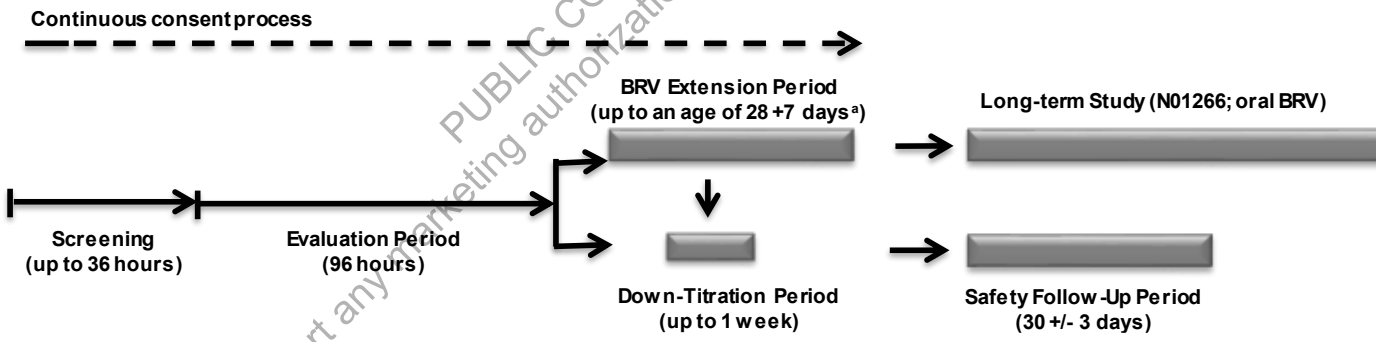
Figure 5-3: Schematic overview of the study for the Confirmatory Cohorts



BRV=brivaracetam; ICF=informed consent form; VEEG=(multichannel) video-electroencephalography
Note: A continuous consent process will be followed. Parent(s) or legal representative(s) will be informed about the study as early as possible and asked to sign the ICF after the occurrence of seizures has been confirmed by VEEG. During the course of the study, parent(s) or legal representative(s) will be updated about the care of their neonate, and continuous consent will be ensured by meetings between the Investigator (or designee) and the subject's parent(s) or legal representative(s).
[a] The anticipated duration of the BRV Extension Period is up to 28 days of postnatal age (+7 days).

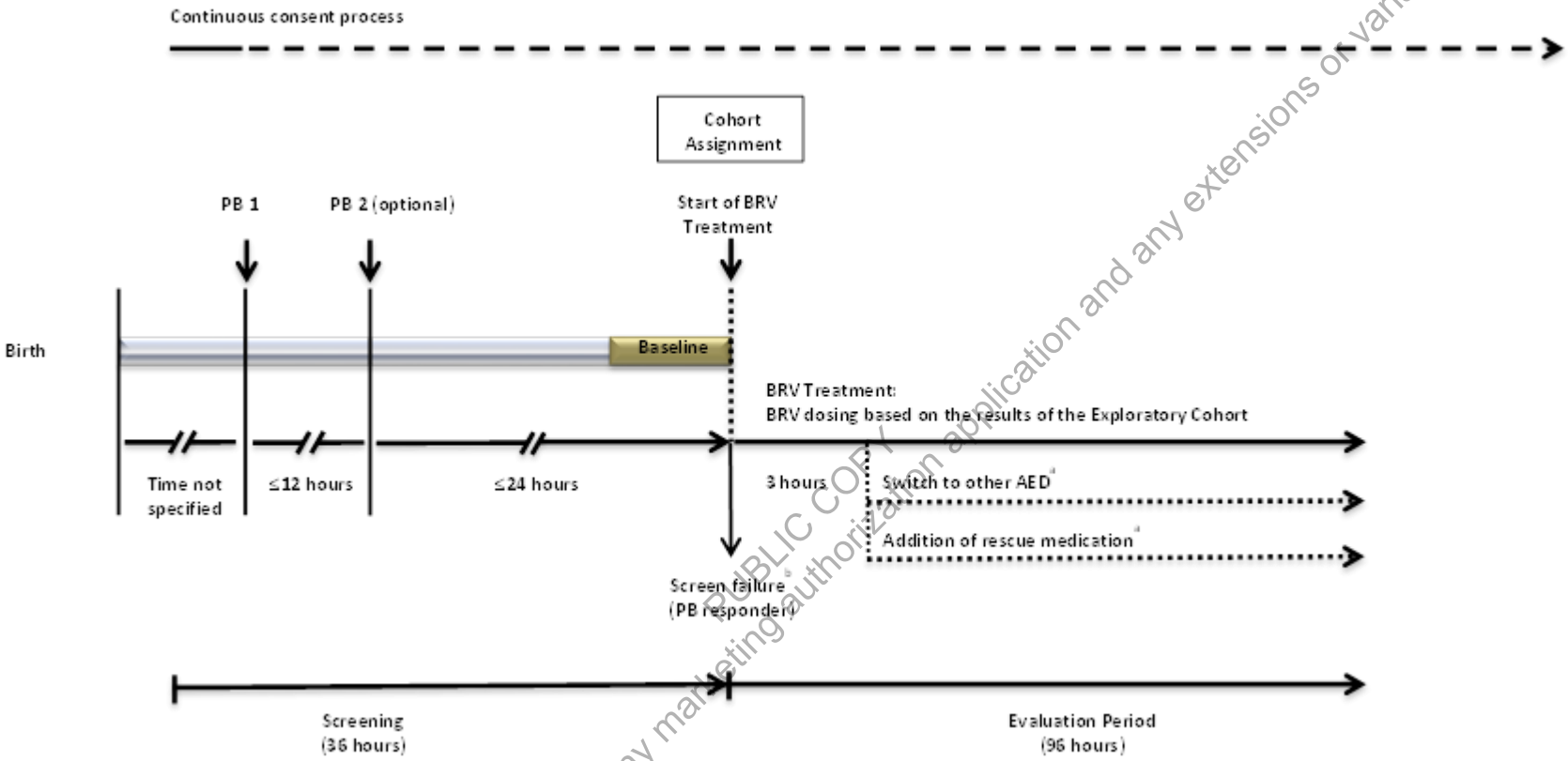
For adjustment of dosing and time intervals, Figure 5-3 was changed to:

Figure 5-3: Schematic overview of the study for the Confirmatory Cohorts



BRV=brivaracetam; ICF=Informed Consent form; VEEG=(multichannel) video-electroencephalography
Note: A continuous consent process will be followed. Parent(s) or legal representative(s) will be informed about the study as early as possible and asked to sign the ICF after the occurrence of seizures has been confirmed by VEEG. During the course of the study, parent(s) or legal representative(s) will be updated about the care of their neonate, and continuous consent will be ensured by meetings between the Investigator (or designee) and the subject's parent(s) or legal representative(s).
[a] The anticipated duration of the BRV Extension Period is up to 28 days of postnatal age (+7 days).

Figure 5-4: Screening and Evaluation Periods (Confirmatory Cohorts)



AED=antiepileptic drug; BRV=brivaracetam; ICF=informed consent form; PB=phenobarbital

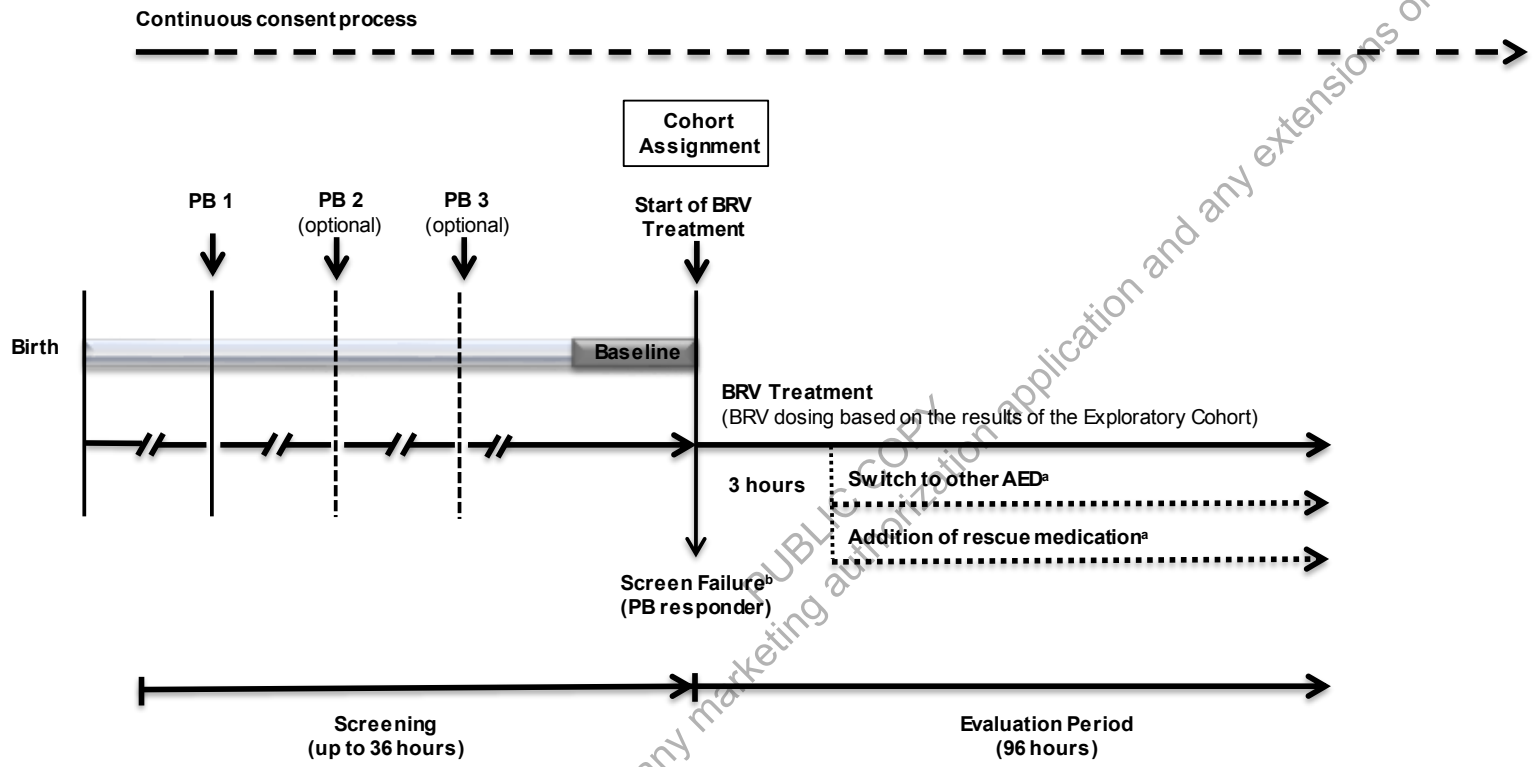
Note: The Screening Period is from signing and dating of the written ICF up to Cohort Assignment. The first iv dose of PB (standard of care) can be administered between 36 hours and 2 hours prior to the first administration of BRV (depending on the number of PB doses and time between PB doses and the interval between PB treatment and first administration of BRV). The initial PB treatment may have been administered prior to the subject's enrollment in the study.

[a] Switching to another AED or addition of rescue medication should only occur following 3 hours after the first BRV administration.

[b] If seizures are adequately controlled with previous AED treatment per SOC, subjects will be considered screen failures and will not be permitted to enter the Evaluation Period.

For adjustment of dosing and time intervals, Figure 5-4 was changed to:

Figure 5-4: Screening and Evaluation Periods (Confirmatory Cohorts)



AED=antiepileptic drug; BRV=brivaracetam; ICF=Informed Consent form; PB=phenobarbital

Note: The Screening Period is from signing and dating of the written ICF up to Cohort Assignment. The Screening Period is up to 36 hours prior to the first administration of BRV (depending on the number of PB doses and time between PB doses and the interval between PB treatment and first administration of BRV). The PB treatment may have been administered prior to the subject's enrollment in the study and/or at a location other than the study site.

[a] Switching to another AED or addition of rescue medication should only occur following 3 hours after the first BRV administration.

[b] If seizures are adequately controlled with AED treatment per SOC, subjects will be considered screen failures and will not be permitted to enter the Evaluation Period.

Table 11-1: Laboratory measurements

Hematology	Biochemistry	Urinalysis	Endocrinology
Basophils	Calcium	Albumin	TSH
Eosinophils	Chloride	Bacteria	T_3
Lymphocytes	Potassium	Glucose	T_4
Atypical lymphocytes	Sodium	pH	
Monocytes	Glucose	RBC	
Neutrophils	BUN	WBC	
Hematocrit	Creatine kinase		
Hemoglobin	AST		
MCH	ALT		
MCHC	GGT		
MCV	Total bilirubin		
Platelet count	LDH		
RBC count	Total cholesterol		
WBC count			

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=gamma-glutamyltransferase; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WBC=white blood cell

For clarification of laboratory assessments, Table 11-1 was split into mandatory and optional measurements:

Table 11-1: Mandatory laboratory measurements

Hematology	Biochemistry
Basophils	Calcium
Eosinophils	Chloride
Lymphocytes	Potassium
Atypical lymphocytes	Sodium
Monocytes	Glucose
Neutrophils	Urea/BUN[a]
Hematocrit	Creatine kinase
Hemoglobin	AST
MCH	ALT
MCHC	ALP
MCV	GGT
Platelet count	LDH
RBC count	Total bilirubin
WBC count	Direct (conjugated) bilirubin

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=gamma-glutamyltransferase; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; WBC=white blood cell

[a] Urea or BUN to be tested depending on the local lab´s standard panel for neonates.

