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LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
bid	twice a day
BRV	brivaracetam
cEEG	continuous electroencephalogram
CRO	contract research organization
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
eCRF	electronic Case Report form
ECG	electrocardiogram
EDC	electronic data capture
GCP	Good Clinical Practices
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
iv	intravenous
IVRS	Interactive Voice Response System
LEV	levetiracetam
LTFU	long-term follow-up
MS	mass spectrometry
NCES	nonconvulsive electrographic seizures
NCSE	nonconvulsive status epilepticus
Neuro ICU	neurological intensive care unit
PHT	phenytoin
PK	pharmacokinetic
SAE	serious adverse event
SOP	standard operating procedure
SSSE	self-sustaining status epilepticus
TEAE	treatment-emergent adverse event
vEEG	video electroencephalogram

ETHICS

Independent Ethics Committee or Institutional Review Board

The study protocol, amendments, and subject informed consent were reviewed by a national, regional, or Independent Ethics Committee (IEC) or Institutional Review Board (IRB).

Ethical conduct of the study

This study was conducted in accordance with the current version of the applicable regulatory and International Conference on Harmonisation (ICH)-Good Clinical Practice (GCP) requirements, the ethical principles that have their origin in the principles of the Declaration of Helsinki, and the local laws of the countries involved.

Subject information and consent/assent

Subject's informed consent was 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.

Prior to obtaining informed consent, information was given in a language and at a level of complexity understandable to the subject in both oral and written form by the Investigator (or designee). The subject had the opportunity to discuss the study and its alternatives with the Investigator.

Prior to participation in the study, the written Informed Consent form was signed and dated by the subject, or his/her legal representative, and by the person who conducted the informed consent discussion (Investigator or designee). The subject or his/her legal representative received a copy of the signed and dated Informed Consent form. The Investigator (and their delegated staff) was responsible for knowing and complying with the requirements for Legally Authorized Representative in their state and institution. As part of the consent process, the subject consented to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The protocol for this study was written and approved by UCB BIOSCIENCES Inc. (hereafter referred to as UCB), who sponsored the study. This study enrolled 1 subject at 1 Investigative site before it was terminated due to low enrollment. There was no coordinating Investigator. Key personnel involved in the study included:

- Safety Monitoring Committee:
  - [redacted], MD (Independent Medical Critical Care Expert): University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania
  - [redacted], MD (UCB Study Physician)
  - [redacted], MB, BCh, BAO (UCB Drug Safety Lead)
  - [redacted], MD (PRA Study Physician)
  - [redacted], MS, MD (UCB Biostatistician)

  - Non-Voting Members: [redacted] (PRA Biostatistician) and [redacted] (PRA Project Manager)

- Administration: N01394 was administered and monitored by a Contract Research Organization (CRO) with oversight by UCB. The CRO was PRA Health Sciences, Raleigh, North Carolina.

  Medical review was provided by the CRO. [redacted], MD, Senior Medical Director at PRA, International in San Diego, CA provided medical monitoring and review of safety data.

- UCB Lead Clinical Development Representative: [redacted], PhD, Raleigh, North Carolina
- UCB Clinical Therapeutic Area Physician: [redacted], MD, Raleigh, North Carolina
- UCB Statistician: [redacted], MD, Raleigh North Carolina
- UCB Clinical trial supply management: [redacted], Belgium
- Central laboratory facility: ACM Medical Laboratory Incorporated, Rochester, New York
- Central EEG reading services: Biomedical Systems Corporation, Saint Louis, Missouri
- Interactive Voice Response System (IVRS): Perceptive eClinical Ltd, Nottingham, United Kingdom

1 INTRODUCTION

N01394 was designed to evaluate the safety, tolerability, and efficacy of the intravenous (iv) brivaracetam (BRV) formulation in the treatment of nonconvulsive electrographic seizures (NCES). This study aimed to compare the efficacy of BRV versus phenytoin (PHT) in subjects with NCES. Phenytoin was selected as the comparator for this study as it is the most widely used antiepileptic drug (AED) for NCES and nonconvulsive status epilepticus (NCSE).

