A 12-MONTH NONINTERVENTIONAL OBSERVATIONAL MULTINATIONAL STUDY TO EVALUATE EFFECTIVENESS, TOLERABILITY, AND QUALITY OF LIFE OF BRIVARACETAM ADJUNCTIVE THERAPY IN EARLIER TREATMENT LINES IN ADULT PATIENTS WITH HISTORY OF PARTIAL-ONSET SEIZURES IN DAILY CLINICAL PRACTICE

PROTOCOL EP0103 AMENDMENT 2.0

BRITOBA: BRIVARACETAM ADJUNCTIVE THERAPY IN EARLY TREATMENT LINE COMBINATIONS

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Confidentiality Statement

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date**	**Type of amendment**
Amendment 2.0	24 Oct 2022	Non-substantial
Amendment 1.0	17 Nov 2021	Non-substantial
Original Protocol	18 Mar 2020	Not applicable

Amendment 2.0 (24 Oct 2022)

Overall Rationale for the Amendment

During the startup and execution of this noninterventional study (NIS), enrollment challenges appeared which were not foreseen in the planning of the initial concept in the real-world setting and its sample size. Most of the challenges were associated with the COVID-19 pandemic situation and some of the selection criteria for the target patient's population were reported as challenging in the participating countries. Therefore, the decision was made to revise the initial concept of the study taking into account the limitations of the clinical routine and real-world setting circumstances that occurred in the participating sites during the last 2 years with the COVID-19 pandemic situation, as follows:

- Study enrollment will close at the end of December 2022 as the planned 24 months of enrollment will have elapsed.
- Per the enrollment projection it is expected that approximately 400 patients will be enrolled by the end of December.

The reduction of the sample size still preserves the primary objective and main interest of the study, allowing a timely generation of value for patients treated with BRV.

Section # and name	Description of change	Brief rationale
Section 1: Updated the current approval status of BRV in the EU.	Revised text to state that the extension of the indication in the EU for the treatment of POS to include patients 2 years to less than 16 years of age was approved on 24 Feb 2022.	At the time of the previous protocol amendment, BRV was approved for patients down to 4 years of age.
Section 5: Study design Section 6: Study duration, number of patients, and sites	Updated the study design description to reflect the reduction in sample size from 600 patients to approximately 400 patients.	Due to unforeseen delays in enrollment during the COVID-19 pandemic, the originally planned number of study participants requires reduction to allow the closure of enrollment after the allocated 2-year period.
Section 5.1.1: Visit 1, Section 5.1.2: Visit 2, Section 5.1.3: Visit 3, Section 5.1.4: Visit 4, Section 5.1.5: Visit 5, Section 5.2: Schedule of Activities Section 11: Assessment of effectiveness and health related quality of life variables	Text updated so that for patients not using the Helpilepsy application and who choose to complete their visit via a telephone call, the physician can read the questionnaires over the phone and record their responses. In prior text these questionnaires were not completed if the patient was not either using Helpilepsy or attending the visit in person to complete a paper version of the questionnaire.	In real world clinical practice, it is often standard routine that physicians read questionnaires over the phone to their patients when necessary and record their responses. The COVID-19 pandemic situation prompted this change as patients were spending less time in the clinic and remote visits were being conducted.
Section 12.2.3.1: Analysis of other effectiveness variables	Removed text describing that machine learning techniques will be used to model Baseline predictors of BRV effectiveness in early treatment line combinations.	Reduction of the sample size requires the removal of this planned analysis as bias may be introduced by the smaller number of patients in the study.
Section 12.4: Determination of sample size	Added text and data supporting the sample size recalculation.	Due to unforeseen delays in enrollment during the COVID-19 pandemic, the originally planned number of study participants requires reduction to allow the closure of enrollment after the allocated 2-year period.

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Note: If a nonserious adverse event or other safety relevant information is reported, UCB must be informed within 1 week of receipt of this information by the site. If a serious adverse event, adverse event of special interest, or pregnancy is reported, UCB must be informed within 1 working day of receipt of this information by the site.

DECLARATION AND SIGNATURE OF TREATING PHYSICIAN

I confirm that I have carefully read and understood this noninterventional study protocol (Protocol Amendment 2.0) and agree to conduct this study as outlined in this noninterventional study protocol, as well as local laws and requirements.

I will ensure that all physicians and other staff members read and understand all aspects of this noninterventional study protocol.

I have received and have read all study-related information provided to me.

The objectives and content of this noninterventional study 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.

Treating physician

_____	_____
Printed name	Date/Signature

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LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
AESI	adverse event of special interest
BAE	behavioral adverse event
BRV	brivaracetam
CDMS	clinical data management system
CGIC	Clinical Global Impression of Change
CI	confidence interval
COVID-19	Coronavirus Disease 2019
CRO	contract research organization
eCRF	electronic Case Report Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LEV	levetiracetam
MedDRA	Medical Dictionary for Regulatory Activities
NDDI-E	Neurological Disorders Depression Inventory for Epilepsy
NIS	noninterventional study
PDCF	Patient Data Consent form
PGIC	Patient Global Impression of Change
POS	partial-onset seizures
PPS	Per-Protocol Set
PRO	Patient-reported outcome
PS	Patient Safety
QoL	quality of life
QOLIE-10-P	Patient-Weighted Quality of Life in Epilepsy Inventory-10-P
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	Summary of Product Characteristics
SOP	standard operating procedure
SS	Safety Set
SSQ	Seizure Severity Questionnaire
TEAE	treatment-emergent adverse event
TSQM-9	Treatment Satisfaction Questionnaire for Medication-9
WPAI:GH	Work Productivity and Activity Impairment Questionnaire: General Health

1 BACKGROUND AND RATIONALE FOR THE STUDY

In the European Union, Briviact® (Nubriveo® in Italy) (brivaracetam [BRV]) was initially approved, as adjunctive therapy for the treatment of partial-onset seizures (POS), in patients 16 years of age and older with epilepsy on 14 Jan 2016. The extension of the indication in Europe for the treatment of POS to include patients 2 years to less than 16 years of age was approved on 24 Feb 2022. In Canada (Brivlera®), BRV was originally indicated as adjunctive therapy in the management of POS in adult (≥18 years of age) patients with epilepsy who are not satisfactorily controlled with conventional therapy. The extension of the indication in Canada for the treatment of POS to include patients ≥4 years of age was approved for the oral formulations of BRV on 22 Mar 2020.

Three formulations have been developed for commercial use: film-coated tablets for oral administration (10, 25, 50, 75, and 100mg), an oral solution (10mg/mL), and a solution for intravenous injection/infusion (10mg/mL). Brivaracetam film-coated tablets, oral solution, and solution for intravenous injection/infusion show the same area under the concentration-time curve, while the maximum plasma concentration is slightly higher after intravenous administration.

Brivaracetam ((2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1H-pyrrol-1-yl]butanamide) is a 2-pyrrolidone derivative and displays a high and selective interaction with a brain-specific binding site, synaptic vesicle protein 2A. This binding site appears to be the major target for its pharmacological activity.

Brivaracetam is rapidly and completely absorbed throughout the gastrointestinal tract. The extent of BRV absorption is not affected by food. The pharmacokinetics are dose-proportional from 10mg to 600mg. Brivaracetam is weakly bound to plasma proteins (≤20%). The volume of distribution is 0.5L/kg, a value that is close to that of total body water. The plasma half-life of BRV is approximately 9 hours; the total plasma clearance in patients was estimated to be 3.6L/hour. The main metabolic pathway of BRV is by hydrolysis of the acetamide group by amidase to the corresponding carboxylic acid, while a second pathway is the ω1-hydroxylation mediated by CYP2C19. The combination of these 2 pathways results in the hydroxyacid metabolite. These 3 metabolites are not pharmacologically active. There is no evidence of chiral inversion of BRV. Brivaracetam is eliminated primarily by oxidative metabolism and by excretion in the urine. More than 95% of the dose, including metabolites, is excreted in urine within 72 hours after dosing; less than 10% of BRV is excreted unchanged in urine.