Table 11-2: Optional laboratory measurements

Biochemistry	Urinalysis[b]	Endocrinology[c]
Total cholesterol[a]	Protein	TSH
	Bacteria	T_4
	Glucose	
	pH	
	RBC	
	WBC	

RBC=red blood cell; T_4=thyroxine; TSH=thyroid-stimulating hormone; WBC=white blood cell

[a] Total cholesterol to be measured if this is part of the local lab´s standard panel for neonates.

[b] Urinalysis to be performed only if a urine sample was obtained for clinical purposes.

[c] TSH and T_4 to be recorded for the study only if measured for neonatal screening of congenital hypothyroidism prior to or during study participation.

17.4 Protocol Amendment 4

Rationale for the amendment

The primary purpose of this nonsubstantial protocol amendment is to update the laboratory measurement section where creatinine was inadvertently not included as a mandatory laboratory measurement. Creatinine is needed for monitoring of renal function. Clarification for optional laboratory measurements has also been provided.

Specific changes

Change #1

Table 11-1

Creatinine has been added as a new laboratory parameter and in addition, the following footnote b was added:

[b] During the first days of life, creatinine will only be collected if the site assesses this parameter per standard of care.

Change #2

Table 11-2 Footnote b

[b] Urinalysis to be performed only if a urine sample was obtained for clinical purposes.

Has been changed to

[b] Urinalysis to be performed only if a urine sample was obtained for clinical purposes. A urine dipstick is acceptable.

17.5 Protocol Amendment 5

Rationale for the amendment

The purpose of this substantial amendment is to implement the changes from the agreed Pediatric Investigation Plan for BRV in order to help improve enrollment rate (to date, 1 subject has been enrolled). The primary change is to remove restriction in terms of concomitant medication by replacing PB only with SOC for the Exploratory Cohort and one or more of the following AEDs: PB, MDZ, PHT, LEV (≤60mg/kg/day) or LDC for the Confirmatory Cohort. Also, the age range has been modified. Additionally, subjects will be proposed to enroll into a new long-term follow-up study.

A brief list of modifications to the protocol include the following:

- Age at enrollment modified
- Phenobarbital no longer required as first line treatment prior to BRV; replaced by "ENS treatment per SOC (first line, second line, or subsequent treatment; choice of treatment, dose and dosing at the Investigator´s discretion)" for the Exploratory Cohort and "one or more of the following AEDs: PB, MDZ, PHT, LEV (≤60mg/kg/day) or LDC (first line, second line or subsequent treatment; dose and dosing at the Investigator´s discretion)" for the Confirmatory Cohorts
- 2-hour Baseline EEG and 48-hour VEEG removed from the Exploratory Cohort; required ENS to be confirmed by the Investigator via local EEG
- Duration of the 2-hour Baseline Period shortened to up to 1 hour for the Confirmatory Cohorts and separated by seizure activity: "at least 1 hour" for subjects with intermittent ENS and "up to 30 minutes" for subjects in status epilepticus
- Definition of status epilepticus for neonates enrolled into this study was added
- Treatment with "MDZ only" during the first 3 hours of the Evaluation Period removed from the Confirmatory Cohort; duration of the Evaluation Period hence shortened from 51 to 48 hours
- Historical control changed from "MDZ" to "one or more AED treatments"
- The initiation of LEV treatment after the first time BRV is introduced is prohibited throughout the study for the Confirmatory Cohorts
- Inclusion Criteria 2a and 3, Exclusion Criteria 1a and 2 modified
- Use of concomitant medication and rescue medication adapted
- PK variables split into "primary" and "other" PK variables
- Safety variables categorized as "secondary safety variable" and "other safety variables"
- Reference to N01266 removed since this study will be closed before the last N01349 subject was able to participate in that study for 3 years. Those subjects may instead roll-over to EP0132. Study number replaced by generic term "long-term study"
- Clarified that enrollment will be put on hold during the first DMC (that was always the plan but not explicitly mentioned in the protocol)
- Marketing status of BRV updated

Specific changes

Section Impacted	Key components of previous text	Key components of amended text	Rationale
STUDY CONTACT INFORMAT-ION	Removed study physican [redacted] name, address, and contact information	Added [redacted] relevant information	Study physician has changed
Section 1 Summary	Subjects will first receive 1 to 3 doses of phenobarbital (PB) (total therapeutic administered dose of 20 to 40mg/kg; dosing regimen at the Investigator's discretion). If they do not have adequate seizure control after receiving PB, they may be enrolled into N01349, but they must stop PB treatment.	Subjects will first receive antiepileptic drugs (AEDs) for the treatment of electroencephalographic neonatal seizures (ENS) (first-line, second-line, or subsequent treatment, which may have started prior to the subject's admission into the study site; dose and dosing regimen at the Investigator's discretion). If they do not have adequate seizure control after the treatment with AEDs, they may be enrolled into N01349.	PB no longer required as first-line treatment prior to BRV
Section 1 Summary	For the Exploratory Cohort (first step), enrolled subjects will receive one or multiple doses or continuous infusion of a therapeutic dose of midazolam (MDZ) (dose and dosing frequency of MDZ is at the discretion of the Investigator) prior to receiving BRV	For the Exploratory Cohort (first step), enrolled subjects will receive 1 or more AEDs per standard of care (SOC) for the treatment of ENS (first-line, second-line, or subsequent treatment; choice of treatment, dose, and dosing frequency is at the discretion of the Investigator) prior to receiving BRV	Historical control changed from MDZ to "1 or more AED treatments"

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 1 Summary	The primary objective of this study is to evaluate the PK of BRV in neonates who have seizures that are not adequately controlled with PB treatment, and to identify the optimal BRV dose (Exploratory Cohort) for the treatment of subjects enrolled into the Confirmatory Cohorts of this study. Secondary objectives include the evaluation of the short-term safety and tolerability of BRV in neonates and the evaluation of the efficacy of BRV in severe and nonsevere seizure burden (defined as total minutes of ENS per hour) in neonates with seizures that are not adequately controlled with PB treatment	The primary objective of this study is to evaluate the PK of BRV in neonates who have seizures that are not adequately controlled with previous AED treatment, and to identify the optimal BRV dose (Exploratory Cohort) for the treatment of subjects enrolled into the Confirmatory Cohorts of this study. Secondary objectives include the evaluation of the short-term safety and tolerability of BRV in neonates and the evaluation of the efficacy of BRV in severe and nonsevere seizure burden (defined as total minutes of ENS per hour) in neonates with seizures that are not adequately controlled with previous AED treatment	PB no longer required as first line treatment prior to BRV
Section 1 Summary	Subjects must be of 34 weeks to less than 42 weeks of gestational age (GA) at birth and up to 28 days of postnatal age at the time of enrollment.	At enrollment, subjects must be at least 34 weeks of corrected gestational age (CGA). In addition, term neonates up to 27 days of postnatal age (PNA) and preterm neonates up to 40 weeks of postmenstrual age (PMA) and 27 days of PNA can be enrolled.	Age at enrollment was modified

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 1 Summary	Subjects must have a confirmed diagnosis of ENS by multichannel video-electroencephalography (VEEG) of ≥2 minutes of cumulative ENS or ≥3 identifiable ENS within the 2 hours prior to entering the Evaluation Period (ENS is defined as a seizure lasting for at least 10 seconds on VEEG), despite receiving PB for the treatment of repeated seizures. The maximum study duration per subject will be up to 75 days, which consists of a Screening Period, Baseline Period, Evaluation Period, BRV Extension Period, Down-Titration Period (Confirmatory Cohorts only), and Safety Follow-Up Period. All subjects who participate in the BRV Extension Period must be offered entry into the long-term study N01266, if they meet the eligibility criteria. Before entering the long-term study, subjects must be on oral BRV	Subjects must have a confirmed diagnosis of ENS by multichannel video-electroencephalography (VEEG) of ≥2 minutes of cumulative ENS or ≥3 identifiable ENS prior to entering the Evaluation Period (ENS is defined as a seizure lasting for at least 10 seconds on VEEG), despite receiving AED treatment. The maximum study duration per subject will be up to 75 days, which consists of a Screening Period, Baseline Period (Confirmatory Cohorts only), Evaluation Period, BRV Extension Period, Down-Titration Period (Confirmatory Cohorts only), and Safety Follow-Up Period. All subjects who participate in the BRV Extension Period must be offered entry into a long-term study, if they meet the eligibility criteria. Before entering the long-term study, subjects must be on oral BRV	Clarification

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 1 Summary	The PK variables are the plasma concentrations of BRV, the area under the curve (AUC), volume of distribution, and clearance of BRV in neonates. Further, PK assessments will include plasma concentrations of concomitant antiepileptic drugs (AEDs) (PB and phenytoin [PHT]).	The PK variables are the plasma concentrations of BRV, the area under the curve (AUC), volume of distribution, and clearance of BRV in neonates. Further, PK assessments will include plasma concentrations of concomitant phenobarbital (PB) and phenytoin (PHT) if administered	Clarification
Section 1 Summary	The efficacy of BRV will be analyzed based on the following variables:	The efficacy of BRV will be analyzed for the Confirmatory Cohorts based on the following variables:	Clarification

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 1 Summary	A BRV responder is defined as a subject who achieves a reduction in seizure burden (ENS in minutes per hour), compared to the seizure burden measured during the 2-hour Baseline Period immediately prior to BRV administration, evaluated for a 2-hour period starting 1 hour after the start of initial BRV treatment. Reduction in seizure burden is defined as at least 80% reduction in nonsevere seizure burden (nonsevere seizure burden is defined as ≤50% seizure activity on VEEG in any 30-minute timespan) or at least 50% reduction in severe seizure burden (severe seizure burden is defined as >50% seizure activity on VEEG in any 30-minute timespan); timespans of 30 minutes refer to the following intervals within the 2-hour period: 0 to ≤30 minutes, >30 to ≤60 minutes, >60 to ≤90 minutes, and >90 to ≤120 minutes.	A BRV responder is defined as a subject who achieves a reduction in seizure burden (ENS in minutes per hour), without need for rescue medication, compared to the seizure burden measured during the Baseline Period immediately prior to BRV administration, evaluated for a 2-hour period starting 1 hour after the start of initial BRV treatment. Reduction in seizure burden is defined as at least 80% reduction in nonsevere seizure burden (nonsevere seizure burden is defined as ≤50% seizure activity on VEEG in all 30-minute timespans) or at least 50% reduction in severe seizure burden (severe seizure burden is defined as >50% seizure activity on VEEG in any 30-minute timespan). Timespans of 30 minutes refer to the following intervals within the 2-hour period: 0 to ≤30 minutes, >30 to ≤60 minutes, >60 to ≤90 minutes, and >90 to ≤120 minutes.	Clarification
Section 1 Summary	Key efficacy variables	Secondary efficacy variables	Changed key efficacy variables to efficacy variables

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 2.1 Epidemology and treatment of targeted disease	Minor editorial changes	Accepted	Not applicable
Section 2.2 Background information regarding product	Removed outdated background information	Updated with new background information	To provide more current marketing information
Section 2.2 Background information regarding product	The following text was removed: The study was amended to allow direct enrollment of at least 100 subjects 4 years to <17 years of age who have focal epilepsy. Subject participation in N01266 will extend from study entry for approximately 3 years.	No additional text was added	Removed study information for N01266

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 2.3 Rationale for the study	N01349 represents the first study of BRV in neonatal subjects, and will evaluate the PK, efficacy, and safety of BRV in neonates (with an age of 34 weeks to less than 42 weeks of GA at birth and up to 28 days of postnatal age at the time of enrollment) with repeated EEG seizures. A historical control group treated with MDZ from literature (matched in age and condition) will be used for the evaluation of efficacy.	N01349 represents the first study of BRV in neonatal subjects, and will evaluate the PK, efficacy, and safety of BRV in neonates (up to 27 days of PNA and preterm neonates up to 40 weeks of PMA and 27 days of PNA.	Age at enrollment was modified
Section 3.1 Primary objective and Section 3.2 Secondary objectives	Removed “PB”	Added “previous AED”	PB no longer required as first line treatment prior to BRV