This study was stopped due to low enrollment; the termination date was [redacted]. One subject enrolled but discontinued from the study prematurely due to lack of efficacy. No serious adverse events (SAEs) were reported. Safety data for this subject are provided as an attachment to this clinical study report (CSR).

2 STUDY OBJECTIVES

The purpose of this exploratory study was to evaluate the efficacy, safety, and tolerability of iv BRV versus iv PHT in adult subjects experiencing NCES.

The primary objective of the study was to compare the efficacy of BRV and PHT, both administered intravenously, in adult subjects experiencing NCES.

The secondary objective of the study was to compare the safety and tolerability of BRV and PHT, both administered intravenously in adult subjects experiencing NCES.

The exploratory objective of the study was to evaluate the efficacy of BRV compared to PHT, both administered orally in adult subjects following iv administration.

3 INVESTIGATIONAL PLAN

3.1 Overall study design

N01394 was a Phase 2, open-label, multicenter, parallel-group, exploratory study in subjects experiencing NCES caused by brain insult. Subjects were to be treated intravenously with BRV or PHT. The study was designed to assess seizure freedom for 12 hours using continuous electroencephalogram (cEEG) with video monitoring.

The total duration of the study was planned to be a maximum of 32 weeks per subject including a 4-week Down-Titration Period and a 2-week Study Drug-Free Period followed by a Safety Visit.

Subjects were to be hospitalized in a neurological intensive care unit (Neuro ICU) or equivalent closely monitored environment. Subjects were to have at least 1 NCES confirmed by EEG within a 6-hour period prior to the initiation of treatment, which required treatment with an AED according to the physician's clinical judgment. The study was to consist of 2 parts: iv Acute Treatment Period (Part A) and oral/iv Follow-Up Treatment Period (Part B).

Sixty subjects were planned to be screened in order to enroll 50 subjects in a 1:1 ratio to iv BRV or iv PHT with stratification based on categorized age (<65 years versus ≥65 years) across approximately 15 sites. This study was stopped due to low enrollment; the termination date was [redacted]. One subject enrolled, but discontinued from the study prematurely due to lack of efficacy.

Treatments administered were to be BRV 200mg as a bolus or PHT 20mg/kg infusion both at a rate of 50mg/min. A second acute dose of BRV (100mg) or PHT (dose based on serum levels) could have been administered no sooner than 15 minutes after the first dose if seizures recurred.

On Day 5 or earlier, subjects were to transition into the oral/iv Follow-Up Treatment Period (Part B) if the subject either required further iv BRV or iv PHT treatment or the subject was able to transition from iv to oral BRV or PHT. Treatment was to continue in the oral/iv Follow-Up Treatment Period for a maximum of 6 months.

Follow-Up Visits were to occur at Months 1, 3, and 6. At the end of Month 6, subjects on oral BRV may have been eligible for conversion to a long-term follow-up (LTFU) study (N01372) for continued treatment with BRV. Subjects on iv BRV or subjects who required further treatment with PHT were to exit the study and would not have been eligible to enter N01372.

A 4-week Down-Titration Period was planned that was to be followed by a 2-week Study Drug-Free Period ending with a final Safety Visit for subjects who were not entering the LTFU study.

As mentioned above, N01394 was stopped early due to low enrollment. The termination date was [redacted]. One subject enrolled, but discontinued from the study prematurely due to lack of efficacy.

3.2 Changes to the conduct of the study

The original study protocol for N01394 was approved 06 Dec 2012. There were 3 subsequent amendments to the protocol:

- Protocol N01394 Amendment 1: 15 Mar 2013
- Protocol N01394 Amendment 2: 11 Jul 2013
- Protocol N01394 Amendment 3: 25 Jun 2014

All protocol amendments were in effect before the 1 study subject entered N01394. Details of the changes made with each amendment can be found in Amendment 3 of the study protocol (N01394-protocol-amend-3 Section 17).