The efficacy of BRV for the adjunctive therapy of POS was established in 3 Phase 3 randomized, double-blind, placebo-controlled, fixed-dose, multicenter studies in subjects 16 years of age and older. The daily dose of BRV ranged from 5 to 200mg/day across these studies. All studies had an 8-week baseline period followed by a 12-week treatment period with no up-titration. A total of 1558 patients received study drug, of which 1099 received BRV. Study enrollment criteria required that patients had uncontrolled POS despite treatment with either 1 or 2 concomitant antiepileptic drugs (AEDs). Patients were required to have at least 8 POS events during the Baseline Period. Adjunctive BRV administration at doses of 50mg/day to 200mg/day without titration resulted in statistically significant and clinically relevant reductions in seizure frequency, including seizure freedom. Brivaracetam was effective and well tolerated when started at these therapeutic doses. Low incidences of adverse events (AEs) and low study

discontinuation rates due to AEs were also observed with BRV. A recent small, open-label, Phase 3 study evaluating nonpsychotic behavioral AEs (BAEs) in patients receiving levetiracetam (LEV) who switched to BRV showed that, at the end of the 12-week treatment period, 93.1% patients (27/29) who switched to BRV had clinically meaningful reductions in BAEs, which suggests that patients experiencing BAEs associated with LEV may benefit from switching to BRV (Yates et al, 2015).

The present study, EP0103, is a post-marketing, multinational, observational, prospective NIS to evaluate effectiveness, tolerability, and quality of life (QoL) of adjunctive BRV therapy in earlier treatment line combinations in adult patients with history of POS.

Patients will be treated according to usual medical diagnostic and therapeutic procedures; commercially available BRV will be prescribed according to standard clinical practice for BRV. The decision to prescribe BRV is separate from the decision to include the patient in the study. Other than the completion of questionnaires, no additional clinical procedures will be applied to patients except at the discretion of the physician in the standard practice of medicine.

Real-time disease monitoring will be assessed with an epilepsy-specific electronic patient-reported outcome (PRO) application, Helpilepsy (on a voluntary basis; see Section 18.1). The Helpilepsy application is expected to be used by approximately half of the patients enrolled in the study with respective agreement. For those patients who do not use the Helpilepsy application, seizure information and PROs will be collected via paper questionnaires and based on the medical chart information. Patient-reported questionnaires will be completed voluntarily by patients. Safety reporting will be completed according to all national and international regulations.

Recently-published data on the post-marketing BRV adjunctive experience are consistent and confirm BRV to be an effective and well tolerated therapeutic option in difficult-to-treat populations with drug-resistant epilepsy who had tried more than 3 AEDs before initiating BRV (Villanueva et al, 2019; Steinhoff et al, 2017; Steinig et al, 2017; Zahnert et al, 2018; Menzler et al, 2019). The observations of these studies allow for the hypothesis that patients in earlier AED regimens might significantly benefit from combination with BRV (Villanueva et al, 2019). In this NIS study, patients in earlier treatment line combinations are defined as patients who have failed no more than 3 lifetime AEDs for the treatment of seizures, including all prior and concomitant AEDs at Baseline (Visit 1) before BRV initiation.

This NIS study was designed to close this existing data gap focusing on evidence for BRV adjunctive therapy and on exploring possible predictions of response in earlier treatment line combinations.

2 STUDY TYPE

EP0103 is a post-marketing, multinational, observational, prospective NIS to evaluate effectiveness, tolerability, and QoL of adjunctive BRV therapy in earlier treatment line combinations in adult patients with history of POS. In addition, this study may allow the exploration of predictions of response in patients in earlier treatment line combinations.

Brivaracetam will be prescribed according to standard clinical practice.

3 STUDY OBJECTIVES

3.1 Primary objective

The primary objective of the study is to evaluate the effectiveness of BRV in earlier treatment line combinations in patients with POS with or without secondary generalization for approximately 12 months of treatment.

3.2 Secondary objectives

The secondary objectives of the study are:

- To assess the effectiveness of BRV treatment in earlier treatment line combinations

3.3 Other objectives

The other objectives of the study are:

- To assess the QoL outcomes under BRV in earlier treatment line combinations
- To evaluate the speed of onset and sustained effectiveness of BRV in clinical practice, among patients who are using the Helpilepsy application
- To describe patient profiles for BRV in earlier treatment line combinations
- To assess the safety and tolerability profile (including BAEs) of BRV in earlier treatment line combinations
- To assess Baseline predictors associated with BRV effectiveness in earlier treatment line combinations

4 STUDY VARIABLES

4.1 Primary variable

The primary variable of the study is seizure freedom for at least 6 consecutive months over a 12-month observation period.

4.2 Secondary variables

The secondary variables are:

- BRV retention at 3, 6, 9, and 12 months
- Seizure freedom at 3, 6, 9, and 12 months
- POS frequency (seizures per 28 days) at Baseline, 3, 6, 9, and 12 months
- Change (absolute and percent) in POS frequency from Baseline to 3, 6, 9, and 12 months
- Response based on percent change in POS frequency at 3, 6, 9, and 12 months (response is defined as a reduction of ≥50% from Baseline)
- Discontinuation of BRV due to lack of effectiveness
- Time to discontinuation of BRV treatment

4.3 Other variables

The other effectiveness variables are:

- Self-reported seizure frequency collected via the Helpilepsy application at each available timepoint (daily during the first week, weekly during the rest of the first month, and monthly during the rest of the study period).
- Time to first seizure after first dose of BRV

The other QoL variables are:

- Patient Global Impression of Change (PGIC) rating at 3, 6, 9, and 12 months
- Clinical Global Impression of Change (CGIC) rating at 3, 6, 9, and 12 months
- Patient Weighted Quality of Life in Epilepsy Inventory-10-P (QOLIE-10-P) total score at Baseline, 6, and 12 months
- Change in QOLIE-10-P total score from Baseline to 6 and 12 months
- Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9) scores for each scale at Baseline, 3, 6, 9, and 12 months
- Change in TSQM-9 scores for each scale from Baseline to 3, 6, 9, and 12 months
- Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH) scores for each scale at Baseline, 3, 6, 9, and 12 months
- Change in WPAI:GH scores for each scale from Baseline to 3, 6, 9, and 12 months
- Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) total score at Baseline, 6, and 12 months
- Change in NDDI-E total score from Baseline to 6 and 12 months
- Seizure Severity Questionnaire (SSQ) rating for item 5 and 8 at Baseline, 3, 6, 9, and 12 months

The other safety variables are:

- Incidence of treatment-emergent adverse events (TEAEs)
- Incidence of behavioral TEAEs
- Incidence of serious TEAEs
- Incidence of serious behavioral TEAEs
- Incidence of study drug-related TEAEs
- Incidence of study drug-related, behavioral TEAEs
- Incidence of TEAEs leading to BRV discontinuation
- Incidence of behavioral TEAEs leading to BRV discontinuation
- Incidence of adverse events of special interest (AESI) and other safety relevant information

- Incidence of prior AED-related AEs leading to discontinuation of respective AED
- Discontinuation of BRV due to a TEAE

5 STUDY DESIGN

EP0103 is a post-marketing, multinational, observational, prospective NIS conducted at approximately 100 sites in Europe (Germany, Italy, Spain, and France) and Canada, with a planned 18- to 24-month Enrollment Period and an observation period of approximately 12 months per patient. Brivaracetam will be prescribed according to standard clinical practice. Brivaracetam is indicated as adjunctive therapy in the treatment of POS with or without secondary generalization. Based on the 24-month enrollment timeline, it is estimated that approximately 400 patients will enroll in the study.

Each patient will be followed for approximately 12 months with 5 study visits (Visits 2 and 4 may be conducted by telephone) as per standard clinical practice. The decision by the treating physician to prescribe BRV is made before participating in the NIS. The treating physician exclusively determines the BRV dose and treatment period. The study will end for each patient after the last visit within the observational period of approximately 12 months. Patients who discontinue BRV treatment will be withdrawn from the study. Patients can continue on BRV treatment after completion of their participation in this study.

Apart from requesting completion of patient-reported questionnaires (which is a voluntary decision by the patient), no additional clinical procedures will be applied except as required in the standard practice of medicine. The choice of medical treatment is made independently by the treating physician in the regular course of practice and is not influenced by this NIS protocol. For patients who refuse to complete the questionnaires, the data will be handled as missing information.

The study consists of only 1 cohort and up to 2 interim analyses are planned.

Patients have the option of completing the questionnaires and reporting seizure frequency using the Helpilepsy application for Visits 1 to 5. Helpilepsy (see Section 18.1) is a digital solution electronic PRO application for real-time disease monitoring for use by patients and physicians.

Five visits (or telephone calls) are planned in the study observational period of approximately 12 months in total (see Section 5.1 and Table 5-1).