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 4.1 PK variables (Exploratory and Confirmatory Cohorts)	The PK variables, all of which are primary, are as follows: • Plasma concentrations of BRV and its metabolites ucb-42145 (acid), ucb-100406-1 (hydroxy), and ucb-107092-1 (hydroxyacid) • AUC, volume of distribution, and clearance of BRV • Plasma concentrations of concomitant AEDs (PB and PHT) •	Section 4.1.1 Primary PK variable The primary PK variable is as follows: • Plasma concentrations of BRV following first dose on Day 1 Section 4.1.2 Other PK variables • Plasma concentrations of BRV on other occasions • Plasma concentrations of BRV metabolites ucb-42145 (acid), ucb-100406-1 (hydroxy), and ucb-107092-1 (hydroxyacid) • AUC, volume of distribution, and clearance of BRV • Plasma concentrations of concomitant AEDs if administered	PK variables were split into “Primary and Other PK variables”
Section 4.2.1	Title: Key efficacy variables	Title: Secondary efficacy variables	Clarification throughout Section 4.2.1

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 4.2.1 Secondary efficacy variables	A BRV responder is defined as a subject who achieves the following reduction in seizure burden (ENS in minutes per hour) compared to the seizure burden measured during the 2-hour Baseline Period immediately prior to BRV administration, evaluated for a 2-hour period starting 1 hour after the start of initial BRV treatment: – At least 80% reduction in nonsevere seizure burden (Nonsevere seizure burden is defined as ≤50% seizure activity on VEEG in any 30-minute timespan)	• A BRV responder is defined as a subject who achieves the following reduction in seizure burden (ENS in minutes per hour) without need for rescue medication, compared to the seizure burden measured during the Baseline Period immediately prior to BRV administration, evaluated for a 2-hour period starting 1 hour after the start of initial BRV treatment: – At least 80% reduction in nonsevere seizure burden (Nonsevere seizure burden is defined as ≤50% seizure activity on VEEG in all 30-minute timespans)	Updated the definition of a BRV responder

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 4.2.1 Secondary efficacy variables	For this study, an ENS is defined as an EEG seizure lasting for at least 10 seconds on VEEG. Baseline seizure burden is defined as seizure burden measured on the continuous VEEG (total ENS in minutes per hour) during a period of 2 hours immediately prior to the first administration of study drug.	For this study, an ENS is defined as an EEG seizure lasting for at least 10 seconds on VEEG. Baseline seizure burden is defined as seizure burden measured on the continuous VEEG (total ENS in minutes per hour) during a period of up to 1 hour immediately prior to the first administration of study drug.	For this study, updated the ENS definition
Section 4.2.1 Secondary efficacy variables	• Absolute and percentage reduction in average seizure burden measured by continuous VEEG from Baseline to the end of the 96-hour Evaluation Period • Proportion of BRV responders during the 96-hour Evaluation Period (measured at the end of the 96-hour Evaluation Period)	• Absolute reduction in average seizure burden measured by continuous VEEG from Baseline to the end of the 96-hour Evaluation Period • Percent reduction in average seizure burden measured by continuous VEEG from Baseline to the end of the 96-hour Evaluation Period • Proportion of BRV responders at the end of the 96-hour Evaluation Period	"Absolute and percentage reduction in average seizure burden" were given 2 separate bullet points. Clarified that the proportion of BRV responders "at the end of the 96-hour Evaluation Period".

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 4.2.1 Secondary efficacy variables	• Proportion of subjects who are seizure-free by time interval at 3 hours, at 3-hour intervals thereafter through 24 hours, and every 12 hours to 24 hours following the start of the initial BRV treatment • Absolute and percent difference in clinical seizures at the end of the 24-hour Evaluation Period from Baseline for neonates with motor seizures at the time of inclusion	• Proportion of subjects who are seizure-free by time interval at 3 hours, at 3-hour intervals thereafter through 24 hours, and every 12 hours to 24 hours thereafter up until the end of the 96-hour evaluation period following the start of the initial BRV treatment • Absolute difference in clinical seizures at the end of the 24-hour Evaluation Period from Baseline for neonates with motor seizures at the time of inclusion • Percent difference in clinical seizures at the end of the 24-hour Evaluation Period from Baseline for neonates with motor seizures at the time of inclusion	Timepoint clarifications and “absolute and percent difference in clinical seizures“ were given 2 separate bullet points

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 4.2.2 Other efficacy variables	• Absolute and percentage reduction from Baseline in seizure burden at evaluation periods of 0 hours to 3 hours, >3 hours to 6 hours, >6 hours to 12 hours, >12 hours to 24 hours, >24 hours to 36 hours, >36 hours to 48 hours, >48 hours to 72 hours, and >72 hours to 96 hours after the start of initial BRV treatment	• Absolute reduction from Baseline in seizure burden at evaluation periods of 0 hours to 3 hours, >3 hours to 6 hours, >6 hours to 12 hours, >12 hours to 24 hours, >24 hours to 36 hours, >36 hours to 48 hours, >48 hours to 72 hours, and >72 hours to 96 hours after the start of initial BRV treatment • Percent reduction from Baseline in seizure burden at evaluation periods of 0 hours to 3 hours, >3 hours to 6 hours, >6 hours to 12 hours, >12 hours to 24 hours, >24 hours to 36 hours, >36 hours to 48 hours, >48 hours to 72 hours, and >72 hours to 96 hours after the start of initial BRV treatment	"Absolute and percentage reduction from Baseline in seizure burden" were given 2 separate bullet points.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 4.3 Safety variables (Exploratory and Confirmatory Cohorts)	The safety variables are as follows: • AEs as reported by the Investigator • Change from Baseline in EEG-parameters (assessment of sedation) to the end of the Evaluation Period	Section 4.3.1 Secondary safety variable The secondary safety variable is as follows: • AEs as reported by the Investigator Section 4.3.2 Other safety variables • Change from Baseline in EEG-parameters (assessment of sedation) to the end of the Evaluation Period (Confirmatory Cohorts only)	Separated safety variables into “Secondary” and “Other” Clarification

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 5.1 Study description	N01349 consists of 2 steps including a comparison with a historical control from literature (MDZ treatment from literature of subjects matched in age and condition) for the evaluation of efficacy. For the Exploratory Cohort (first step), enrolled subjects will receive one or multiple therapeutic doses or continuous infusion of MDZ (dose and dosing frequency of MDZ are at the discretion of the Investigator) prior to receiving BRV.	N01349 consists of 2 steps including a comparison with a historical control group (matched in age and condition) treated with AEDs comparable SOC and diagnostic methods from literature will be used for the evaluation of efficacy. For the Exploratory Cohort (first step), enrolled subjects will receive one or more AEDs for the treatment of ENS per SOC (first-line, second-line, or subsequent treatment; choice of treatment, dose, and dosing frequency are at the discretion of the Investigator) prior to receiving BRV.	Historical control changed from "MDZ" to "one or more AED treatments"
Section 5.1 Study description	Removed reference to N01266	Not applicable	Reference to N01266 removed since this study will be closed before the last N01349 subject was able to participate in that study for 3 years.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 5.1 Study description	Interpretation of the VEEGs will be done by local readers but may be supported by the blinded central reader, as needed. Subjects will be evaluated with VEEG monitoring at least during the Baseline, Evaluation, and Down-Titration (Confirmatory Cohorts only) Periods.	Interpretation of VEEGs recorded for the Confirmatory Cohorts will be done by local readers but may be supported by the blinded central reader, as needed. Subjects assigned to the Confirmatory Cohorts will be evaluated with VEEG monitoring at least during the Baseline, Evaluation, and Down-Titration Period.	Clarification
Section 5.1 Study description	However, every effort should be made to avoid VEEG interruption of the 2-hour Baseline VEEG and during the first 3 hours after the start of the initial BRV administration for the Confirmatory Cohort.	However, every effort should be made to avoid VEEG interruption of the Baseline VEEG and during the first 3 hours after the start of the initial BRV administration.	Clarification
Section 5.1 Study description	The schedule of assessments during the BRV Extension, Down-Titration, and Safety Follow-Up Periods for both the Exploratory and Confirmatory Cohorts are presented in Table 5-3	The schedule of assessments during the BRV Extension, Down-Titration (Confirmatory Cohorts only), and Safety Follow-Up Periods for both the Exploratory and Confirmatory Cohorts are presented in Table 5-3.	Clarification

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 5.1.1 Exploratory Cohort	For the Exploratory Cohort, at least 6 subjects who do not have adequate seizure control after receiving 1 to 3 doses of PB (PB treatment may have started prior to the subject's admission into the study site; total therapeutic administered dose of 20 to 40mg/kg; dosing regimen at the Investigator's discretion) will be enrolled and dosed with one or multiple therapeutic doses of MDZ (dose and dosing frequency of MDZ are at the discretion of the Investigator). Phenobarbital treatment must be discontinued prior to entering the Evaluation Period. Approximately 3 hours after the initiation of MDZ dosing, an initial low dose of BRV (0.5mg/kg [bid]) will be administered according to the standard of care. Treatment with MDZ will continue in parallel with BRV treatment. After the Exploratory Cohort completes the study, a PK and safety data review will be performed by the	For the Exploratory Cohort, at least 6 subjects who do not have adequate seizure control after they received one or more AEDs per SOC for the treatment of ENS (first-line, second-line, or subsequent treatment, which may have started prior to the subject's admission into the study site; choice of treatment, dose, and dosing regimen at the Investigator's discretion) will be enrolled. The AED treatment per SOC can be continued when BRV dosing is initiated. Alternatively, another AED treatment (choice of treatment, dose, and dosing regimen at the Investigator´s discretion) must be initiated and continue in parallel with BRV treatment. At any time after AED treatment per SOC for the treatment of ENS (first-line, second-line, or subsequent treatment) was initiated, an initial low dose of BRV (0.5mg/kg [bid]) will be administered at the Investigator´s discretion. After the Exploratory Cohort completes the study, a PK	PB no longer required as first line treatment prior to BRV. Historical control changed from "MDZ" to "one or more AED treatments". Clarification that enrollment will be put on hold during the first DMC

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	Data Monitoring Committee (DMC).	and safety data review will be performed by the DMC. During the review of data from the Exploratory Cohort, the enrollment of subjects will be on hold.	
Section 5.1.1 Exploratory Cohort	• Screening Period: from signing and dating of the written Informed Consent form (ICF) up to Cohort Assignment.	• Screening Period: from signing and dating of the written ICF up to initiation of the first BRV dose.	For consistency, "Cohort Assignment" changed globally to "up to initiation of the first BRV dose".
Section 5.1.1 Exploratory Cohort	The Screening Period is up to 36 hours prior to the first administration of MDZ (depending on the number of PB doses and time between PB doses and the interval between PB treatment and first administration of MDZ). The PB treatment may have been administered prior to the subject's enrollment in the study and/or at a location other than the study site. – Baseline Period (included in the Screening Period): 2 hours immediately prior to the start of MDZ infusion. The occurrence	The Screening Period starts up to 36 hours prior to the first administration of BRV. Phenobarbital, MDZ, PHT, LEV, or LDC may have been administered prior to the subject's enrollment into the study and/or at a location other than the study site. Subjects will enter the Evaluation Period and start BRV treatment as soon as the occurrence of ENS per inclusion criterion 2a is confirmed by the Investigator based on local EEG.	Two-hour Baseline EEG and 48-hour VEEG removed from the Exploratory Cohort; required ENS to be confirmed by the Investigator via local EEG

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	of ENS during the 2-hour Baseline Period must be confirmed either by the local or central VEEG reader prior to drug administration. Preferably, the central VEEG reader should confirm the required ENS. Video-EEGs that are acquired per standard of care prior to consenting and meet study-specific technical and quality requirements (eg, ability for immediate cloud-based central review) can be used as part of the Baseline assessment VEEG.		