3.3 Selection of study population

As described in the N01394 protocol, subjects enrolled were to be ≥16 years of age, with a body weight ≥40kg, and with a diagnosis of a brain insult including traumatic brain injury, having NCES confirmed by EEG, lasting a minimum of 10 seconds but not >30 minutes (minimum of 1 seizure in the last 6 hours). Treatment with an AED was required according to the physician's clinical judgment.

Subjects were expected to be under cEEG monitoring with video surveillance in the Neuro ICU for at least 36 hours from the first administration of study drug.

Main exclusion criteria:

- Subject has a lifetime history of suicide attempt (including an actual, interrupted, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response "Yes" to either Question 4 or Question 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at Visit 1.

- Subject has known allergic reaction or intolerance to pyrrolidine derivatives and/or investigational medicinal product (IMP) excipients.
- Subject has a known hypersensitivity to any components of the IMP or comparative drugs.
- Subject has a history of severe adverse hematologic or cutaneous reaction to any drug.
- Subject with status epilepticus or NCSE (ie, 1 continuous, convulsive or nonconvulsive, unremitting seizure lasting >30 minutes during Visit 1).
- Subject has been diagnosed with anoxic brain injury.
- Subject has a known history of status epilepticus during the 6 months preceding Visit 1.
- Subject is currently treated with levetiracetam (LEV) or PHT or has been treated within the last 30 days before Visit 1 with LEV or PHT.
- Subject is on felbamate with <18 months exposure before Visit 1.
- Subject has presence of any sign (clinical or imaging techniques) suggesting a rapidly progressing process such that the subject is not expected to survive >48 hours.
- Subject has any clinical condition that would impair reliable participation in the study or necessitate the use of medications not allowed by the protocol.
- Subject has liver failure, as judged by the Investigator.
- Subject has end stage renal disease (creatinine clearance <15mL/min).
- Subject is pregnant or is a lactating woman.

3.4 Discussion of study design and selection of dose

N01394 aimed to compare the efficacy of BRV versus phenytoin (PHT) in subjects with NCES. Phenytoin was selected as the comparator for this study as it is the most widely used AED for NCES and NCSE.

Phenytoin is an AED that has been available for several decades and has been extensively used in the Neuro ICU for the treatment of NCES. Intravenous PHT is indicated for the control of status epilepticus of the tonic-clonic (grand mal) type and prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury (Phenytoin [package insert]. New York, NY: Parke Davis.; 2011). Current literature suggests a dose range of PHT 15 to 20mg/kg for the treatment of status epilepticus or nonconvulsive seizures (Ruegg and Dichter, 2003; Varelas and Spanaki, 2010). The mechanism of action of PHT is thought to be through fast inactivation of the voltage gated sodium channels. Unfortunately, there are several disadvantages to the use of PHT. Known adverse events (AEs) after rapid iv administration are hypotension, cardiac arrhythmias, respiratory arrest, soft tissue irritation, and inflammation (Phenytoin [package insert]. New York, NY: Parke Davis.; 2011). Phenytoin induces hepatic enzymes, leading to potential drug-drug interactions. Additionally, PHT has nonlinear, zero-order pharmacokinetic (PK), making dosing difficult. In addition, PHT is highly protein bound but is easily displaced by other highly bound drugs (eg, valproic acid, salicylic acid, ibuprofen, penicillin, and sulfonamides) or by endogenous substances present in acutely ill patients. Therefore, newer AEDs with an available iv formulation, such as BRV, may have advantages in the setting of the Neuro ICU.

Existing reports consistently indicate that iv LEV is effective, [redacted], and well tolerated in a wide range of severe, acute seizure conditions. Although limited in number, reports have also shown evidence of the efficacy of LEV in NCSE (Farooq et al, 2007). Both LEV and BRV have specific affinity for the SV2A target site, which is the primary mechanism of action for both LEV and BRV.