5.1 Visits

5.1.1 Visit 1: Baseline/first day of BRV treatment

Visit 1 (Baseline) should be the patient's first day of BRV treatment. The following data will be collected at Visit 1:

- Patient Data Consent form (PDCF) signed (at the site or remotely, via mail)
- Verification of selection criteria
- Demographics and other characteristics (including age at enrollment, sex, educational status, and employment status)

- General epilepsy history (year of first epilepsy diagnosis, lifetime AEDs including reasons for discontinuation, and etiology)
- Medical history
- Concomitant AED and non-AED medication use
- Prior AED-related AEs leading to discontinuation of respective AED (collected from 6 months prior to Baseline [Visit 1]).
- Reason for BRV initiation
- Date and dose of first BRV treatment
- Documentation of seizure information based on the prior 3 months
- Questionnaires and assessments: QOLIE-10-P, SSQ, NDDI-E, TSQM-9, and WPAI:GH

  Note: At Visit 1 (Baseline), patients answer questionnaires based upon their prior treatments. Questionnaires may be completed within the Helpilepsy application. If the patient is not using the Helpilepsy application, then the site staff should provide paper-based questionnaires. Questionnaires should be answered prior to BRV treatment initiation. If the patient is in agreement to complete the questionnaires over the phone, the physician will read the questions directly and record the patient's responses.
- Adverse events

5.1.2 Visit 2: approximately 3 months

Visit 2 will occur at approximately 3 months following initiation of BRV therapy. The following data will be collected at Visit 2:

- Concomitant AED and non-AED medication use
- Dates and doses of BRV treatment and, if discontinued, date of discontinuation and reason
- Documentation of seizure information since the prior visit
- Questionnaires and assessments: SSQ, CGIC, PGIC, TSQM-9, and WPAI:GH

  Note: Patient-reported outcome questionnaires may be completed within the Helpilepsy application. If a patient visiting the site is not using the Helpilepsy application, then the site staff should administer paper-based questionnaires if the patient has agreed to complete these questionnaires. If the patient is in agreement to complete the questionnaires over the phone, the physician will read the questions directly and record the patient's responses.
- Adverse events
- Document any patient withdrawals

5.1.3 Visit 3: approximately 6 months

Visit 3 will occur at approximately 6 months following initiation of BRV therapy. The following data will be collected at Visit 3:

- Concomitant AED and non-AED medication use

- Dates and doses of BRV treatment and, if discontinued, date of discontinuation and reason
- Documentation of seizure information since the prior visit
- Questionnaires and assessments: QOLIE-10-P, SSQ, NDDI-E, CGIC, PGIC, TSQM-9, and WPAI:GH

  Note: Patient-reported outcome questionnaires may be completed within the Helpilepsy application. If the patient is not using the Helpilepsy application, then the site staff should administer paper-based questionnaires if the patient has agreed to complete these questionnaires. If the patient is in agreement to complete the questionnaires over the phone, the physician will read the questions directly and record the patient's responses.
- Adverse events
- Document any patient withdrawals

5.1.4 Visit 4: approximately 9 months

Visit 4 will occur at approximately 9 months following initiation of BRV therapy. The following data will be collected at Visit 4:

- Concomitant AED and non-AED medication use
- Dates and doses of BRV treatment and, if discontinued, date of discontinuation and reason
- Documentation of seizure information since the prior visit
- Questionnaires and assessments: SSQ, CGIC, PGIC, TSQM-9, and WPAI:GH

  Note: Patient-reported outcome questionnaires may be completed within the Helpilepsy application. If a patient visiting the site is not using the Helpilepsy application, then the site staff should administer paper-based questionnaires if the patient has agreed to complete these questionnaires. If the patient is in agreement to complete the questionnaires over the phone, the physician will read the questions directly and record the patient's responses.
- Adverse events
- Document any patient withdrawals

5.1.5 Visit 5: approximately 12 months/End of Study

Visit 5 will occur at approximately 12 months following initiation of BRV therapy. The following data will be collected at Visit 5:

- Concomitant AED and non-AED medication use
- Dates and doses of BRV treatment and, if discontinued, date of discontinuation and reason
- Documentation of seizure information since the prior visit
- Questionnaires and assessments: QOLIE-10-P, SSQ, NDDI-E, PGIC, CGIC, TSQM-9, and WPAI:GH

  Note: Patient-reported outcome questionnaires may be completed within the Helpilepsy application. If the patient is not using the Helpilepsy application, then the site staff should

administer paper-based questionnaires if the patient has agreed to complete these questionnaires. If the patient is in agreement to complete the questionnaires over the phone, the physician will read the questions directly and record the patient's responses.

- Adverse events
- Document completion of patient participation including date and dose of final BRV treatment in the study (patients may continue on BRV treatment after completion of their participation in this study)

5.2 Schedule of activities

The schedule of activities is presented in Table 5-1.

Table 5-1: Schedule of activities

	Visits				
	1[a]	2[a]	3[a]	4[a]	5[a]
Assessment	**Baseline**[b]	**3 months**[c]	**6 months**[c]	**9 months**[c]	**12 months**[c] **EOS**
PDCF signed	X				
Verification of selection criteria	X				
Demographics and other characteristics [d]	X				
General epilepsy history [e]	X				
Medical history	X				
Concomitant AEDs	X	X	X	X	X
Concomitant non-AEDs	X	X	X	X	X
Prior AED-related AEs leading to discontinuation of respective AED [f]	X				
Reason for BRV initiation	X				
BRV treatment [g]	X	X	X	X	X
Documentation of seizure information [h]	X	X	X	X	X
QOLIE-10-P [i]	X		X		X
SSQ [i]	X	X	X	X	X
NDDI-E [i]	X		X		X
CGIC		X	X	X	X
PGIC [i]		X	X	X	X
TSQM-9 [i]	X	X	X	X	X
WPAI:GH [i]	X	X	X	X	X
AEs	X	X	X	X	X
Withdrawal criteria		X	X	X	
Document completion of patient participation [j]					X

AED=antiepileptic drug; BRV=brivaracetam; CGIC=Clinical Global Impression of Change; EOS=End of Study; NDDI-E=Neurological Disorders Depression Inventory for Epilepsy; PDCF=Patient Data Consent form; PGIC=Patient Global Impression of Change; PRO=patient-reported outcome; QOLIE-10-P=Patient-Weighted Quality of Life in Epilepsy Inventory-10-P; SSQ=Seizure Severity Questionnaire; TSQM-9=Treatment Satisfaction Questionnaire for Medication-9; WPAI:GH=Work Productivity and Activity Impairment Questionnaire: General Health

Table 5-1: Schedule of activities

	Visits				
	1[a]	2[a]	3[a]	4[a]	5[a]
Assessment	**Baseline**[b]	**3 months**[c]	**6 months**[c]	**9 months**[c]	**12 months**[c] **EOS**

Note: For patients who discontinue the study early, the treating physician should collect data as specified for Visit 5 (EOS Visit).

[a] This visit can be completed via a telephone call with the site.

[b] First Day of BRV treatment.

[c] Visits 2, 3, 4, and 5 will be conducted at approximately 3, 6, 9, and 12 months, respectively, from the Baseline Visit.

[d] Demographics include: age at enrollment, sex, educational status, and employment status.

[e] To include year of first epilepsy diagnosis, lifetime AEDs (excluding benzodiazepines or other rescue medications used short term per physician discretion and any AED not taken for at least 7 days [1 week]) including reasons for discontinuation, and etiology.

[f] Collected from 6 months prior to Baseline (Visit 1).

[g] Dates and doses of BRV treatment and, if discontinued, date of discontinuation and reason.

[h] The treating physician will evaluate at each visit the frequency and type of seizures experienced by the patient since the prior study visit. At Baseline, seizure frequency will be based on the prior 3 months to estimate the frequency per 28 days. Alternatively, seizure frequency information can be collected via the Helpilepsy application (on a voluntary basis). Seizure frequency data may be recorded by patients using the Helpilepsy application daily during the first week, weekly during the rest of the first month, and monthly during the rest of the study period.

[i] Patient-reported outcome questionnaires (QOLIE-10-P, SSQ, NDDI-E, PGIC, TSQM-9, and WPAI:GH) may be completed within the Helpilepsy application. If a patient visiting the site is not using the Helpilepsy application, then the site staff should administer paper-based questionnaires at each visit if the patient has agreed to complete these questionnaires. For those patients who are not using the Helpilepsy application and who have completed their visits via a telephone call, the physician may read the questionnaires over the phone and record their responses. At Visit 1, questionnaires should be answered prior to BRV treatment initiation.