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 5.1.1 Exploratory Cohort	• Evaluation Period (in total, 51 hours: 3 hours for the evaluation of MDZ and 48 hours for the evaluation of BRV): The first MDZ infusion marks the starting point of the Evaluation Period. Subjects will receive iv MDZ (one or multiple therapeutic doses or continuous infusion; MDZ dose and dosing frequency are at the discretion of the Investigator). Three hours after the initial dose of MDZ, a low dose of BRV (0.5mg/kg) will be administered as an approximately 15-minute iv infusion; additional 3 doses of BRV(0.5mg/kg) can be administered every 12 hours for 48 hours (at the discretion of the Investigator).	• Evaluation Period (48 hours): The first BRV infusion marks the starting point of the Evaluation Period. At any time after AED treatment per SOC for the treatment of ENS (first-line, second-line, or subsequent treatment) was initiated, a low dose of BRV (0.5mg/kg) will be administered as an approximately 15-minute iv infusion; additional 3 doses of BRV(0.5mg/kg) can be administered every 12 hours for 48 hours (at the discretion of the Investigator). The AED treatment per SOC can be continued when BRV dosing is initiated. Otherwise, another AED treatment (choice of treatment, dose, and dosing regimen at the Investigator´s discretion) must be initiated and continue in parallel with BRV treatment.	Treatment with “MDZ only” during the first 3 hours of the Evaluation Period removed from the Confirmatory Cohort; duration of the Evaluation Period hence shortened from 51 to 48 hour. Historical control changed from “MDZ” to “one or more AED treatments”. Other updates for clarification purposes.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 5.1.2 Confirmatory Cohorts	A total of at least 36 subjects without adequate seizure control after receiving 1 to 3 doses of PB (PB treatment may have started prior to the subject's admission into the study site; total therapeutic administered dose of 20 to 40mg/kg; dosing regimen at the Investigator's discretion) will enter the Confirmatory Cohorts. Phenobarbital treatment must be discontinued prior to entering the Evaluation Period.	A total of at least 36 subjects without adequate seizure control after receiving one or more of the following AEDs prior to or at the time of enrollment: PB, MDZ, PHT, LEV (≤60mg/kg/day), or LDC (first-line, second-line, or subsequent treatment, which may have started prior to the subject's admission into the study site; dose and dosing regimen at the Investigator's discretion) will enter the Confirmatory Cohorts. The AED treatment can be continued if the subject is on a stable dose for at least 1 hour at the time the first BRV infusion is initiated.	Phenobarbital no longer required as first line treatment prior to BRV; replaced by "one or more of the following AEDs: PB, MDZ, PHT, LEV (≤60mg/kg/day) or LDC (first-line, second-line or subsequent treatment; dose and dosing at the Investigator´s discretion)" for the Confirmatory Cohorts. Other edits for clarification purposes.
Section 5.1.2 Confirmatory Cohorts	Screening Period: from signing and dating of the written ICF up to Cohort Assignment. • The Screening Period is up to 36 hours prior to the first administration of BRV (depending on the number of PB doses and time between PB doses and the interval between PB treatment and first administration of BRV). The	Screening Period: from signing and dating of the written ICF up to initiation of the first BRV dose. • The Screening Period starts up to 36 hours prior to the first administration of BRV. Phenobarbital, MDZ, PHT, LEV (≤ 60mg/kg/day), or LDC may have been administered prior to the subject's enrollment into the	Clarified to define Baseline Period as part of Screening Period. Definition of status epilepticus for neonates enrolled into this study was added

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	PB treatment may have been administered prior to the subject's enrollment in the study and/or at a location other than the study site. • Baseline Period (included in the Screening Period): 2 hours immediately prior to the start of BRV infusion. The occurrence of ENS during the 2-hour Baseline Period must be confirmed either by the local or central VEEG reader prior to drug administration.	study and/or at a location other than the study site. ◦ Baseline Period (included in the Screening Period): ○ For subjects with **intermittent ENS**: at least 1 hour prior to entering the Evaluation Period ○ For subjects in **status epilepticus:** up to 30 minutes prior to entering the Evaluation Period. At least 15 minutes of continuous seizures, or 50% of cumulative seizure activity during a 30-minute interval are to be confirmed on EEG before the administration of BRV can start. As soon as subjects are considered to be in status epilepticus, steps required for the preparation of the initial BRV infusion can be initiated (eg, assignment of BRV kits through interactive response technology [IRT] and the	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
		dilution of BRV solution for iv infusion), even if the required EEG recording is not completed by that time. • Status epilepticus in neonates for the purpose of this study is defined as follows: o 15 minutes of continuous or cumulative electrographic or electroclinical seizure within 30 minutes The occurrence of ENS during the Baseline Period must be confirmed either by the local or central VEEG reader prior to BRV administration.	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 5.1.3 Study duration per subject	The maximum study duration per subject will be up to 75 days (Screening Period, Baseline Period, Evaluation Period, BRV Extension Period, Down-Titration Period, and Safety Follow-Up Period). The individual study duration will be shorter depending on the type of cohort to which subjects will be assigned, the age at enrollment, and the decision to enter into the BRV Extension Period.	The maximum study duration per subject will be up to 75 days (Screening Period [including Baseline Period (Confirmatory Cohorts only)], Evaluation Period, BRV Extension Period, Down-Titration Period [Confirmatory Cohorts only], and Safety Follow-Up Period). The individual study duration will be shorter depending on the type of cohort to which subjects will be assigned, the age at enrollment, and the decision to enter the BRV Extension Period.	Clarification
Table 5-1 Schedule of assessments - Screening and Evaluation Periods (Exploratory Cohort)	Column heading 2: -36h to -2h Column Heading 3: Baseline Period MDZ -2h to 0h	Column heading 2: -36h to 0h Column heading 3: Timepoint immediately before first BRV administration	Updated to reflect changes throughout protocol

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Table 5-1 Schedule of assessments - Screening and Evaluation Periods (Exploratory Cohort)	Not applicable	Time point immediately before first BRV administration: Vital signs Physical and neurological examination Sarnat scale for subjects with HIE Body weight Added the following to -36h to 0h: Primary cause of seizure Psychometric parameters: N-PASS and EEG-parameters	Updates based on updates made throughout the protocol
Table 5-1 Schedule of assessments - Screening and Evaluation Periods (Exploratory Cohort)	PB infusion VEEG-removed AEDs-removed AED PK sample	AED treatment per SOC AED PK sample (only when PB and PTH are used)	Change as reflected throughout protocol

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Table 5-1 Schedule of assessments - Screening and Evaluation Periods (Exploratory Cohort)	Footnote a Screening Period is from signing and dating of the written ICF up to Cohort Assignment. Footnote c The occurrence of ENS during the 2-hour Baseline Period must be confirmed either by the local or central VEEG reader prior to drug administration. Preferably, the central VEEG reader should confirm the required ENS. Footnote d Measurement of body weight is optional at 24 and 48 hours. Dosage of BRV during the Evaluation Period will be based on the subject's weight measured prior to the start of the first BRV administration. However, dosage calculation can be adjusted to a more recent weight measurement, upon discretion of the Investigator, if weight is measured during the Evaluation Period.	Footnote a Screening Period is from signing and dating of the written ICF up to initiation of the first BRV dose. Footnote c The occurrence of ENS prior to entering the Evaluation Period must be confirmed by the local VEEG reader prior to initial BRV administration. Footnote d Measurement of body weight is mandatory prior to BRV treatment and optional at 24 and 48 hours. Dosage of BRV during the Evaluation Period will be based on the subject's weight measured prior to the start of the first BRV administration. However, dosage calculation can be adjusted to a more recent weight measurement, upon discretion of the Investigator, if weight is measured during the Evaluation Period.	Change as reflected throughout protocol

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Table 5-2 Schedule of assessments - Screening and Evaluation Periods (Confirmatory Cohorts)	Column 2: -36h to -2h Column 3: -2h to 0h	Column 2: -36h to up to -1h Column 3: Up to -1h to 0h	Change as reflected throughout protocol
Table 5-2 Schedule of assessments - Screening and Evaluation Periods (Confirmatory Cohorts)	PB infusion AED PK sample	AED treatment (PB, MDZ, PHT, LEV [≤60mg/kg/day], or LDC)[a] Assessment to be completed during the Screening Period (both visits) and at all timepoints after 6h during the Evaluation Period AED PK sample (only when PB and PHT are used)	Change as reflected throughout protocol

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Table 5-2 Schedule of assessments - Screening and Evaluation Periods (Confirmatory Cohorts)	Footnote a: Screening Period is from signing and dating of the written ICF up to Cohort Assignment. Not applicable Footnote d: The occurrence of ENS during the 2-hour Baseline Period must be confirmed either by the local or central VEEG reader prior to drug administration. Preferably, the central VEEG reader should confirm the required ENS.	Footnote a: Screening Period is from signing and dating of the written ICF up to initiation of the first BRV dose. Footnote b added: The duration of the Baseline EEG depends on seizure activity. Subjects with intermittent seizures will enter the Evaluation Period based on at least 1 hour of EEG recording. Subjects in status epilepticus will enter the Evaluation Period based on up to 30 minutes of EEG recording, ie, as soon as 15 minutes of continuous seizures or 50% of cumulative seizure activity is confirmed on EEG. Subsequent footnotes were re-alphabetized. Footnote e: The occurrence of ENS during the Baseline Period must be confirmed either by the local or central VEEG reader prior to drug administration. Preferably, the central VEEG reader should confirm the required ENS.	Change as reflected throughout protocol

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 5.3 Schematic diagrams	Figure 5-1, Figure 5-2, Figure 5-3, and Figure 5-4	Figure 5-1, Figure 5-2, Figure 5-3, and Figure 5-4	All figures updated to reflect protocol changes
Section 5.4.1 Rationale for study design	Thus, study N01349 was designed to include PB as the first line of treatment, and only those subjects who do not have adequate seizure control with PB will be permitted to continue in the study	Thus, study N01349 was designed for a flexible treatment of ENS, and only those subjects who do not have adequate seizure control with previous AED treatment will be permitted to continue in the study	PB no longer required as first line treatment prior to BRV
Section 5.4.1 Rationale for the study design	Thus, only neonates with an age at birth of 34 weeks to less than 42 weeks of GA (and up to 28 days of postnatal age at the time of enrollment) with repeated neonatal seizures (assessed by VEEG) will be enrolled in N01349.	At enrollment, subjects must be at least 34 weeks of CGA. In addition, term neonates up to 27 days of PNA and preterm neonates up to 40 weeks of PMA and 27 days of PNA can be enrolled.	Age at enrollment has been modified

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 6.1 Inclusion Criteria	2a. Confirmation on VEEG of ≥2 minutes of cumulative ENS or ≥3 identifiable ENS within the 2 hours prior to entering the Evaluation Period (ENS is defined as a seizure lasting for at least 10 seconds on VEEG), despite receiving PB (total therapeutic administered dose of 20 to 40mg/kg) for the treatment of repeated seizures. The occurrence of ENS during the 2-hour period must be confirmed either by the local or central VEEG reader prior to drug administration. Preferably, the central VEEG reader should confirm the required ENS.	2a. Confirmation on VEEG of ≥2 minutes of cumulative ENS or ≥3 identifiable ENS prior to entering the Evaluation Period (ENS is defined as a seizure lasting for at least 10 seconds on VEEG), despite receiving previous AED treatment for the treatment of electroencephalographic seizures. The occurrence of ENS during an up to 1-hour period must be confirmed either by the local or central VEEG reader prior to drug administration. Preferably, the central VEEG reader should confirm the required ENS	Based on agency recommendation, the 2-hour Baseline EEG has been removed. For clarification 2-hour period was replaced with up to 1-hour period
Section 6.1 Inclusion Criteria	3. Subject is male or female, with an age at birth of 34 weeks to less than 42 weeks of GA and up to 28 days of postnatal age at the time of enrollment.	3. Subject is male or female and must be at least 34 weeks of CGA. In addition, term neonates up to 27 days of PNA and preterm neonates up to 40 weeks of PMA and 27 days of PNA can be enrolled	Based on feedback from Investigators, the age of subjects allowed to participate in the study will be extended to help with enrollment.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 6.2 Exclusion Criteria	1a. Subject received AED treatment (other than the required 1 to 3 doses of PB [total therapeutic administered dose of 20 to 40mg/kg] for the treatment of repeated seizures) prior to entering the Evaluation Period.	1a. Subject receiving AED treatment other than PB, MDZ, PHT, LEV (≤60mg/kg/day), or LDC for the treatment of seizures prior to or at the time of enrollment (Confirmatory Cohorts only).	Phenobarbital no longer required as first line treatment prior to BRV
Section 6.2 Exclusion Criteria	2. Subject with seizures responding to PB (total therapeutic administered dose of 20 to 40mg/kg), pyridoxine treatment, or correction of metabolic disturbances (hypoglycemia, hypomagnesemia or hypocalcemia).	2. Subject with seizures responding to previous AED treatment immediately prior to BRV treatment, pyridoxine treatment, or correction of metabolic disturbances (hypoglycemia, hypomagnesemia, or hypocalcemia).	Phenobarbital no longer required as first line treatment prior to BRV
Section 7.1 Description of investigational medicinal products	Refer to the pharmacy manual for further details on the handling of BRV.	Refer to the IMP Handling Manual for further details on the handling of BRV.	Clarification
Section 7.1 Description of investigational medicinal products	Not applicable	After the completion of the study, BRV treatment per SOC may be continued as prescribed but will not be provided by the Sponsor.	Clarification

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 7.2 Treatments to be administered	Subjects in the Exploratory Cohort will be dosed with iv MDZ (dosing and dosing frequency of MDZ are at the discretion of the Investigator). Three hours after the start of MDZ infusion, BRV dosing (0.5mg/kg bid) will start according to the standard of care. Treatment with MDZ will continue in parallel with BRV treatment.	Subjects in the Exploratory Cohort will be dosed with BRV (0.5mg/kg bid) according to the sites standard procedures. Treatment with AEDs per SOC (first-line, second-line, or subsequent treatment) will continue in parallel with BRV treatment.	Historical control changed from "MDZ".
Section 7.2 Treatments to be administered	Not applicable	Treatment with previous AEDs (PB, MDZ, PHT, LEV [≤60mg/kg/day], or LDC) is permitted to continue if the subject is on a stable dose from 1 hour prior to initiation of the BRV treatment.	Clarification
Section 7.3 Packaging	Commercial MDZ will be used for this study and will not be provided by the Sponsor.	Other AED treatments will be used for this study and will not be provided or covered by the Sponsor.	Historical control changed from "MDZ".