Brivaracetam (0.82mg/kg) and LEV (6.5mg/kg) were orally dosed to male Crl NMRI (Han) mice (6 to 7 weeks old). Blood and brain samples were collected 0.083, 0.25, 0.5, 1, 2, 4 and 6 hours postdose with 3 animals per condition. Plasma and brain homogenates were prepared and analyzed by liquid chromatography/mass spectrometry (MS)-MS for the parent drug. Similar conditions were tested in a parallel preclinical seizure model (audiogenic mice) comparing the 2 compounds for their time course of activity.

The brain-to-plasma ratios for parent drug concentration showed that BRV equilibrates into the brain more rapidly than LEV. This finding was accompanied by more rapid onset of action of BRV in the audiogenic mice model.

Intravenous administration of BRV (10mg/kg to 100mg/kg) 10 minutes after the end of perforant path stimulation markedly attenuated both behavioral and electrographic expression of self-sustaining status epilepticus (SSSE) in a dose dependent manner. The total time spent in seizures was significantly reduced from a dose of 20mg/kg (RRLE01L0601). Combined treatment of low doses of BRV (0.3mg/kg to 10mg/kg) together with diazepam (1mg/kg) markedly reduced the duration of SSSE, the cumulative seizure time, as well as the number of seizures when compared to saline-treated animals, suggesting a synergistic interaction between BRV and diazepam in the treatment of SSSE in rats (RRLE08B1107). These results demonstrate potent and efficacious seizure suppression by BRV alone and in combination with diazepam against status epilepticus.

Due to the high frequency of seizures in the study population and use of video electroencephalogram (vEEG) for at least the first 36 hours and cEEG to document all events, the iv Acute Treatment Period (Part A) in N01394 of up to 5 days was expected to be sufficient time to determine the response to acute treatment.

3.5 Treatments

3.5.1 Description of investigational medicinal product

N01394 enrolled 1 subject at 1 investigative site (Site [redacted], Investigator name [redacted]). The batch numbers of drug product shipped to this site are listed in Table 3–1.

Table 3–1: Batch numbers for study drug

Study drug by dose	Batch number
Intravenous drug	
BRV 50mg/5mL vial	BX1009208
PHT 250mg/5mL ampoule	BX1009209, BX1011281
Oral tablet	
BRV 10mg [redacted] tablets	BX1009210, BX1011282
BRV 25mg [redacted] tablets	BX1009211, BX1011283

BRV=brivaracetam; iv=intravenous; PHT=phenytoin

3.5.2 Treatments to be administered

According to the N01394 protocol, BRV solution for iv injection was to be supplied in 50mg/5mL vials. The rate of bolus administration was 50mg (5mL) undiluted BRV/min.

Subjects randomized to the BRV treatment group were to receive an acute iv dose of BRV 200mg as a bolus. If seizures recurred, a second iv bolus of BRV 100mg could have been given no sooner than 15 minutes after the first bolus. If the second bolus was not needed within 12 hours after the first iv bolus, BRV was to be continued as 100mg iv dose every 12 hours twice a day (bid). The total dose for the first 24 hours of treatment was not to exceed a maximum dose of 400mg/day.

BRV oral doses were supplied as 10mg [redacted] tablets or 25mg [redacted] tablets. The Sponsor provided oral BRV 10mg and 25mg tablets in high-density polyethylene bottles that were to be administered as a 100mg dose bid for a total daily dose of 200mg.

According to the N01394 protocol, PHT solution for infusion (liquid) was to be supplied in 250mg/5mL ampoules.

Subjects randomized to the PHT treatment group would have received an acute iv dose of PHT 20mg/kg at a rate of 50mg/min. If seizures recurred, a second acute dose of PHT would have been given no sooner than 15 minutes after the first dose to maintain unbound serum levels within the range of 1 to 2mg/L. Treatment with PHT was to be continued with at least 2 daily divided doses according to site practice, and the daily PHT dose was to be adapted according to the physician's clinical judgment.