[j] Includes date and dose of final BRV treatment in this study.

6 STUDY DURATION, NUMBER OF PATIENTS, AND SITES

Up to 100 study sites will enroll approximately 400 patients with POS. This study is expected to last for 3 years; approximately 18 to 24 months will be needed for enrollment. Each patient will be observed for a planned 12-month period with 5 planned visits or telephone calls.

7 ANTICIPATED REGIONS AND COUNTRIES

The study will be performed in specialized epilepsy centers in Europe (Germany, Italy, Spain, and France) and Canada.

8 SELECTION AND WITHDRAWAL OF PATIENTS

8.1 Selection criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

1. The patient must be 18 years of age or older.
2. The decision by the treating physician to prescribe BRV must be made independent from participation in the NIS and is in line with the drug's license and the (local) Summary of Product Characteristics (SmPC).
3. A PDCF must be signed and dated by the patient.
4. The patient must be considered by the treating physician to be reliable and capable of adhering to the protocol.
5. The patient must not have received prior BRV treatment.
6. The patient must have a history of epilepsy for at least 6 months.
7. The patient must have a history of partial-onset (focal) seizures. The patient must have had at least 1 POS (focal aware [simple partial], focal with impaired awareness [complex partial], or focal to bilateral tonic clonic seizure [secondarily generalized tonic clonic]) within 3 months prior to Baseline (Visit 1).
8. The patient must be receiving ≥1 AED at the start of BRV treatment. The patient must have failed no more than 3 lifetime AEDs used for the treatment of seizures, including all prior and concomitant AEDs at Baseline (Visit 1) before BRV initiation (excluding benzodiazepines or other rescue medications used short term per physician discretion and any AED not taken for at least 7 consecutive days [1 week]).

8.2 Withdrawal criteria

Patients are free to withdraw from the NIS at any time, without prejudice to their continued care. Patients who have not initiated BRV within 90 days of initial data consent will be considered to have met withdrawal criteria. Patients who discontinue BRV treatment will be withdrawn from the study.

The BRV treatment period is exclusively determined by the treating physician. Study participation concludes after approximately 12 months or at the time the patient withdraws his/her consent. Physicians are free to add or withdraw any medication or to withdraw the patient from the study at their own discretion.

The primary reason for withdrawal from the NIS must be documented in the patient's electronic Case Report Form (eCRF). When the primary reason for withdrawal is lack of effectiveness or an AE, both must be reported as described in Section 10.4.

The treating physician should attempt to obtain information on patients in the case of withdrawal or discontinuation. For patients who discontinue the study early, the treating physician should collect data as specified for Visit 5 (EOS Visit). For patients considered as lost to follow up, the treating physician should make an effort (at least 1 phone call and 1 written message to the patient), and 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 the reason(s) for removing the patient, must be recorded in the source documents.

9 PRESCRIBED TREATMENT(S)

Patients will be treated with commercially available BRV and with other commercially available AEDs, as prescribed by treating physicians, in accordance with standard clinical practice.

9.1 Numbering of patients

Each patient will be assigned a 5-digit number when entering the study that serves as the patient identifier throughout the study.

10 ASSESSMENT OF SAFETY

For the safety assessment of BRV, causal relationship, seriousness, and outcome of AEs will be collected during the observation period. It is the task of the treating physician to make a judgment regarding a possible causal relationship with the intake of BRV.

10.1 AEs/SAEs and other safety relevant information

In order to ensure complete safety data collection, all AEs and other safety relevant information occurring during the study (ie, after signing the PDCF), must be reported. This includes all AEs not present prior to the signing the PDCF and all AEs that recur or worsen after signing the PDCF (eg, underlying or concomitant disease).

For information on the identification and description of AEs/serious adverse events (SAEs) and other safety relevant information, refer to Section 10.3.

Details for completion of the Adverse Event Report form for NIS are described in Section 10.3.

10.2 Definitions

10.2.1 Adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a medicinal 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 product, whether or not related to the medicinal product.

A TEAE is defined as an AE which has an onset on or after the date of first BRV administration up to 4 weeks after BRV discontinuation. Behavioral AEs will be defined in the Statistical Analysis Plan (SAP).

10.2.2 Serious adverse event

An AE is serious if one or more of the following criteria are met:

- Death
- Life threatening: An event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe
- Inpatient hospitalization or prolongation of existing hospitalization: If a hospitalization is planned prior to the patient receiving the first dose of medicinal product, it is not classified as serious. However, if a hospitalization is unplanned and is a result of an adverse experience, this is considered an SAE
- Persistent or significant disability/incapacity
- Congenital anomaly or birth defect
- An important medical event or an event requiring significant intervention: Medical and scientific judgment must be exercised in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the above definition. These are usually considered serious.

10.2.3 Adverse event of special interest

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

All AESIs in the context of this NIS are summarized in Table 10-1.

Table 10-1: MedDRA preferred terms for AESIs

• autoimmune nephritis	• tubulointerstitial nephritis
• nephritis	• tubulointerstitial nephritis and uveitis syndrome
• nephritis allergic	• drug induced liver injury

AESI=adverse event of special interest; MedDRA=Medical Dictionary for Regulatory Activities

10.2.4 Other safety relevant information

Other safety relevant information includes the following:

- Off-label use: Situation where BRV is intentionally used for a medical purpose not in accordance with the authorized product information
- Misuse: Situation where BRV is intentionally and inappropriately used not in accordance with the authorized product information
- Abuse: Persistent or sporadic, intentional excessive use of BRV, which is accompanied by harmful physical or psychological effects (2010/84/EU Article 1)

- Medication error: Any unintentional error in the prescribing, dispensing, or administration of BRV while in the control of the health-care professional or patient.
- Occupational exposure: Exposure to BRV (as defined in 2010/84/EU Article 1) as a result of one's professional or non-professional occupation
- Lack of therapeutic effectiveness of BRV
- Overdose of BRV (see Section 10.7)
- Suspected transmission of an infectious agent via BRV
- Suspected adverse reaction associated with a suspected or confirmed falsified medicinal product or quality defect (combined complaint) of BRV
- Unexpected therapeutic effect of BRV

10.3 Identification and description of AEs/SAEs and other safety relevant information

The treating physician is requested to inform patients of the need to report any AE/SAE and other safety relevant information, including pregnancy (see Section 10.6), during the study.

The patient will be given the opportunity to report AEs/SAEs and other safety relevant information spontaneously. A general prompt will also be given at each study visit to detect AEs/SAEs or other safety relevant information; for example:

"Did you notice anything unusual about your health (since your last visit)?"

In addition, the treating physician should review any self-assessment procedures employed. Patient-reported outcome questionnaires will be utilized in this study to allow an aggregate view of trending of outcomes over time. Symptoms reported by the patient in these questionnaires will not be routinely reported to Patient Safety (PS) as individual events, as the limited data from individual cases would be unlikely to contribute significantly to the safety profile of BRV. However, if the patient reports AEs/SAEs in addition to the symptoms being collected in the questionnaires, the physician must promptly report these as AEs/SAEs. All AEs/SAEs will be tabulated and reported in the Clinical Study Report.

Signs or symptoms of the condition/disease for which the prescribed treatment is being studied should be recorded as AEs/SAEs 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 treating physician from the patient's history or the Baseline Period.

When recording an AE/SAE or any other safety relevant information, the treating physician should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms, signs, or medical procedures. The Adverse Event Report form and source documents should be consistent.

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 Adverse Event Report form for NIS.

10.4 Reporting of AEs/SAEs and other safety relevant information

If a nonserious AE or other safety relevant information is reported, UCB must be informed within 1 week of receipt of this information by the site. If an SAE, AESI, or pregnancy is reported, UCB must be informed within 1 working day of receipt of this information by the site (see Contact Details for the Transmission of AEs and Other Safety Relevant Information to UCB). The treating physician must forward to UCB (or its representative) a duly completed Adverse Event Report form for NIS 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. Relevant information recorded on the Adverse Event Report form for NIS will be entered into the global safety database of UCB.

The causal relationship between BRV and an AE/SAE must be assessed by the treating physician for each AE/SAE.