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 7.5 Handling and storage requirements	Appropriate storage conditions must be ensured either by controlling the temperature (eg, room, refrigeration unit) or by completing a temperature log in accordance with local requirements on a regular basis (eg, once a week), showing actual minimum/maximum temperatures reached over the time interval.	Appropriate storage conditions must be ensured either by controlling the temperature (eg, room, refrigeration unit) or by completing a temperature log in accordance with local requirements on a regular basis (eg, once per working day), showing actual minimum/maximum temperatures reached over the time interval.	Clarification

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 7.8.1 Permitted concomitant treatments (medications and therapies)	Concomitant treatment with AEDs is permitted as follows: **Prior** to first BRV administration: • PB • MDZ (Exploratory Cohort only) **After** first BRV administration: • Any AEDs (including MDZ) – Exploratory Cohort: from first BRV administration • Confirmatory Cohorts: from 3 hours following first BRV administration	For the Exploratory Cohort, concomitant treatment with AEDs is permitted at any time. For the Confirmatory Cohorts, concomitant treatment with AEDs is permitted to continue in parallel with BRV treatment if subjects are on a stable dose from 1 hour prior to initiation of BRV treatment. Changes to concomitant AEDs are permitted from 3 hours onward following first BRV administration.	PB is no longer required as first-line treatment prior to BRV; historical control changed from MDZ.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 7.8.2 Prohibited concomitant treatments (medications and therapies)	For subjects treated with BZDs, at least 1 week should elapse before receiving the initial BRV dose. For the Exploratory Cohort, subjects will not be permitted to receive treatments for neonatal seizures (other than the specified PB doses and MDZ) prior to the first BRV administration. For the Confirmatory Cohorts, subjects will not be permitted to receive treatments for neonatal seizures (other than the specified PB doses) prior to and for the first 3 hours after the first BRV administration. The use of LEV is prohibited throughout the study for both the Exploratory and Confirmatory Cohorts.	For the Confirmatory Cohorts, subjects will not be permitted to change concomitant treatment for neonatal seizures for the first 3 hours after the first BRV administration. The initiation of LEV treatment after the first time BRV is introduced is prohibited throughout the study for the Confirmatory Cohorts.	Clarification

Section Impacted	Key components of previous text	Key components of amended text	Rationale
7.8.3 Rescue medication	Rescue medication in this study is considered as any treatment with AEDs. Rescue medication can be given at any time if considered necessary by the Investigator. However, during the Evaluation Period rescue medication should not be administered – if possible – in the following time frames: • Prior to BRV dosing for the Exploratory Cohort (except for MDZ as scheduled in the Protocol). • During the first 3 hours after the initial dose of BRV for the Confirmatory Cohorts. If this occurs, subjects will be considered BRV nonresponders.	Any treatment initiation with a new AED, or any increase of dose or frequency of an existing concomitant AED for the treatment of seizures during the Evaluation Period is considered rescue treatment. Rescue medication can be given at any time if considered necessary by the Investigator. However, during the Evaluation Period rescue medication should not be administered – if possible – in the following time frames: • During the first 3 hours after the initial dose of BRV for the Confirmatory Cohorts. If this occurs, subjects will be considered BRV nonresponders for the evaluation of the main efficacy variable.	Clarification
Section 8.1.1 Screening Period	The Screening Period will be from the signing and dating of the written ICF by the parent(s) or legal representative(s) of the subject to the end of the Baseline Period. Any AEs, AEDs,	The Screening Period will be from the signing and dating of the written ICF by the parent(s) or legal representative(s) up to initiation of the first BRV dose. Any AEs, AEDs, concomitant	Text has been updated to reflect the changes to the study schedule of assessments. Other text changes were also made to provide consistent language throughout the protocol. Section heading 8.1.2 Baseline Period was deleted and text

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	concomitant medications, and medical procedures will be collected after the ICF is signed. The subject's eligibility to participate in this study will be assessed. The subject identification card will be dispensed. The Screening Period is up to 36 hours prior to the first administration of MDZ (depending on the number of PB doses and time between PB doses and the interval between PB treatment and first administration of MDZ). Body weight measurements can be taken between 36 hours and 2 hours for the determination of PB dosage (mg/kg). The PB treatment may have started prior to the subject's admission to the study and/or at a location other than the study site but should be completed prior to the 2-hour Baseline Period.	medications, and medical procedures will be collected after the ICF is signed. The subject's eligibility to participate in this study will be assessed. The subject identification card will be dispensed. The Screening Period starts up to 36 hours prior to the first administration of BRV. Phenobarbital, MDZ, PHT, LEV (≤ 60mg/kg/day), or LDC may have been administered prior to the subject's enrollment into the study and/or at a location other than the study site. Subjects will enter the Evaluation Period and start BRV treatment as soon as the occurrence of ENS per inclusion criterion 2a is confirmed by the Investigator based on local EEG. The following assessments will be performed immediately before the first administration of BRV is initiated: • Verification of inclusion/exclusion criteria. Confirmation on VEEG of	merged with Section 8.1.1. All subsequent section headings were updated.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	At the determination of the Investigator, subjects achieving adequate seizure control after initial PB treatment (total therapeutic administered dose of 20 to 40mg/kg; dosing regimen at the Investigator's discretion) will be considered PB responders. Those subjects will be classified as screen failures and will not be assigned to BRV treatment	≥2 minutes of cumulative ENS or ≥3 identifiable ENS prior to entering the Evaluation Period (ENS is defined as a seizure lasting for at least 10 seconds on VEEG), despite treatment with one or more AEDs per SOC • Vital signs (blood pressure, pulse rate, respiratory rate [including apneas], oxygen saturation [pulse oximetry], and body temperature) • Physical and neurological examination (Sarnat scale for subjects with HIE; physical examination will include a check for the presence of skin rash and skin hypersensitivity) • Body weight • Head circumference (to be taken within 7 days prior to drug administration, or at birth for subjects ≤7 days old) • Heart rate monitoring • Safety laboratory assessments (hematology, biochemistry,	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
		liver enzymes, and endocrinology) • Thompson score (for subjects with HIE) • Mechanical ventilation • AEs as reported by the Investigator • Recording of AEDs, concomitant medications, and medical procedures Laboratory measurements will be performed by local laboratories unless historical data is available. Historical safety laboratory assessments, previously collected as standard of care, may be accepted from referring hospitals as measurement prior to first use of BRV if performed 36 hours prior to the start of the Evaluation Period. In this case, test results will be considered medical history. Prior laboratory assessment results should be available and verified prior to initiation of the first BRV infusion. At the determination of the Investigator, subjects achieving	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
		adequate seizure control following AED treatment per SOC will be considered AED responders. Those subjects will be classified as screen failures and will not be assigned to BRV treatment.	

Section 8.1.2 Baseline Period	The Baseline Period is included in the Screening Period; the period begins 2 hours before and ends at the initiation of the MDZ infusion. The occurrence of ENS during the 2-hour Baseline Period must be confirmed either by the local or central VEEG reader prior to drug administration. Preferably, the central VEEG reader should confirm the required ENS. Video-EEGs that are acquired per standard of care prior to consenting and meet study-specific technical and quality requirements (eg, ability for immediate cloud-based central review) can be used as part of the Baseline assessment VEEG. The following assessments will be performed during the Baseline Period: • Verification of inclusion/exclusion criteria. Confirmation on VEEG of ≥2 minutes of cumulative ENS or ≥3 identifiable ENS within the 2 hours prior to entering the Evaluation Period (ENS is defined as a seizure lasting for at least 10 seconds	Not applicable	This section heading was deleted, and text merged into Section 8.1.1. Subsequent headings were renumbered

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	on VEEG), despite PB treatment prior to Baseline • Demographic data Medical history (including Apgar score) • Vital signs (blood pressure, pulse rate, respiratory rate, oxygen saturation [pulse oximetry] including apneas, and body temperature) • Physical and neurological examination (Sarnat scale for subjects with HIE; physical examination will include a check for the presence of skin rash and skin hypersensitivity) • Length • Body weight • Head circumference (Baseline measurement should be taken within 7 days prior to drug administration, or at birth for subjects ≤7 days old) • Primary cause of seizure (HIE, hemorrhage, or infarction; CNS		

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	malformations; CNS infections; undetermined causes) • N-PASS and EEG parameters for the assessment of sedation • Video-EEG • Heart rate monitoring • Safety laboratory assessments (hematology, biochemistry, liver enzymes, and endocrinology) • Thompson score (for subjects with HIE) • Mechanical ventilation • AEs as reported by the Investigator Baseline laboratory measurements will be performed by local laboratories unless historical data is available. Historical safety laboratory assessments, previously collected as standard of care, may be accepted from referring hospitals as Baseline measurement if performed 36 hours prior to the start of the Evaluation Period. In		

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	this case, test results will be considered medical history. Prior laboratory assessment results should already be available at Baseline and verified prior to initiation of the MDZ infusion.		
Section 8.1.4 Evaluation Period	The first MDZ infusion marks the starting point of the Evaluation Period. The Evaluation Period will last for 51 hours in total (3 hours for the evaluation of MDZ and 48 hours for the evaluation of BRV). After the enrollment of subjects, the weight of the subject will be measured and MDZ will be administered. The following assessments will be performed at the start of and 3 hours after the initial MDZ administration: • Vital signs (blood pressure, pulse rate, respiratory rate, oxygen saturation [pulse oximetry] including apneas, and body temperature); only at the start of MDZ administration • Video-EEG	Section 8.1.3 Evaluation Period The first BRV infusion marks the starting point of the 48-hour Evaluation Period. An initial iv dose of BRV (0.5mg/kg) will be administered as an approximately 15-minute infusion. At the discretion of the Investigator, 3 additional iv BRV doses can be administered, up to a total of 4 iv BRV doses (0.5mg/kg bid) during the 48-hour BRV Evaluation Period. The following assessments will be performed after the end of the first BRV infusion:	Text has been updated to reflect the changes to the study schedule of assessments. Other text changes were also made to provide consistent language throughout the protocol.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	• Heart rate monitoring • AEs as reported by the Investigator • AEDs, concomitant medications, and medical procedures • Infusion site reaction monitoring Three hours post-start of initial MDZ infusion, an initial iv dose of BRV (0.5mg/kg) will be administered as an approximately 15-minute infusion. At the discretion of the Investigator, 3 additional iv BRV doses can be administered, up to a total of 4 iv BRV doses (0.5mg/kg bid) during the 48-hour BRV Evaluation Period. The following assessments will be performed after the first BRV administration:		

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 8.1.4.2 Extension Period Visit 2	The EPV2 will be performed on the same day when the subject enters the long-term study. The following assessments will be performed:	The EPV2 should be performed on the same day when the subject enters the long-term study. The following assessments will be performed:	Clarification
Section 8.2.1 Screening Period	The Screening Period will be from the signing and dating of the written ICF by the parent(s) or legal representative(s) of the subject to the end of the Baseline Period. Any AEs, AEDs, concomitant medications, and medical procedures will be collected after the ICF is signed. The subject's eligibility to participate in this study will be assessed. The subject identification card will be dispensed.	The Screening Period will be from the signing and dating of the written ICF by the parent(s) or legal representative(s) of the subject up to initiation of the first BRV dose. Any AEs, AEDs, concomitant medications, and medical procedures will be collected after the ICF is signed. The subject's eligibility to participate in this study will be assessed. The subject identification card will be dispensed. The Screening Period starts up to 36 hours prior to the first administration of BRV. The treatment with one or more of the following AEDs prior to or at the time of enrollment: PB, MDZ, PHT, LEV (≤60mg/kg/day), or LDC (first-line, second-line, or subsequent treatment; choice of treatment, dose, and dosing	Text has been updated to reflect the changes to the study schedule of assessments. Other text changes were also made to provide consistent language throughout the protocol.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	The Screening Period is up to 36 hours prior to the first administration of BRV (depending on the number of PB doses and time between PB doses and the interval between PB treatment and first administration of BRV). Body weight measurements can be taken between 36 hours and 2 hours for the determination of PB dosage (mg/kg). The PB treatment may have started prior to the subject's enrollment in the study and/or at a location other than the study site but should be completed prior to the 2-hour Baseline Period. At the determination of the Investigator, subjects achieving adequate seizure control after initial PB treatment (total therapeutic administered dose of 20 to 40mg/kg; dosing regimen at the Investigator's discretion) will be considered PB responders.	regimen at the Investigator's discretion) may have started prior to the subject's enrollment in the study and/or at a location other than the study site. At the determination of the Investigator, subjects achieving adequate seizure control following any of the following AEDs: PB, MDZ, PHT, LEV (≤60mg/kg/day), or LDC will be considered AED responders.	
Section 8.2.2 Baseline Period	The Baseline Period will be2 hours immediately prior to the start of BRV infusion.	Section 8.2.1.1 Baseline Period The Baseline Period will be up to	Section heading numbering changed because Baseline is part of Screening. Text has been updated to reflect the changes to the study schedule of assessments. Other