3.5.3 Duration of treatment

The planned total duration of the study was a maximum of 32 weeks per subject including a 4-week Down Titration Period and a 2-week Study Drug-Free Period followed by a final Safety Visit for subjects not entering the LTFU study:

The study was to consist of 2 parts: iv Acute Treatment Period (Part A) for up to 4 days followed by oral/iv Follow-Up Treatment Period (Part B). At the end of Month 6, subjects on oral BRV were to be eligible for conversion to a LTFU study (N01372) for continued treatment with BRV.

4 MEASUREMENTS AND EVALUATIONS

The N01394 protocol planned for the assessment of efficacy, PK, and safety; however, as the study was stopped early and only 1 subject was enrolled, these analyses were not performed. Safety data was collected and reviewed as planned, but no analyses or summaries were performed.

4.1 Safety measurements

The N01394 protocol planned safety variables were:

- Occurrence of treatment-emergent AEs (TEAE)
- Withdrawal due to AEs
- Occurrence of SAEs
- Occurrence of injection-related AEs (local site and systemic reactions)
- Occurrence of status epilepticus
- Laboratory safety assessments (hematology, biochemistry, and urinalysis)
- Vital signs (systolic blood pressure, diastolic blood pressure, respiratory rate, body temperature, and heart rate) and body weight
- Electrocardiograms (ECGs)
- Physical and neurological examinations

5 DATA QUALITY ASSURANCE

All data quality assurance procedures were delegated by UCB to PRA Health Sciences.

PRA Health Sciences monitored the study to meet the Sponsor's monitoring standard operating procedures (SOPs), ICH-GCP guidelines, and applicable regulatory requirements, and ensured that study initiation, conduct, and closure were adequate.

Source data verification ensured accuracy and credibility of the data obtained. During monitoring visits reported data were reviewed with regard to being accurate, complete, and verifiable from source documents (eg, subject files, recordings from automated instruments, tracings [ECG]).

N01394 was performed using electronic data capture (EDC). The Investigator was responsible for prompt reporting of accurate, complete, and legible data in the electronic Case Report forms (eCRFs) and in all required reports.

6 STATISTICAL METHODS

There were no statistical analyses performed for N01394. The planned statistical analyses were presented in the N01394 clinical study protocol (N01394-protocol-amend-3 Section 13).

The study was terminated early due to enrollment challenges. Only 1 subject was enrolled who had discontinued before the study termination. Medical review did not raise any concerns based on the available safety data. The efficacy data collected were incomplete and insufficient, thus a full analysis of the efficacy data was not feasible. As a result, abbreviated key listings were prepared and are included in N01394 CSR Attachment 1.

7 STUDY POPULATION RESULTS

7.1 Subject disposition

Disposition data are provided in N01394 CSR Attachment 1.

One subject (N01394-[redacted]) signed an Informed Consent form for entry into N01394 on [redacted]. This subject was randomized to BRV treatment and received BRV iv followed by BRV oral tablets (see Extent of exposure, Section 10.1). This subject discontinued prematurely from the study on [redacted]; the discontinuation reason reported was lack of efficacy.

7.2 Demographic and other Baseline characteristics

Demographic and baseline characteristics data, including medical history and concomitant medications, are provided in N01394 CSR Attachment 1.

One subject was enrolled in N01394 (N01394-[redacted]). This subject was enrolled at Investigative site [redacted]. The demographic and baseline characteristics for this subject are summarized in Table 7–1.