10.5 Follow up on AEs/SAEs and other safety relevant information

The treating physician will cooperate with UCB in providing any clarification that may be needed regarding the safety aspects of the reported cases.

An AE/SAE should be followed until it has resolved, has a stable sequelae, the treating physician determines that it is no longer clinically significant, or the patient is lost to follow up.

If an AE/SAE is still ongoing at the end of the study for a patient, follow up should be provided until resolution/stable level of sequelae, or until the treating physician no longer deems that it is clinically significant, or until the patient is lost to follow up.

10.6 Pregnancy and breastfeeding

Treating physicians are required to report the pregnancy of a patient, pregnancy of a patient's partner, and a patient who is breastfeeding.

Pregnancy, outcome (birth, miscarriage, abortion), and breastfeeding will be documented on the Pregnancy Report and Outcome form provided to the treating physician by UCB in case of reported pregnancy. The progression of the pregnancy and the eventual birth (if applicable) must be followed up using the Pregnancy Report and Outcome form in which the treating physician has to report on the health of the mother and of the child. Every reasonable attempt should be made to follow the development and health of the child for at least 30 days after birth for any significant medical issues or development delay.

If the patient is lost to follow up or refuses to give information, written documentation of attempts to contact the patient needs to be provided by the treating physician and filed at the site. UCB's local PS department is the primary contact for any questions related to the data collection for the pregnancy, birth and follow up, and breastfeeding.

In cases where the partner of a male patient included in this NIS becomes pregnant, the treating physician or designee is asked to contact the patient to request consent of the partner via the Partner Pregnancy Consent form that should be available in the treating physician's site file. In case of questions about the consent process, the treating physician may contact UCB's local PS department. The treating physician will complete the Pregnancy Report and Outcome form and send it to UCB's local PS department only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form.

UCB's local PS department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.

10.7 Overdose of prescribed treatment

Overdose of prescribed treatment refers to the administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information.

Overdose should be reported on the Adverse Event Report form for NIS, independently of whether there is an AE associated with the excessive dosing or not.

Any AE/SAE associated with excessive dosing of any drug must be reported and followed as any other AE/SAE.

10.8 Safety signal detection

Reported AEs from this study will be reviewed periodically, together with other safety information received at UCB, to detect as early as possible any safety concern(s) related to the treatment so that treating physicians, patients, and regulatory authorities will be informed appropriately and as early as possible.

11 ASSESSMENT OF EFFECTIVENESS AND HEALTH-RELATED QUALITY OF LIFE VARIABLES

Within this NIS, the Helpilepsy application (Section 18.1) will be offered as an option to the participating sites and patients. The use of the Helpilepsy application within the study is limited to data collection on seizure frequency and patient-reported questionnaires. For those patients who do not use the Helpilepsy application, seizure information and PROs can be collected via paper questionnaires and based on the medical chart information. Alternatively. if the patient is in agreement to complete the questionnaires over the phone, the physician may read the questions directly and record the patient's responses. The treating physician will evaluate at each visit, as part of standard practice with the patient, the frequency and type of seizures experienced by the patient since the prior study visit (or based on the prior 3 months at Baseline).

Patient-reported outcome assessments will be available in the local language for each participating country (the official languages of each country will be used). In addition, an English version of each questionnaire will be available for each country.

The QOLIE-10-P version 2 will be used to evaluate the health-related QoL of study patients (Cramer et al, 1996; Cramer and Van Hammée, 2003). The QOLIE-10-P is an adaptation of the original QOLIE-31 instrument (Cramer et al, 1998). The QOLIE-10-P is a brief survey to be completed by the patient of health-related QoL for adults with epilepsy. There are 10 questions about health and daily activities, one question about how much distress is felt about problems and worries related to epilepsy, and a review of what bothers the patient most (see (Section 18.2.1).

The Clinical Global Impression scales (Guy and Bonato, 1970) were initially developed for a risk-benefit estimation within the treatment of mentally ill patients. The 4 global scales (Severity of Illness, Change in Severity from Baseline, Therapeutic Efficacy, and Tolerability of Treatment) are used as different measures of treatment outcome in different kinds of pharmacological studies. The Change in Severity scale (CGIC) is used in this NIS and ranges

from 1 (very much improved) to 7 (very much worse). This scale requires the clinician to rate the severity of the patient's illness at the time of assessment (see Section 18.2.3).

The PGIC (Hurst and Bolton, 2004) is a 7-point categorical rating scale in which the patient rates the changes in functioning over time from 1 (very much improved) to 7 (very much worse) (see Section 18.2.4). The PGIC is to be completed during an interview between the patient and the treating physician or designee.

The TSQM is a general tool for assessing a patient's satisfaction with medications designed to treat, control, or prevent a wide variety of conditions. It includes 14 items and 4 subscales (reported by the patients): Effectiveness (Questions 1 to 3), Side Effects (Questions 4 to 8), Convenience (Questions 9 to 11), and Global Satisfaction (Questions 12 to 14). In this study, an abbreviated 9-item TSQM (TSQM-9) (Bharmal, 2009) without the side effects subscale will be used (see Section 18.2.5).

The WPAI:GH (Reilly et al, 1993) consists of six items measuring absenteeism, presenteeism (attending work while not physically or mentally capable of working), overall work productivity loss, and activity impairment (Section 18.2.7). Only employed respondents will provide data for the work-related items, but all respondents will provide data for activity impairment.

The SSQ (Cramer et al, 2002) is a facilitated interview during which a clinician reviews seizure attributes with the patient and an observer (someone who regularly observes the seizures). In this study, a modified version of the SSQ will be used that is comprised only of items 5 and 8 of the questionnaire and will be reported by the patients (see Section 18.2.6).

The NDDI-E (Gilliam et al, 2006) is a 6-item questionnaire validated to screen for depression in people with epilepsy (see Section 18.2.2). The NDDI-E will be completed by the patients.

Although there is no direct correlation between the results of the questionnaires/scales and occurrence of AEs, the treating physician should evaluate any significant change for the potential reporting of an AE.

Retention will be based on the number of patients remaining in the study and on BRV treatment at each study visit.

12 STATISTICS

Descriptions of statistical methods are presented below and will be described in more detail in the SAP.

12.1 Definition of analysis sets

The All Patients Documented set is defined as all patients included in the study with valid data consent and for whom at least Visit 1 (Baseline) is documented. The All Patients Documented set will be used for patient disposition and patient data listings only.

The Safety Set (SS) is defined as all patients included in the All Patients Documented set for whom it cannot be excluded that they received treatment with BRV at least once in the study. The SS will be used for the analysis of all study variables.

The Per-Protocol Set (PPS) is defined as all patients in the SS who are treated according to the approved SmPC during their Observation Period, representing the on-label use of BRV in Europe and Canada. Any patients with a documented protocol deviation may be excluded from the PPS. The PPS will be used for the analysis of all study variables.

12.2 Planned analyses

All variables will be summarized using descriptive statistics. For continuous variables, summary statistics (number of available observations, mean, standard deviation, minimum, median, maximum, and 25% and 75% quartiles where relevant) will be tabulated. Categorical variables will be summarized by the number of patients and the percent of patients in each category.

Data from patients who prematurely withdraw from the study will be analyzed up to the final visit attended. Data from patients who withdraw the data consent are used up to the date of withdrawal of consent.

Subgroup analyses of specific endpoints may include number of lifetime AEDs (defined as AEDs used for at least 7 consecutive days (1 week); Section 8.1), number of concomitant AEDs, treatment line in adjunctive therapy (ie, BRV added as first, second, third or later adjunctive treatment), and comorbidity. Further sensitivity analysis may also be performed. Details of these analyses will be described in the SAP.

12.2.1 Analysis of the primary variable

The primary variable of the study is seizure freedom for at least 6 consecutive months over the 12-month observation period. It will be summarized as the number and percentage of patients with no seizures for at least 6 consecutive months at any time within the total observation period of 12 months. A 2-sided 95% confidence interval (CI) for the seizure freedom rate will also be presented.

12.2.2 Analysis of secondary variables

Seizure freedom at 3 months defined as no seizure from Baseline to 3 months, at 6 months defined as no seizure from Baseline to 6 months, at 9 months defined as no seizure from Baseline to 9 months, and at 12 months defined as no seizure from Baseline to 12 months, will be analyzed using the same methodology as for the primary variable.

Patients who terminate the study early will be assigned to the relevant visit per the schedule of activities (ie, at 3, 6, 9 months [Section 5.2]) and not the End of Study Visit (12 months).