Section Impacted	Key components of previous text	Key components of amended text	Rationale
		1 hour immediately prior to the start of initial BRV infusion and depend on seizure activity: - For subjects with intermittent ENS: at least 1 hour prior to entering the Evaluation Period - For subjects in status epilepticus: up to 30 minutes prior to entering the Evaluation Period. At least 15 minutes of continuous seizures or 50% of cumulative seizure activity during a 30-minute interval are to be confirmed on EEG before the administration of BRV can start. As soon as subjects are considered to be in status epilepticus, steps required for the preparation of the initial BRV infusion can be initiated (eg, assignment of BRV kits through interactive IRT and the dilution of BRV solution for iv infusion), even if the required EEG recording is not completed by that time.	text changes were also made to provide consistent language throughout the protocol.
	The occurrence of ENS during the 2-hour Baseline Period must be confirmed either by the local or central VEEG reader prior to drug administration.	The occurrence of ENS during the Baseline Period must be confirmed either by the local or central VEEG reader prior to drug administration.	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	• Verification of inclusion/exclusion criteria. Confirmation on VEEG of ≥2 minutes of cumulative ENS or ≥3 identifiable ENS within the 2 hours prior to entering the Evaluation Period (ENS is defined as a seizure lasting for at least 10 seconds on VEEG), despite PB treatment prior to Baseline	• Verification of inclusion/exclusion criteria. Confirmation on VEEG of ≥2 minutes of cumulative ENS or ≥3 identifiable ENS within the 1 hour prior to entering the Evaluation Period (ENS is defined as a seizure lasting for at least 10 seconds on VEEG), despite treatment with one or more AEDs per SOC	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 8.2.3 Evaluation Period	Not applicable	The AED treatment initiated prior to first administration of BRV can be continued if the subject is on a stable dose for at least 1 hour at the time the first BRV infusion is initiated.	Text has been updated to reflect the changes to the study schedule of assessments. Other text changes were also made to provide consistent language throughout the protocol.
Section 8.2.4 BRV Extension Period	Extension Period Visit 2 will be performed on the same day when the subject enters the long-term study N01266 (see Section 8.2.4.2). If study N01266 is performed outside the N01349 hospital, an interval of up to 3 days between the N01349 EPV2 and N01266 Entry Visit is allowed.	Extension Period Visit 2 will be performed on the same day when the subject enters the long-term study (see Section 8.2.4.2). If the long-term study is performed outside the N01349 hospital, an interval of up to 3 days between the N01349 EPV2 and long-term study Entry Visit is allowed.	Text changes were made to provide consistent language throughout the protocol.
Section 8.2.4.2 Extension Period Visit 2	This visit will be performed on the same day when the subject enters the long-term study.	This visit should be performed on the same day when the subject enters the long-term study.	Text changes were made to provide consistent language throughout the protocol.
Section 10.1	Title: Assessment of the key efficacy variables	Title: Assessment of secondary efficacy variables (Confirmatory Cohort[s] only)	Text changes were made to provide consistent language throughout the protocol.
Section 10.1	The main efficacy variable is:	The main secondary efficacy variable is:	Text changes were made to provide consistent language throughout the protocol.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	A BRV responder is defined as a subject who achieved the following reduction in seizure burden (ENS in minutes per hour) compared to the seizure burden measured during the 2-hour Baseline Period immediately prior to BRV administration, evaluated for a 2-hour period starting 1 hour after the start of initial BRV treatment (Nonsevere seizure burden is defined as ≤50% seizure activity on VEEG in any 30-minute timespan) For this study, an ENS is defined as EEG seizure lasting for at least 10 seconds on VEEG. Baseline seizure burden is defined as seizure burden measured on the continuous VEEG (total ENS in minutes per hour) during a period of 2 hours immediately prior to the first administration of study drug.	A BRV responder is defined as a subject who achieved the following reduction in seizure burden (ENS in minutes per hour) without need for rescue medication, compared to the seizure burden measured during the Baseline Period immediately prior to BRV administration, evaluated for a 2-hour period starting 1 hour after the start of initial BRV treatment (Nonsevere seizure burden is defined as ≤50% seizure activity on VEEG in all 30-minute timespans) For this study, an ENS is defined as EEG seizure lasting for at least 10 seconds on VEEG. Baseline seizure burden is defined as seizure burden measured on the continuous VEEG (total ENS in minutes per hour) during a period of up to 1 hour immediately prior to the first administration of study drug.	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	For the analysis of the main efficacy variable (Section 4.2.1), subjects that are switched to another AED or have been administered any rescue medication (including BZDs) during the first 3 hours after initiation of BRV treatment will be considered BRV nonresponders. Subjects must not have switched to another AED or used >1 dose of rescue medication (including BZDs) following the first 3 hours after initiation of BRV treatment to be considered BRV responders for the analysis of the following key efficacy variables:	For the analysis of the main secondary efficacy variable (Section 4.2.1), subjects who started another AED, increased the dose or frequency of administration of an AED ongoing at the time the first BRV infusion started, or are switched to another AED, or have been administered any rescue medication for the treatment of ENS during the first 3 hours after initiation of BRV treatment will be considered BRV nonresponders. For the analysis of the following secondary efficacy variables, subjects who started another AED, increased the dose or frequency of administration of an AED ongoing at the time the first BRV infusion started, or are switched to another AED, or have been administered any rescue medication for the treatment of ENS following the first 3 hours after initiation of BRV treatment will be considered BRV responders: • Absolute reduction in average seizure burden measured by continuous VEEG from	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	• Absolute and percentage reduction in average seizure burden measured by continuous VEEG from Baseline to the end of the 96-hour Evaluation Period • Proportion of BRV responders during the 96-hour Evaluation Period (measured at the end of the 96-hour Evaluation Period) • Seizure freedom at the end of the Down-Titration Period (Confirmatory Cohorts only) • Proportion of subjects who are seizure-free by time interval at 3 hours, at 3-hour intervals thereafter through 24 hours, and every 12 hour to 24 hours following the start of the initial BRV treatment • Absolute and percent difference in clinical seizures at the end of the 24-hour Evaluation Period from	Baseline to the end of the 96-hour Evaluation Period • Percent reduction in average seizure burden measured by continuous VEEG from Baseline to the end of the 96-hour Evaluation Period -Proportion of BRV responders at the end of the 96-hour Evaluation Period • Seizure freedom at the end of the Down-Titration Period • Proportion of subjects who are seizure-free by time interval at 3 hours, at 3-hour intervals thereafter through 24 hours, and every 12 hours to 24 hours following the start of the initial BRV treatment • Absolute difference in clinical seizures at the end of the 24-hour Evaluation Period from Baseline for neonates with motor seizures at the time of inclusion	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	Baseline for neonates with motor seizures at the time of inclusion	• Percent difference in clinical seizures at the end of the 24-hour Evaluation Period from Baseline for neonates with motor seizures at the time of inclusion	
Section 10.2 Assessment of other efficacy variables	To further evaluate BRV efficacy, a descriptive comparison will be conducted of the main efficacy variable data from N01349 with published responder rates for MDZ (historical control group matched in age and condition) effective for the treatment of neonatal seizures in subjects of similar age (<29 days of postnatal age) and condition (neonatal seizures as noted in N01349 eligibility criteria). A recent study (Weeke et al, 2016) provides response rates for second line MDZ treatment of neonatal seizures in a similar population and with primary endpoints comparable to N01349.	To further evaluate BRV efficacy, a descriptive comparison will be conducted of the main efficacy variable data from N01349 with published responder rates for one or more AED treatments from literature (historical control group matched in age and condition) effective for the treatment of neonatal seizures in subjects of similar age (<29 days of postnatal age) and condition (neonatal seizures as noted in N01349 eligibility criteria). A recent study (Weeke et al, 2016) provides response rates for second line AED treatment of neonatal seizures in a similar population and with primary endpoints comparable to N01349.	Historical control changed from "MDZ" to "one or more AED treatments"
Section 10.3 Seizure burden	Seizure burden is defined as the total minutes of ENS per hour. Seizure burden information will	Seizure burden is defined as the total minutes of ENS per hour. Seizure burden information will be	Clarification

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	be recorded via a continuous VEEG. Seizure burden at Baseline will be evaluated over a 2-hour period.	recorded for the Confirmatory Cohorts via a continuous VEEG. Seizure burden at Baseline will be evaluated over a period of at least 1 hour (subjects with intermittent seizures) or up to 30 minutes (subjects in status epilepticus).	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
11.1.1.1 Adverse event	Signs or symptoms of the condition/disease for which the IMP is being studied should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the Investigator from the subject's history or the Baseline Period.	Signs or symptoms of the condition/disease for which the IMP is being studied should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the Investigator from the subject's history or based on assessments performed prior to the first administration of BRV.	Clarification
Section 11.3.3 Vital signs	Vital sign measurements, including systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, oxygen saturation (pulse oximetry), and body temperature, should be measured at the study timepoints as described in…	Vital sign measurements, including systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate (including apneas), oxygen saturation (pulse oximetry), and body temperature, should be measured at the study timepoints as described in…	Text changes were made to provide consistent language throughout the protocol.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 13.1 Definition of analysis sets	The Pharmacokinetic Per-Protocol Set will consist of all subjects who provide at least 1 measureable post-Baseline plasma sample (with recorded sampling time) on at least 1 post-Baseline visit with documented study drug intake times. This analysis set will be used for the Exploratory Cohort and the Confirmatory Cohort(s). The Full Analysis Set will be used for the analysis of seizure data and will consist of all subjects in the SS who have a minimum of 2 hours of interpretable VEEG data from both the Baseline period and the first 3 hours of the post-Baseline period after initial BRV treatment.	The Pharmacokinetic Per-Protocol Set will consist of all subjects who provide at least 1 measurable plasma sample (with recorded sampling time) on at least 1 post-Baseline visit with documented study drug intake times. This analysis set will be used for the Exploratory Cohort and the Confirmatory Cohort(s). The Full Analysis Set will be used for the analysis of seizure data (efficacy) and will consist of all subjects in the SS who have a minimum of 2 hours of interpretable VEEG data from both the Baseline period and the first 3 hours of the post-Baseline period after initial BRV treatment.	Clarification