Table 7–1: Demographic and baseline characteristics for N01394 subject (N01394-[redacted])

Characteristic	
Age (years)	[redacted]
Sex	[redacted]
Race	[redacted]
Ethnicity	[redacted]
Country	[redacted]
Planned study treatment arm	BRV

BRV=brivaracetam: CSR=clinical study report
Data source: N01394 CSR Attachment 1

The medical history and concomitant medications reported for Subject N01394-[redacted] are listed in N01394 CSR Attachment 1 and show a history of [redacted]. Of the reported medications, several AEDs were taken concomitantly during N01394. These were [redacted], [redacted] ([redacted]®, Otsuka Pharmaceutical Company, Tokyo, Japan), [redacted] ([redacted]; UCB, Smyrna, GA), [redacted] ([redacted]®, GlaxoSmithKline, Research Triangle Park, NC), [redacted] ([redacted]®; Lundbeck, Deerfield, IL), [redacted].

8 EFFICACY RESULTS

No efficacy analyses were performed. The efficacy data collected from the 1 subject enrolled in the study were incomplete and insufficient to conduct the planned analyses.

9 CLINICAL PHARMACOLOGY RESULTS

There were no clinical pharmacology analyses performed.

10 SAFETY EVALUATION

10.1 Extent of exposure

Exposure data are provided in N01394 CSR Attachment 1. Subject N01394-[redacted] received BRV iv in Part A of the study. The initial iv dose of BRV 200mg was administered on [redacted], after which the subject was administered 3 subsequent iv doses of BRV 100mg according to protocol on [redacted] evening (approximately 4 hours after initial dose), [redacted] morning, and [redacted] evening (approximately 12 hours apart). The subject started oral dosing (Part B of the study) on [redacted] and continued on oral dosing for approximately 1 month.

10.2 Adverse Events

There were no SAEs reported for Subject N01394-[redacted].

Adverse events reported are summarized in Table 10–1.

Table 10–1: Adverse events for N01394 subject (N01394-[redacted])

Adverse event verbatim term	Severity	Causality (as determined by the Investigator)	Outcome
[redacted]	Moderate	Not related	Recovered/resolved
	Mild	Not related	Recovered/resolved
	Mild	Not related	Recovered/resolved
	Moderate	Not related	Recovered/resolved
	Mild	Not related	Recovered/resolved

iv=intravenous; CSR=clinical study report
Data source: N01394 CSR Attachment 1

Five AEs were reported by this subject. All were of mild to moderate intensity and were not considered to be related to study drug by the Investigator. All AEs resolved. No AEs were reported in association with the AE of [redacted] and the [redacted] resolved within 1 day.

10.3 Clinical laboratory evaluation

Clinical laboratory evaluation data are provided in N01394 CSR Attachment 1. There were no medically relevant laboratory results for Subject N01394-[redacted].

10.4 Vital sign measurements and physical examination findings

Vital signs and ECG data are provided in N01394 CSR Attachment 1. There were no medically relevant results for Subject N01394-[redacted].

Electrocardiograms (ECGs) were not done at all protocol-specified time points; however, all ECGs that were done were normal. At Visit 6 (Day 5) of N01394, the last day of BRV iv dosing, 4 ECGs readings were not done, but the fifth ECG at this visit was done and was normal. There were 4 ECGs done after Visit 6 and all were normal.

11 DISCUSSION AND OVERALL CONCLUSIONS

N01394 was designed to evaluate the safety, tolerability, and efficacy of the iv BRV formulation in the treatment of NCES. This study aimed to compare the efficacy of BRV versus PHT in subjects with NCES.

This study was stopped due to low enrollment; the termination date was [redacted]. One subject enrolled but discontinued from the study prematurely. Medical review did not raise any concerns based on the available safety data. No efficacy analyses were performed. The efficacy data collected from the 1 subject enrolled in the study were incomplete and insufficient to conduct the planned analyses. The Investigator reported the reason for study discontinuation as lack of efficacy. No SAEs were reported.

No conclusions could be made from this study due to the limited data.

12 REFERENCES

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13 APPENDIX

N01394 Attachment 1: Listings of clinical safety data for subject N01394-[redacted]