For seizure frequency variables, Baseline seizure frequency will be based on the 3 months prior to Visit 1 (Baseline) to estimate the frequency per 28 days.

The following variables will be summarized using descriptive statistics:

- POS frequency (seizures per 28 days) at Visit 1 (Baseline), Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 9), and Visit 5 (Month 12)
- Absolute and percent change in POS frequency (seizures per 28 days) from Visit 1 (Baseline) to Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 9), and Visit 5 (Month 12)

The following variables will be summarized using number and percentage of patients:

- BRV retention, defined as patients remaining in the study and on BRV treatment, at Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 9), and Visit 5 (Month 12)
- Response based on percent change in POS frequency, defined as patients experiencing a ≥50% reduction in POS frequency (seizures per 28 days), from Visit 1 (Baseline) to Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 9), and Visit 5 (Month 12)
- Discontinuation of BRV due to lack of effectiveness

Time to discontinuation of BRV treatment will be analyzed using Kaplan-Meier methods, and the median time to event will be presented along with the 25% and 75% quartiles.

12.2.3 Analysis of other variables

Other variables comprise the variables defined in Section 4.3.

12.2.3.1 Analysis of other effectiveness variables

Self-reported seizure frequency collected through the Helpilepsy application at each available timepoint (daily during the first week, weekly during the rest of the first month, and monthly during the rest of the study period) will be summarized using descriptive statistics.

Machine learning techniques will be used to model Baseline predictors of BRV effectiveness in early treatment line combinations. This statistical modeling technique will fit a LASSO regression model with the seizure frequency at each subsequent timepoint as the dependent variable, and all possible Baseline characteristics as independent variables. This exploratory analysis will be documented separately and completed by the Real-world Evidence team outside of the primary SAP.

Time to first seizure after first dose of BRV will be analyzed using Kaplan Meier methods, and the median time to event will be presented along with the 25% and 75% quartiles.

12.2.3.2 Analysis of other QoL variables

The following variables will be summarized using descriptive statistics:

- QOLIE-10-P total score at Visit 1 (Baseline), Visit 3 (Month 6), and Visit 5 (Month 12), and change from Baseline in QOLIE-10-P total score
- TSQM-9 scores for each scale at Visit 1 (Baseline), Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 9), and Visit 5 (Month 12), and change from Baseline in TSQM-9 scores

- WPAI:GH scores for each scale at Visit 1 (Baseline), Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 9), and Visit 5 (Month 12), and change from Baseline in WPAI:GH scores
- NDDI-E total score at Visit 1 (Baseline), Visit 3 (Month 6), and Visit 5 (Month 12), and change from Baseline in NDDI-E total score

The following variables will be summarized using number and percentage of patients:

- PGIC rating at Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 9), and Visit 5 (Month 12), as well as patients who improved, had no change, or worsened in PGIC
- CGIC rating at Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 9), and Visit 5 (Month 12), as well as patients who improved, had no change, or worsened in CGIC
- SSQ rating for items 5 and 8 at Visit 1 (Baseline), Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 9), and Visit 5 (Month 12)

12.2.3.3 Analysis of other safety variables

Adverse events will be coded for analysis with the latest version of the Medical Dictionary for Regulatory Activities (MedDRA®).

For each of the following event types, frequency tables with the number of events, the number of patients who experience the event, and the percentage of patients who experience the event will be presented by MedDRA system organ class and preferred term:

- TEAEs and behavioral TEAEs
- TEAEs and behavioral TEAEs by time of occurrence and by different treatment combinations
- Serious TEAEs and serious behavioral TEAEs
- Study drug-related TEAEs and study drug-related behavioral TEAEs
- TEAEs and behavioral TEAEs leading to permanent discontinuation of BRV
- AESI and other safety relevant events
- Prior AED-related AEs leading to discontinuation of respective AED

Discontinuation of BRV due to a TEAE will be summarized using number and percentage of patients.

While it is expected that many of the patients in this study may receive 1, 2, or more doses of any Coronavirus Disease 2019 (COVID-19) vaccines during the observation period, a sensitivity analysis will be performed of COVID-19-vaccine-related TEAEs as well as total TEAEs excluding COVID-19-vaccine related TEAEs.

12.3 Planned interim analysis and data monitoring

Two informal interim analyses (snapshot analyses) are planned for this NIS if sufficient data are collected to evaluate emerging trends and systematic errors, as follows:

- A first snapshot analysis is expected to be performed with a data cut-off date approximately in Q2 of 2022.

- A second snapshot analysis is expected to be performed with a data cut-off date approximately in Q2 of 2023.

Details of these snapshot analyses will be described in the SAP.

12.4 Determination of sample size

A sample size of 600 patients was originally selected for this study to account for a dropout rate of approximately 15%. This was expected to result in 500 patients being included in the SS with a 2-sided 95% CI for a single proportion using the large sample normal approximation would extend 0.044 from the observed proportion for an expected proportion of 0.50.

As planned, the study enrollment will close end after 24 months of enrollment have elapsed. Due to unforeseen delays in enrollment such as the COVID-19 pandemic, it is expected that enrollment will be approximately 400 patients after the allocated 2-year enrollment period. The following scenarios demonstrate the resulting CIs for the potential sample sizes and that these are sufficient to evaluate the primary objective of the study.

Using the same expected 6-month seizure freedom rate of 50% as the original calculation, Table 12-1 contains scenarios considering a range of total number of patients and the resulting CIs for each N. A drop-out rate of approximately 15% of patients is assumed between enrolled patients and those completing 12 months of follow up to be evaluable for the primary variable of the study. Preliminary data from EP0103 suggest a premature discontinuation rate of 14% (internal data, not published).

Table 12-1: Total sample size calculation, assuming a 2-sided 95% CI (α=0.05) for a single proportion using the large sample normal approximation

Total enrolled patients (N)	Number of patients completing 12 months FU (assuming approx. 15% drop-out)	Expected SF rate (%)	Distance (±) from expected SF rate	95% CI around expected SF rate
350	300	50%	5.7%	(44.3%, 55.7%)
380	320	50%	5.5%	(44.5%, 55.5%)
400	340	50%	5.3%	(44.7%, 55.3%)

approx.=approximately; CI=confidence interval; FU=follow up; SF=seizure freedom
Source: nQuery +nTerim software, version 2.0.

For 400 patients enrolled, the current discontinuation rate suggests 340 patients would remain after premature discontinuations. If the expected proportion is 50%, a 2-sided 95% CI for a single proportion using large sample normal approximation would extend 5.3% from the observed proportion corresponding to a CI of 44.7% to 55.3%.

A more conservative scenario would propose 380 enrolled patients prior to the end of enrollment, with 320 patients remaining after premature discontinuations. Thus, in this scenario, a 2-sided 95% CI for a single proportion using large sample normal approximation will extend 5.5% from the observed proportion if the expected proportion is 50%. This corresponds to a CI of 44.5% to 55.5%. As such, reduction of the sample size still preserves the primary objective and scientifically meaningful outcome of the study.

13 STUDY MANAGEMENT AND ADMINISTRATION

13.1 Monitoring

Monitoring of the study will be delegated by UCB to a contract research organization (CRO). The CRO will monitor the study to meet the CRO's monitoring standard operating procedures (SOPs) and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate.

13.1.1 Source data quality and validity

In order to safeguard and assure data quality, a site management plan will be developed that will include details on site monitoring visits, site management by telephone, and source data verification.

A central monitoring approach will be applied so monitoring activities are focused on the areas with the highest potential to impact data quality. Ongoing document review, data review, and analysis will be performed remotely by UCB/the CRO to examine the data collected in order to check compliance and identify unusual data patterns, deviations from protocol, or missing or invalid data. On-site monitoring visits will be performed on a for-cause basis.

The treating physician 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 treating physician(s)/institution(s) will permit direct access to source data/documents for study-related monitoring, audits, Independent Ethics Committee (IEC)/Institutional Review Board (IRB) review, and regulatory inspection(s). 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).

13.2 Data handling

13.2.1 Electronic Case Report Form completion

The treating physician is responsible for reporting of accurate and complete data in the eCRF and in all required reports promptly within the specified time.

Any change or correction to the eCRF after first entry and saving must be accompanied by a reason for the change. Corrections made after the treating physician's review and approval (by means of a password/electronic signature) of the completed eCRF must be reapproved by the treating physician. The treating physician should maintain a list of personnel authorized to enter data into the eCRF. Detailed instructions will be provided in the eCRF Completion Guideline.