Section Impacted	Key components of previous text	Key components of amended text	Rationale
13.3.1 Exploratory Cohort	Based on the plasma samples collected for the Exploratory Cohort, relevant PK parameters including AUC, C_{max}, volume of distribution, and clearance, will be estimated using noncompartmental methods.	Based on the plasma samples collected for the Exploratory Cohort, relevant PK parameters including AUC, C_{max}, volume of distribution, and clearance, will be estimated using noncompartmental methods, with sub-analysis by concomitant use of hypothermia.	Text changes were made to provide consistent language throughout the protocol.
Section 13.5.1	Title: Analysis of key efficacy variables	Title: Analysis of secondary efficacy variables	Text changes were made to provide consistent language throughout the protocol.
Section 13.5.1 Analysis of the key efficacy variables	The main efficacy variable is the proportion of responders to BRV treatment from Baseline to 3 hours after the initial BRV dose. A BRV responder is defined as a subject who achieves at least 80% reduction in nonsevere seizure burden ("nonsevere" seizure burden being defined as ≤50% seizure activity on VEEG in any 30-minute timespan), or at least 50% reduction in severe seizure burden ("severe" seizure burden being defined as >50% seizure activity on VEEG in any 30-minute timespan) compared to	The main secondary efficacy variable is as follows: • Proportion of responders to BRV treatment from Baseline to 3 hours after the initial BRV dose. A BRV responder is defined as a subject who achieves the following reduction in seizure burden (ENS in minutes per hour) without need for rescue medication, compared to the seizure burden measured during the Baseline Period immediately prior to BRV administration, evaluated for a 2-hour period	Text changes were made to provide consistent language throughout the protocol.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	the seizure burden measured during the 2-hour Baseline Period immediately prior to BRV administration, evaluated for a 2-hour period starting 1 hour after the start of initial BRV treatment. Timespans of 30 minutes refer to the following intervals within the 2-hour period: 0 to ≤30 minutes, >30 to ≤60 minutes, >60 to ≤90 minutes, and >90 to ≤120 minutes. The main efficacy variable will be analyzed using descriptive statistics. Baseline seizure burden is defined as seizure burden measured on the continuous VEEG (total ENS in minutes per hour) during a period of 2 hours immediately prior to the first administration of BRV.	starting 1 hour after the start of initial BRV treatment: – At least 80% reduction in nonsevere seizure burden (Nonsevere seizure burden is defined as ≤50% seizure activity on VEEG in all 30-minute timespans) OR – At least 50% reduction in severe seizure burden (Severe seizure burden is defined as >50% seizure activity on VEEG in any 30-minute timespan). Timespans of 30 minutes refer to the following intervals within the 2-hour period: 0 to ≤30 minutes, >30 to ≤60 minutes, >60 to ≤90 minutes, and >90 to ≤120 minutes. For this study, an ENS is defined as an EEG seizure lasting for at least 10 seconds on VEEG. Baseline seizure burden is defined as seizure burden measured on the continuous VEEG (total ENS in minutes per hour) during a period of up to 1 hour immediately prior	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	Subjects with at least 80% reduction in nonsevere seizure burden or at least 50% reduction in severe seizure burden from Baseline will be categorized as BRV responders. Subjects who drop out due to lack of BRV efficacy, are switched over to another AED treatment, or are administered any rescue medication (including BZDs) will be considered BRV nonresponders.	to the first administration of study drug.	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 13.5.1 Analysis of secondary efficacy variables	For the Confirmatory Cohorts this means: • For the analysis of the main efficacy variable, subjects must not have used any rescue medication (including BZDs) during the first 3 hours after initiation of BRV treatment to be considered BRV responders. • For the analysis of the key efficacy variables (other than the main efficacy variable) and other efficacy variables, subjects must not have used >1 dose of rescue medication following the first 3 hours after initiation of BRV treatment to be considered BRV responders. A single dose of short-acting BZD as rescue medication is allowed, but only after 3 hours subsequent to the initiation of treatment with BRV.	For the Confirmatory Cohorts this means: • For the analysis of the main secondary efficacy variable, subjects must not have used any rescue medication for the treatment of ENS during the first 3 hours after initiation of BRV treatment to be considered BRV responders. • For the analysis of the secondary efficacy variables (other than the main secondary efficacy variable) and other efficacy variables, subjects must not have used any rescue medication for the treatment of ENS following the first 3 hours after initiation of BRV treatment to be considered BRV responders.	Text changes were made to provide consistent language throughout the protocol.
Section 13.5.1 Analysis of secondary	Descriptive statistics will be presented for the following key efficacy variables:	Descriptive statistics will be presented for the following secondary efficacy variables:	Text changes were made to provide consistent language throughout the protocol.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
efficacy variables	• Absolute and percentage reduction in average seizure burden measured by continuous VEEG from Baseline to the end of the 96-hour Evaluation Period • Proportion of BRV responders during the 96-hour Evaluation Period (measured at the end of the 96-hour Evaluation Period) • Absolute and percent difference in clinical seizures at the end of the 24-hour Evaluation Period from Baseline for neonates with motor seizures at the time of inclusion	• Absolute reduction in average seizure burden measured by continuous VEEG from Baseline to the end of the 96-hour Evaluation Period • Percent reduction in average seizure burden measured by continuous VEEG from Baseline to the end of the 96-hour Evaluation Period • Proportion of BRV responders at the end of the 96-hour Evaluation Period • Absolute difference in clinical seizures at the end of the 24-hour Evaluation Period from Baseline for neonates with motor seizures at the time of inclusion • Percent difference in clinical seizures at the end of the 24-hour Evaluation Period from Baseline for neonates with motor seizures at the time of inclusion	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 13.5.2 Analysis of the other efficacy variables	• Absolute and percentage reduction from Baseline in seizure burden at evaluation periods of 0 hours to 3 hours, >3 hours to 6 hours, >6 hours to 12 hours, >12 hours to 24 hours, >24 hours to 36 hours, >36 hours to 48 hours, >48 hours to 72 hours, and >72 hours to 96 hours after the start of initial BRV treatment	• Absolute reduction from Baseline in seizure burden at evaluation periods of 0 hours to 3 hours, >3 hours to 6 hours, >6 hours to 12 hours, >12 hours to 24 hours, >24 hours to 36 hours, >36 hours to 48 hours, >48 hours to 72 hours, and >72 hours to 96 hours after the start of initial BRV treatment • Percentage reduction from Baseline in seizure burden at evaluation periods of 0 hours to 3 hours, >3 hours to 6 hours, >6 hours to 12 hours, >12 hours to 24 hours, >24 hours to 36 hours, >36 hours to 48 hours, >48 hours to 72 hours, and >72 hours to 96 hours after the start of initial BRV treatment	Text changes were made to provide consistent language throughout the protocol.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 13.7 Handling of dropouts or missing data	For subjects who drop out during the Evaluation Period, the number of hours from the start of the Evaluation Period to the time of withdrawal (in hours) will be considered for analysis. Subjects in the Confirmatory Cohorts who drop out due to lack of BRV efficacy, are switched over to another AED treatment, or are administered >1 dose of rescue medication (including BZDs) following the first 3 hours after initial BRV treatment started will be considered BRV nonresponders. The impact of missing data on the assessment of the main efficacy variable will be evaluated with sensitivity analyses with further details to be included in the SAP.	For subjects who dropped out during the Evaluation Period, the number of hours from the start of the Evaluation Period to the time of withdrawal (in hours) will be considered for analysis. Subjects in the Confirmatory Cohorts who started another AED, increased the dose or frequency of administration of an AED ongoing at the time the first BRV infusion started, or are switched to another AED, or have been administered any rescue medication for the treatment of ENS during the first 3 hours after initiation of BRV treatment will be considered BRV nonresponders. The impact of missing data on the assessment of the main secondary efficacy variable will be evaluated with sensitivity analyses with further details to be included in the SAP.	Clarification
Section 13.8.1 Exploratory Cohort	Not applicable	During the DMC review of PK and safety data, the enrollment of subjects will be on hold.	Clarification

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 13.9	No formal sample size calculation has been performed as a single treatment BRV arm is planned for descriptive summary of results and for comparison with the 6 MDZ-treated subjects from the Exploratory Cohort.	No formal sample size calculation has been performed as a single treatment BRV arm is planned for descriptive summary of results and for comparison with the 6 subjects from the Exploratory Cohort.	Text changes were made to provide consistent language throughout the protocol.

17.6 Protocol Amendment 6

Rationale for the amendment

The purpose of this non-substantial amendment is to correct minor inconsistencies of Protocol Amendment 5 identified after finalization.

- Inconsistency concerning the use of LEV was corrected for the Exploratory Cohort.
- Measurement of length before the first administration of BRV was erroneously removed from the Exploratory Cohort in Protocol Amendment 5, and this measurement has been re-inserted.
- The text indicating that Investigators can consult the central reader to confirm seizures before subjects can enter the Evaluation Period was removed in Protocol Amendment 5 from the Exploratory Cohort, but for clarity this has been re-inserted.

The specific changes include the following:

Change #1

Sponsor Study Physician

Added [redacted] to address

Change #2

Section 5.1 Study description

N01349 consists of 2 steps including a comparison with a historical control group (matched in age and condition) treated with AEDs comparable SOC and diagnostic methods from literature will be used for the evaluation of efficacy.

Has been changed to:

N01349 consists of a 2-step design and includes a descriptive comparison with a historical control group (matched in age and condition) from literature treated with AEDs per SOC and diagnostic methods.

Change #3

Section 5.1.1 Exploratory Cohort

The Screening Period starts up to 36 hours prior to the first administration of BRV. Phenobarbital, MDZ, PHT, LEV (≤ 60mg/kg/day), or LDC may have been administered prior to the subject's enrollment into the study and/or at a location other than the study site.

Has been changed to:

The Screening Period starts up to 36 hours prior to the first administration of BRV. Phenobarbital, MDZ, PHT, LEV, or LDC may have been administered prior to the subject's enrollment into the study and/or at a location other than the study site.

Change #4

Section 5.1.1 Exploratory Cohort

The following sentence was re-inserted:

If preferred by the Investigator, the central VEEG reader can be consulted to confirm the required ENS.

Change #5

Section 5.2 Schedule of study assessments

Table 5-1:

Length during the Screening Period (immediately before first BRV administration) was re-inserted as an assessment for the Exploratory Cohort.

Change #6

Section 8.1.1 Screening Period

The following sentence was re-inserted:

If preferred by the Investigator, the central VEEG reader can be consulted to confirm the required ENS.

Change #7

Section 8.1.1 Screening Period

Length during the Screening Period (immediately before first BRV administration) was re-inserted as an assessment.

17.7 Protocol Amendment 7

Rationale for the amendment

The purposes of this substantial amendment are:

- Update the protocol for the new UCB company name (UCB Biopharma SRL).
- Specify the BRV dose recommended by the DMC for the Confirmatory Cohorts.
- Incorporate the measures described in UCB's COVID-19 Contingency Plan for N01349.
- Prolong the BRV Extension Period for up to 90 days postnatal age for sites that may not be ready to transition subjects to EP0156 at the time that N01266 will be closed.
- Correct minor inconsistencies and apply uniform terminology throughout the protocol.

Specific changes

Section impacted	Key components of previous text	Key components of amended text	Rationale
Title page Study contact information	Sponsor: UCB Biopharma SPRL	Sponsor: UCB Biopharma SRL	Sponsor name update
Study contact information	Pediatric Neonatologist: [redacted]	Pediatric Neonatologist: [redacted]	Change in DMC member
Section 1, Summary Section 5.1, Study description Section 5.1.1, Exploratory Cohort	Added text to specify the AEDs enrolled subjects will receive for the Exploratory and Confirmatory Cohorts per SOC.	Per SOC, the AEDs include PB, MDZ, PHT, LEV, or LDC	Alignment with text in Sections 5.1.2 and 8.2.1
Section 1, Summary Section 5.1, Study description Section 5.1.2, Confirmatory Cohort Section 5.4.2, Rationale for dose selection Section 7.2, Treatments to be administered	Added details regarding determination of the BRV dose was determined by the DMC at a meeting held on 05 Nov 2020.	The BRV dose and frequency selected by the DMC for the Confirmatory Cohorts is 1mg/kg bid (2mg/kg/day). Based on data from the Confirmatory Cohorts, the BRV dose may be further adjusted in a staggered approach per DMC discretion.	Specify the BRV dose for the Confirmatory Cohorts as selected by the DMC
Section 1, Summary Section 2.3, Rationale for the study Section 5.4.1, Rationale for study design Section 6.1, Inclusion criteria	Present current terminology for corrected gestational age (CGA).	Removed all prior references to postmenstrual age (PMA) and replaced consistently with CGA.	Consistency of terminology throughout the protocol

Section impacted	Key components of previous text	Key components of amended text	Rationale
Section 1, Summary	No previous text.	Added text describing the possible prolongation of the BRV Extension Period for sites in certain regions that must pause enrollment into N01349 from early Sep 2021 onwards since they may not be ready to transition subjects to the long-term study (EP0156) at the time enrollment into N01266 will be closed.	Flexibility in allowing subjects to remain in N01349 until a long-term study is available.
Section 1, Summary Section 8.2.3, BRV Extension Period (Confirmatory Cohorts)	Original text stated that the maximum study duration would be up to 75 days and the maximum BRV exposure would be up to 42 days.	Clarified text to state that the maximum study duration and the maximum BRV exposure are **expected to be** up to 75 days and up to 42 days, respectively, for most subjects; the exceptions are subjects who remain in the Extension Period for a prolonged duration. New text added to provide the maximum study duration for subjects who remain in the study for up to 90 days of PNA (ie, 130 days [90 days of PNA+ up to 7 days for the Down-Titration Period + up to 33 days for the Safety Follow-Up Period])	Provide study duration information for subjects who may remain in N01349 for a prolonged Extension Period.

Section impacted	Key components of previous text	Key components of amended text	Rationale
Section 4.3.2, Other safety variables Exploratory Cohort: Section 8.1.1, Screening Period Section 8.1.2, Evaluation Period Section 8.1.3.2, Extension Period 2 Section 8.1.3.3, Unscheduled Visits Section 8.1.4, Safety Follow-Up Period Confirmatory Cohorts: Section 8.2.1.1, Baseline Period Section 8.2.2, Evaluation Period Section 8.2.3.2, Extension Period 2 Section 8.2.3.3, Unscheduled Visits Section 8.2.4, Down-Titration Period Section 8.2.5, Safety Follow-Up Period	Heart rate and pulse rate were used interchangeably throughout the protocol.	Heart rate to be presented consistently throughout.	Consistency of terminology throughout the protocol
	Vital signs (blood pressure, pulse rate, respiratory rate, oxygen saturation [pulse oximetry] including apneas, and body temperature; at 0, 3, 6, 12, 24, and 48 hours)	Vital signs (blood pressure, heart rate, respiratory rate [including apneas], oxygen saturation [pulse oximetry], and body temperature; at 0, 3, 6, 12, 24, and 48 hours)	Revised misleading wording to provide clarification on apneas
Section 5.1, Study description Section 11.1.6	A DMC will be in place for the duration of this study and will meet at no longer than 6-	Due to the low enrollment rate, the interval between DMC meetings may exceed 6-month intervals, at the discretion of the DMC.	Scheduling flexibility

Section impacted	Key components of previous text	Key components of amended text	Rationale
	month intervals between meetings.		
Section 5.1.2, Confirmatory Cohorts Section 7.2, Treatments to be administered	The dose for subjects in the Confirmatory Cohort was yet to be determined.	Subjects in the Confirmatory Cohorts will receive iv BRV 1mg/kg bid (2mg/kg/day), as recommended by the DMC on 05 Nov 2020. The DMC will continue to monitor the PK and safety of subjects and dosing may be further adjusted in a staggered approach as determined by the DMC.	Updated the previous text to reflect the dose recommended by the DMC on 05 Nov 2020 and to note that the dose may be further adjusted per DMC discretion.
Section 5.1.2, Confirmatory Cohorts Section 8.2.3, BRV Extension Period (Confirmatory Cohorts)	The maximum anticipated duration of the BRV Extension Period per subject is up to 28 days of postnatal age (+7 days).	In the event that a long-term study is temporarily not available, subjects are allowed to remain in the BRV Extension Period until they reach a PNA of up to 90 days. For those subjects, the assessments planned for Unscheduled Visits (see Section 8.1.3.3) will be conducted in intervals of approximately 30 days during the prolonged Extension Period. The treatment with BRV will be managed through IVRS. Before subjects can roll-over to the long-term study, they must have switched to BRV oral solution.	Clarification that most subjects will remain in the BRV Extension Period for up to 28 (+7 days) of PNA but that subjects may have a prolonged Extension Period for up to 90 days of PNA if the long-term study is not available at the time planned for the subject's transition.
Section 5.1.3, Study duration per subject	The maximum study duration per subject is expected to be up to 75 days	In the event that a long-term study is not available at the time of a subject's planned transition, the maximum study duration for subjects who remain in the study for up to 90 days of PNA and do not enter the long-term study will then be up to 130 days (90 days of PNA, up to 1 week for the Down-Titration Period, and up to 33 days for the Safety Follow-Up Period).	Completeness; added maximum study duration for the subjects who remain for a prolonged BRV Extension Period.

Section impacted	Key components of previous text	Key components of amended text	Rationale
Section 5.1.3, Study duration per subject	The maximum BRV exposure per subject is expected to be up to 42 days	For subjects who remain in the study for up to 90 days of PNA and do not enter the long-term study, maximum BRV exposure per subject is expected to be up to 97 days (up to 90 days of PNA and up to 1 week for the Down-Titration Period).	Completeness; added maximum BRV exposure for the subjects who remain for a prolonged BRV Extension Period.
Section 5.2, Table 5-1 Schedule of study assessments - Screening and Evaluation Periods (Exploratory Cohort)	Medical history including Apgar score	Medical history including Apgar score and HIE	Clarification
	AED treatment	Added the specific AEDs per SOC	Clarification
	Footnote 'j': The recording of AEDs will include BZDs and opiates taken by the mother at the time of delivery.	Added that COVID-19 vaccination will also be recorded as concomitant medication if the mother was pregnant or breastfeeding when vaccinated.	Alignment with the BRV Program Contingency Plan.
Section 5.2, Table 5-2 Schedule of study assessments – Screening and Evaluation Periods (Confirmatory Cohorts)	Medical history including Apgar score	Medical history including Apgar score and HIE	Clarification
	No previously included assessment for neurodevelopmental testing.	Added the Bayley-III assessment at the 96-hour timepoint of the Evaluation Period.	Clarification that subjects completing the Evaluation Period in 28 days of PNA and directly roll over to the long-term study will require that the Bayley assessment be performed at the 96-hour assessment of the Evaluation Period.
	Footnote 'h': Subjects are expected to receive IB BRV bid. The dose and dosing frequency of BRV will be adjusted based on the data collected for the analysis of the Exploratory Cohort.	Subjects will receive iv BRV 1mg/kg bid (2mg/kg/day), as recommended by the DMC on 05 Nov 2020 based on the results of the PK analysis of the Exploratory Cohort as well as an existing PK model from N01263.	Updated dose information based on DMC recommendation.

Section impacted	Key components of previous text	Key components of amended text	Rationale
	Footnote 'n': The recording of AEDs will include BZDs and opiates taken by the mother at the time of delivery.	Added that COVID-19 vaccination will also be recorded as concomitant medication if the mother was pregnant or breastfeeding when vaccinated.	Alignment with the BRV Program Contingency Plan.
Section 5.2, Table 5-3 Schedule of study assessments - BRV Extension Period and Safety Follow-Up Period (Exploratory and Confirmatory Cohorts)	Footnote 'b': Subjects will enter the Safety Follow-Up Period if they withdraw from the study at any time, or do not proceed to the BRV Extension Period, or complete the Down-Titration Period. This visit will occur 30±3 days after the last administration of BRV.	Added the following text to the existing footnote text: For subjects unable to return to the hospital due to COVID-19, the Safety Follow-up visit can be performed remotely. In this case vital signs, the physical and neurological examination, biometric and psychometric parameters, and the laboratory assessment may not be performed.	Alignment with the BRV Program Contingency Plan.
	Footnote 'k': The recording of AEDs will include BZDs and opiates taken by the mother at the time of delivery.	Added that COVID-19 vaccination will also be recorded as concomitant medication if the mother was pregnant or breastfeeding when vaccinated.	Alignment with the BRV Program Contingency Plan.
	Confirmation/diagnosis of epilepsy is planned for EPV1 and EPV2.	Confirmation/diagnosis of epilepsy is only conducted at EPV2 to confirm that the subject qualifies for N01266 or EP0156.	Correction and alignment across sections.

Section impacted	Key components of previous text	Key components of amended text	Rationale
Section 5.2, Table 5-3 Schedule of study assessments - BRV Extension Period and Safety Follow-Up Period (Exploratory and Confirmatory Cohorts) Section 8.1.3.1, Safety Follow-Up Period (Exploratory Cohort) Section 8.2.3.1, Safety Follow-Up Period (Confirmatory Cohorts)	Footnote 'c': Subjects will attend EPV1 at 7±2 days after completion of the Evaluation Period.	Added the following text to the existing footnote text: For subjects unable to return to the hospital due to COVID-19, EPV1 can be performed remotely if BRV oral solution was dispensed at the time when the subject completed the Evaluation Period.	Alignment with the BRV Program Contingency Plan.
Section 5.2, Table 5-3 Schedule of study assessments - BRV Extension Period and Safety Follow-Up Period (Exploratory and Confirmatory Cohorts) Section 8.2.3.3, Unscheduled Visits (Confirmatory Cohorts)	No previous safety laboratory assessments were planned for Unscheduled Visits.	Added footnote 'n' to state "Laboratory assessments (safety) only required for Unscheduled Visits performed during the BRV Extension Period. Added safety laboratory assessments (hematology, biochemistry, liver enzymes, and endocrinology) to Unscheduled Visits.	Alignment with other BRV studies.
Section 5.3, Schematic diagrams Figure 5-1, Schematic Overview of the study (Exploratory Cohort)	Presents Evaluation Period as 96 hours and is missing the Screening Period timeframe.	The Evaluation Period is 48 hours and the Screening Period is up to 36 hours in duration.	Error correction and addition of additional information
Figure 5-2, Screening and Evaluation Periods (Exploratory Cohort)	Administration of AED per SOC first line-, second line-, and third line-treatments	Administration of one or more of the following AEDs: PB, MDZ, PHT, LEV, or LDC	Consistency with updated text describing AED administration per SOC

Section impacted	Key components of previous text	Key components of amended text	Rationale
Figure 5-3, Schematic overview of the study (Confirmatory Cohorts)	Missing Screening Period timeframe. Missing duration of BRV Extension Period for subjects with a prolonged duration of up to 90 days of PNA.	The Screening Period is up to 36 hours in duration. Added duration of BRV Extension Period for subjects with a prolonged duration.	Error correction New information.
Figure 5-4, Screening and Evaluation Periods (Confirmatory Cohorts)	Administration of AED per SOC first line-, second line-, and third line-treatments	Administration of one or more of the following AEDs: PB, MDZ, PHT, LEV (≤60mg/kg/day), or LDC	Consistency with updated text describing AED administration per SOC
Section 6.2, Exclusion criteria	Exclusion criterion #2: Subjects with seizures responding to previous AED treatment immediately prior to BRV treatment, pyridoxine treatment, or correction of metabolic disturbances (hypoglycemia, hypomagnesemia, or hypocalcemia)	Subject with seizures responding **to any of the following**: previous AED treatment immediately prior to BRV treatment, pyridoxine treatment, or correction of metabolic disturbances (hypoglycemia, hypomagnesemia, or hypocalcemia).	Clarify that previous pyridoxine treatment is not an exclusion criterion; subjects are excluded if they responded to pyridoxine treatment.

Section impacted	Key components of previous text	Key components of amended text	Rationale
Section 7.2, Treatments to be administered	Subjects in the Exploratory Cohort will be dosed with BRV (0.5mg/kg bid) according to the sites standard procedures. Administration of BRV is proposed as approximately 15-minute iv infusions. Treatment with previous AEDs (PB, MDZ, PHT, LEV [≤60mg/kg/day], or LDC) is permitted to continue if the subject is on a stable dose from 1 hour prior to initiation of the BRV treatment.	Subjects in the Exploratory Cohort will be dosed during the Evaluation Period with BRV (0.5mg/kg bid) according to the sites standard procedures. Administration of BRV is proposed as approximately 15-minute iv infusions. Treatment with previous AEDs (PB, MDZ, PHT, LEV [≤60mg/kg/day], or LDC) during the Evaluation Period is permitted to continue if the subject is on a stable dose from 1 hour prior to initiation of the BRV treatment.	Clarify that the dosing of subjects in the Exploratory Cohort with BRV 0.5mg/kg bid will occur during the Evaluation Period. Clarify that treatment with previous AEDs is permitted during the Evaluation Period
Section 8.1.3, BRV Extension Period (Exploratory Cohort)	No previous text describing the purpose of the BRV Extension Period.	The BRV Extension Period is intended to bridge the time until subjects are old enough to participate in the long-term study. Subjects completing the Evaluation Period at a PNA of at least 28 days may directly roll over to the long-term study, if they meet the eligibility criteria. Those patients are not required to enter the BRV Extension Period.	Clarify the purpose of the BRV Extension Period
	Added text clarifying that subjects not continuing BRV treatment after the Evaluation Period will enter the Safety Follow-Up Period and not the BRV Extension Period	Subjects not continuing the BRV treatment after they completed the Evaluation Period will not enter the BRV Extension Period but proceed immediately to the Safety Follow-Up Period	Clarification of study design

Section impacted	Key components of previous text	Key components of amended text	Rationale
Section 8.1.4, Safety Follow-Up Visit (Exploratory Cohort) Section 8.2.5, Safety Follow-Up Visit (Confirmatory Cohort)	No previous text	For subjects unable to return to the hospital due to COVID-19, the Safety Follow-Up Visit can be performed remotely. In this case vital signs, the physical and neurological examination, biometric and psychometric parameters, and the laboratory assessment may not be performed.	Alignment with the BRV Program Contingency Plan.
Section 8.2.2 Evaluation Period (Confirmatory Cohort)	No previous text describing the number of doses administered in the Confirmatory Cohorts.	Up to 8 iv doses of BRV (1mg/kg bid) will be administered as an approximately 15-minute infusion during the 96-hour BRV Evaluation Period.	Clarify the number of BRV doses administered in the Confirmatory Cohorts.
Section 8.2.2 Evaluation Period (Confirmatory Cohort)	BRV infusion (dose and dosing frequency of BRV to be confirmed after analysis of the data collected for the Exploratory Cohort).	Text removed.	Text no longer applicable since the DMC has determined the dose for the Confirmatory Cohorts
Section 8.2.2 Evaluation Period (Confirmatory Cohorts)	No previous text	Added Bayley-III as an assessment to be performed following BRV administration during the Evaluation Period for subjects in the Confirmatory Cohort who are continuing into the long-term study and enrolled in countries where a validated translation is available.	Clarification that subjects completing the Evaluation Period in 28 days of PNA and directly roll over to the long-term study will require that the Bayley assessment be performed at the 96-hour assessment of the Evaluation Period.

Section impacted	Key components of previous text	Key components of amended text	Rationale
Section 8.2.3 BRV Extension Period (Confirmatory Cohorts)	No previous text describing the purpose of the BRV Extension Period.	The BRV Extension Period is intended to bridge the time until subjects are old enough to participate in the long-term study. Subjects completing the Evaluation Period at a PNA of at least 28 days may directly roll over to the long-term study, if they meet the eligibility criteria. Those patients are not required to enter the BRV Extension Period.	Clarify the purpose of the BRV Extension Period
	Subjects not entering the BRV Extension Period will proceed immediately to the Down-Titration Period (see Section 8.2.4).	Subjects not continuing the BRV treatment after they completed the Evaluation Period will not enter the BRV Extension Period but proceed immediately to the Down-Titration Period	Clarification
Section 8.2.3.3, Unscheduled Visit (Confirmatory Cohort)	No previous text	For subjects who remain in the BRV Extension Period for a prolonged duration (ie, until they reach a PNA of 90 days), these assessments will be conducted at intervals of 30 (±3 days).	Provide the assessment schedule for subjects who remain for a prolonged BRV Extension Period.

18 DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all subinvestigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB, unless other agreements were made in a separate contract.

Investigator:

Printed name	Date/Signature

19 SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.

Approval Signatures

Name: n01349-protocol-amend-7

Version: 2.0

Document Number: CLIN-000174213

Title: n01349 Protocol Amendment 7

Approved Date: 25 May 2021

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 25-May-2021 14:37:55 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Subject Matter Expert Date of Signature: 25-May-2021 14:40:08 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 25-May-2021 14:55:14 GMT+0000