13.2.2 Database entry and reconciliation

Within this NIS, the Helpilepsy application (Section 18.1) will be offered as an option to the participating sites and patients. The use of the Helpilepsy application within the study is limited to data collection on seizure frequency and from patient-reported questionnaires.

Case Report forms and external electronic data will be entered 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. The data are entered into the eCRFs once and are subsequently verified.

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.

13.2.3 Patient Enrollment log/Patient Identification list

The patient's inclusion will be recorded in the Patient Enrollment log.

The treating physician will keep a Patient Identification Code list. This list remains with the treating physician and is used for unambiguous identification of each patient.

Access to this list may be granted only to members of staff, authorized persons of UCB (or designees), and the competent authorities. The study monitor is also bound to confidentiality. After the end of the study, the identification list will remain with the physician.

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

13.3 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, or unsatisfactory data collection with respect to quality or quantity.

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the treating physicians/institutions and the regulatory authorities of the termination or suspension and the reasons for termination or suspension, in accordance with applicable regulatory requirements. The IEC/IRB and other institutions as per national legislation should also be informed (when applicable) and provided with reasons for termination or suspension by UCB or by the treating physician/institution, as specified by the applicable regulatory requirements.

13.4 Archiving and data retention

The treating physician will maintain adequate records for the study, including eCRFs, medical records, data consent documents, safety reports, and other pertinent data.

All essential documents are to be retained by the treating physician for at least 5 years after the final study report or first publication of the full study results becomes available, whichever comes later. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s). The treating physician must 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 treating physician must also notify UCB should he/she relocate or move the study-related files to a location other than that specified in UCB's study master file.

13.5 Audit and inspection

The treating physician 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 patients have been protected, that documented patients are appropriate for the study, and that all data relevant for evaluation of the prescribed treatment have been processed and reported in compliance with the planned arrangements, the NIS protocol, physician's site organization, ethics committee SOPs, and applicable regulatory requirements.

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

14 ETHICS AND REGULATORY REQUIREMENTS

14.1 Patient Data Consent form

Patient's data consent must be obtained and documented in accordance with local regulations and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining data consent, information should be given in a language and at a level of complexity understandable to the patient in both oral and written form by the treating physician (or designee). Each patient will have the opportunity to discuss the study and its alternatives with the treating physician.

Prior to participation in the study, the written PDCF must be signed and personally dated by the patient, and/or his/her legal representative, and by the person who conducted the data consent discussion (treating physician or designee). Signing of the PDCF may be done at the site or remotely (via mail), if necessary. In the latter case, the PDCF is sent to the patient's home via mail, signed by the patient, and returned to the site. The patient and/or his/her legal representative must receive a copy of the signed and dated PDCF. As part of the consent process, each patient must consent to direct access to his/her medical records for study-related monitoring, auditing, IEC/IRB review, and regulatory inspection.

If the PDCF is amended during the study, the treating physician (or UCB, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended PDCF by the IEC/IRB (when applicable) and use of the amended form.

14.2 Institutional Review Boards and Independent Ethics Committees

The study will be conducted under the auspices of an IEC/IRB.

The treating physician/UCB (or his/her representative) will ensure that an appropriately constituted IEC/IRB that complies with the 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 treating physician/UCB (or his/her representative) will forward copies of the protocol, PDCF, treating physician's curriculum vitae (if applicable), and all other patient-related documents to be used for the study to the IEC/IRB for its review and approval.

Before initiating the NIS, the treating physician will have written and dated full approval from the responsible IEC/IRB for the NIS.

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

14.3 Patient privacy

UCB staff (or designee) will affirm and uphold the patient's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the patient number assigned at enrollment. These data will be stored on servers at UCB headquarters for each respective participating country.

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

14.4 Protocol amendments

Protocol changes may affect the legal and ethical status of the study and may also affect statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective. Substantial changes will only be made as an amendment to the protocol and must be approved by UCB, the IEC/IRB, regulatory authorities, and local institutions (if required), prior to being implemented.

15 STUDY LIMITATIONS

This is an observational study and the analysis of the results will be descriptive in nature.

Enrollment of patients will be carried out by treating physicians at selected sites. Prescription behavior may be influenced by the market access conditions, which may vary per country. The site selection process shall ensure that representative sites regarding treatment routines in all countries are selected. The potential ability to fulfill the study specific documentation requirements, the fact that BRV is actually available/prescribed at the site, and the quality of the sites will be considered as well.

Study procedures should not interfere with the prescribing behavior of treating physicians or with the individual needs of the patients to assure data collection of standardized, reliable clinical data from Baseline to the end of the observation period.

Patients should take BRV as adjunctive treatment, according to the current SmPC. This allows for the use of other AEDs and changes in concomitant AEDs, which may have an influence on the results. Changes in concomitant AEDs will be documented, and pre-existing or newly occurring concomitant diseases, as well as associated concomitant medication, will be recorded. Their possible impact on the course or results of this NIS will be evaluated.

16 FINANCE AND PUBLICATION

Financial arrangements and publication rights will be addressed in the written study agreements between UCB and the physician and/or the institution of the physician, as applicable.

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18 APPENDICES

18.1 Helpilepsy application

Digitalization of health care has opened new opportunities in treating patients and improving their lives. Real-time monitoring, for example via the usage of applications and devices, allows a personalized approach in medicine. Patient outcomes, both clinical and QoL, tracked in a real-time manner by patients and monitored by their treating physicians, could help to improve patient-physician interactions, (ie, could improve efficiency within care pathways). More reliable and granular data, presented in an actionable manner, can help physicians in their decisions. In addition, it could reduce the expenditures associated with additional hospital visits and consultations. Patients can benefit from adjusted treatment decisions based on their data (Institute for Clinical and Economic Review, 2018).

Within this NIS, Helpilepsy (a mobile application for patients, and web-based dashboard for physicians) (www.helpilepsy.com) will be offered as an option to the participating sites and patients who would like to use the digital solution of real-time disease monitoring (once the necessary data privacy agreements are accepted). The Helpilepsy application, which is used across Europe by epilepsy centers, is a Conformité Européenne-certified medical device (class I, under EU/Medical Devices Directive), compliant with local data privacy and security regulations. In addition, the Helpilepsy application is in compliance with the Personal Information Protection and Electronic Documents Act (Canada). Finally, its organization has implemented an International Organization for Standardization 13485 Quality Management System (valid worldwide).

The usage of the Helpilepsy application within the study is done in specific module(s) and data will be collected on seizure frequency and from patient-reported questionnaires (automatically sent to patients to be completed on a voluntary basis). Only these data points will be analyzed within the study. A site manual and a patient manual will be available for training on the use of the Helpilepsy application in this study.

Besides the specific module of the Helpilepsy application developed for this NIS, patients and physicians will receive access to all features of the Helpilepsy application and can test it in their clinical routine. The BRITOBA module access is granted for the total duration of this NIS for physicians and is limited to the duration of study participation for patients. Helpilepsy, without the specific BRITOBA module, will be available for patients and physicians after the study.

To ensure the confidence in the reliability, quality, and integrity of the data, several security measures have been put in place. The Helpilepsy application itself is protected by a password that is known only to the patient in EP0103. Furthermore, the Helpilepsy application also allows for qualified and trained site personnel to access the data of participating patients through a password-protected access.

Study data entered into the Helpilepsy application (in the specific study module) by the patient is fully encrypted within the application and its transmission to the CRO's electronic data capture system.

The patient responds to the questions and acts on the requested activities in the Helpilepsy application. All data collected as part of these activities will be stored in the cloud (Amazon Web Services, Germany). All data are reviewable for the physicians while the patient is at the site. All

data collected by the Helpilepsy application could be extracted (in PDF or Excel format) or printed by the site.

The following information (eg, questionnaire) is copyrighted and UCB does not have permission to disclose the contents.

18.2.2 Neurological Disorders Depression Inventory in Epilepsy

Neurological Disorders Depression Inventory in Epilepsy (NDDI-E)

Name: _____ **Date:** _____

For the statements below, please circle the number that best describes you over the *last two weeks including today.*

	Always or Often	Sometimes	Rarely	Never
Everything is a struggle	4	3	2	1
Nothing I do is right	4	3	2	1
Feel guilty	4	3	2	1
I'd be better off dead	4	3	2	1
Frustrated	4	3	2	1
Difficulty finding pleasure	4	3	2	1

18.2.3 Clinical Global Impression of Change

Clinical Global Impression of Change

Check the box below which describes the subject's condition over the past 4 weeks compared to baseline.

☐1 very much improved

☐2 much improved

☐3 minimally improved

☐4 no change

☐5 minimally worse

☐6 much worse

☐7 very much worse

18.2.4 Patient Global Impression of Change

Patient Global Impression of Change

Over the past 4 weeks, how have you felt compared to before you entered this study? (Please check the number that best describes your condition).

☐1 very much improved
☐2 much improved
☐3 minimally improved
☐4 no change
☐5 minimally worse
☐6 much worse
☐7 very much worse

18.2.5 Treatment Satisfaction Questionnaire for Medication-9

TSQM-9

Abbreviated Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness and convenience of the medication *over the last two to three weeks, or since you last used it* For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

☐[1] Extremely Dissatisfied
☐[2] Very Dissatisfied
☐[3] Dissatisfied
☐[4] Somewhat Satisfied
☐[5] Satisfied
☐[6] Very Satisfied
☐[7] Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

☐[1] Extremely Dissatisfied
☐[2] Very Dissatisfied
☐[3] Dissatisfied
☐[4] Somewhat Satisfied
☐[5] Satisfied
☐[6] Very Satisfied
☐[7] Extremely Satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

☐[1] Extremely Dissatisfied
☐[2] Very Dissatisfied
☐[3] Dissatisfied
☐[4] Somewhat Satisfied
☐[5] Satisfied
☐[6] Very Satisfied
☐[7] Extremely Satisfied

4. How easy or difficult is it to use the medication in its current form?

☐[1] Extremely Difficult
☐[2] Very Difficult
☐[3] Difficult
☐[4] Somewhat Easy
☐[5] Easy
☐[6] Very Easy
☐[7] Extremely Easy

5. How easy or difficult is it to plan when you will use the medication each time?

☐[1] Extremely Difficult
☐[2] Very Difficult
☐[3] Difficult
☐[4] Somewhat Easy
☐[5] Easy
☐[6] Very Easy
☐[7] Extremely Easy

6. How convenient or inconvenient is it to take the medication as instructed?

☐[1] Extremely Inconvenient
☐[2] Very Inconvenient
☐[3] Inconvenient
☐[4] Somewhat Convenient
☐[5] Convenient
☐[6] Very Convenient
☐[7] Extremely Convenient

7. Overall, how confident are you that taking this medication is a good thing for you?

☐[1] Not at All Confident
☐[2] A Little Confident
☐[3] Somewhat Confident
☐[4] Very Confident
☐[5] Extremely Confident

8. How certain are you that the good things about your medication outweigh the bad things?

☐[1] Not at All Certain
☐[2] A Little Certain
☐[3] Somewhat Certain
☐[4] Very Certain
☐[5] Extremely Certain

9. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐[1] Extremely Dissatisfied
☐[2] Very Dissatisfied
☐[3] Dissatisfied
☐[4] Somewhat Satisfied
☐[5] Satisfied
☐[6] Very Satisfied
☐[7] Extremely Satisfied

The following information (eg, questionnaire) is copyrighted and UCB does not have permission to disclose the contents.

18.3 Protocol amendment history

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 1.0 (17 Nov 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rationale for the amendment

EP0103 Protocol Amendment 1.0, dated 17 Nov 2021, was completed to:

- Provide clarification in response to site inquiries
- Provide additional flexibility for the Physician during the study
- Adapt the study to accommodate the COVID-19 pandemic
- Correct minor errors/inconsistencies

Section # and name	Description of change	Brief rationale
Section 1 Background and rationale for the study	Added the 22 Mar 2020 approval of the oral BRV formulations in patients ≥4 years of age in Canada.	Updated approval information.
Section 5 Study design	Revised former text that stipulated that only Visits 2 and 4 could be remote to state that all 5 study visits may be remote (conducted via a call), if needed.	Adaption of the study due to the COVID-19 pandemic.
Section 5.1.1 Visit 1: Baseline/first day of BRV treatment	Revised the text stating that Visit 1 (Baseline) **will be** the patient's first day of BRV treatment to state that Visit 1 **should be** the patients first day of BRV treatment.	Clarification to account for those cases when patients do not receive their first BRV treatment on Visit 1.
Section 5.1.1 Visit 1: Baseline/first day of BRV treatment	Added text that the patient-reported questionnaires completed at Visit 1 (Baseline) will be based upon the patient's prior treatments. Added text to note that for patients who are not using the Helpilepsy application and are completing their visits remotely (via a call), questionnaires will not be completed.	Clarification. Adaptation of the study due to the COVID-19 pandemic.
Section 5.1.1 Visit 1: Baseline/first day of BRV treatment Section 5.2 Schedule of activities	Removed collection of race and ethnicity as part of the demographic data collected at Visit 1.	Compliance with local regulations.

Section # and name	Description of change	Brief rationale
Section 5.1.1 Visit 1: Baseline/first day of BRV treatment Section 5.2 Schedule of activities	Consistently refer to "gender" as "sex."	Consistency with the study CRF.
Section 5.1.1 Visit 1: Baseline/first day of BRV treatment Section 14.1 Patient data consent form	Revised to allow the signing of the PDCF to occur at the site or remotely (via mail), if necessary.	Adaption of the study due to the COVID-19 pandemic.
Section 5.1.3 Visit 3: approximately 6 months Section 5.1.5 Visit 5: approximately 12 months/End of Study	Added text to note that for patients who are not using the Helpilepsy application and are completing their visits remotely (via a call), questionnaires will not be completed.	Adaptation of the study due to the COVID-19 pandemic, allowing all visits to be conducted remotely.
Section 5.2 Schedule of activities	Applied the footnote that states "This visit can be completed via a telephone call with the site" to all study visits.	Adaptation of the study due to the COVID-19 pandemic, allowing all visits to be conducted remotely.
Section 5.2 Schedule of activities	Revised the footnote describing questionnaires to note that for patients who are not using the Helpilepsy application and are completing their visits remotely (via a call), questionnaires will not be completed.	Adaption of the study due to the COVID-19 pandemic.
Section 5.2 Schedule of activities	Revised the existing footnote text stating that questionnaires **will be** administered prior to BRV initiation to note that questionnaires **should be** administered prior to BRV initiation.	Ensure appropriate wording.
Section 5.2 Schedule of activities Section 8.1 Selection criteria Section 12.2 Planned analyses	Clarified the description of lifetime AEDs by not only excluding benzodiazepines, but any other AED used as rescue medication from the classification as a lifetime AED, and adding that an AED should have been taken for at least 7 days (1 week) to be classified as a lifetime AED.	Clarification.

Section # and name	Description of change	Brief rationale
Section 9.1 Numbering of patients	Revised text to state that patients are assigned a 5-digit number for the duration of the study instead of a 7-digit number.	Error correction.
Section 10.2.4 Other safety relevant information	Added text where missing that only other relevant safety information related to BRV will be collected.	Clarification.
Section 12.2 Planned analyses	Revised wording regarding treatment line for more clarity.	Clarification.
Section 12.2 Planned analysts	Removed ‘name of AED’ from the list of possible subgroup analyses of specific endpoints.	Alignment with the SAP.
Section 12.2.3.3 Analysis of other safety variables	Added a sensitivity analysis taking COVID-19 vaccine-related TEAEs into account.	Adaption of the study for the COVID-19 pandemic.
Section 12.3 Planned interim analysis and data monitoring	Updated the snapshot analysis dates for the data cut-off dates currently planned.	Updated information based upon the current study enrollment to date.
Section 18.2.6 Seizure Severity Questionnaire	Updated the version of the SSQ from 3.0 to 2.1.	Error correction.

DECLARATIONS AND SIGNATURES

Declarations and signatures of persons responsible for the study

I confirm that I have carefully read and understand this noninterventional study protocol and agree to conduct this noninterventional study as outlined in this protocol.

Approval Signatures

Name: ep0103-protocol-amendment-2

Version: 1.0

Document Number: CLIN-000204977

Title: EP0103 Protocol Amendment 2.0

Approved Date: 25 Oct 2022

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Medical Date of Signature: 24-Oct-2022 12:41:41 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Qualified Person Date of Signature: 24-Oct-2022 12:56:09 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 25-Oct-2022 07:08:59 GMT+0000