STATISTICAL ANALYSIS PLAN

PROTOCOL SEP093-701

Efficacy and Safety of Eslicarbazepine Acetate as First Add-on to Levetiracetam or Lamotrigine Monotherapy or as Later Adjunctive Treatment for Subjects with Uncontrolled Partial-onset Seizures: A Multicenter, Open-label, Non-randomized Trial

Version Number and Date: Final, 09-JUL-2019

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE - AUTHOR

	Name	Signature	Date
Author:			
Position:			
Company:			

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE - APPROVAL

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
Approved By:			
Position:			
Company:			
Approved By:			
Position:			
Company:			
Approved By:			
Position:			
Company:			
Approved By:			
Position:			
Company:			

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List of Abbreviations

Abbreviation	Full Form
AE	Adverse event
AED	Anti-epileptic drugs
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CGI-I	Clinical Global Impression of Improvement
CI	Confidence Interval
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
eC-SSRS	Electronic Columbia-Suicide Severity Rating Scale
EDV	Early discontinuation visit
EOS	End of study
EQ-5D	EuroQol Five Dimensions Questionnaire
ESL	Eslicarbazepine acetate
HLA	Human leukocyte antigen
ICF	Informed consent form
IPD	Important protocol deviations
IXRS	Interactive Web/Voice Response System
LAEP	Liverpool Adverse Event Profile
LEV	Levetiracetam
LTG	Lamotrigine
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-To-Treat
med	Medication
MOAS	Modified Overt Aggression Scale
NDDI-E	Neurological Disorders Depression Inventory for Epilepsy
OXC	Oxcarbazepine
PCS	Potentially Clinically Significant
PGI-C	Patient's Global Impression of Change

PP	Per Protocol
POMS-SF	Profile of Mood States Short-form
POS	Partial-onset seizures
PT	Preferred term
QD	Once daily
QOL	Quality of life
QOLIE-31-P	Quality of Life in Epilepsy-Patient-Weighted (31-item)
SAE	Serious adverse event
SOC	System organ class
SSF	Standard seizure frequency
T3	Triiodothyronine
T4	Thyroxine
TSH	Thyroid stimulating hormone
WBC	White blood cell
WHO-DRUG	World Health Organization drug dictionary

1. Introduction

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety populations data for Protocol SEP093-701. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version 3.02 dated 04Oct 2018.

2. Study Objectives

2.1. Primary Objective

The primary objective is to evaluate the effectiveness (measured by study retention rate) of ESL administered once daily (QD) as the first adjunctive therapy to levetiracetam (LEV) or lamotrigine (LTG) or as later adjunctive therapy in subjects with POS over a 24-week maintenance period in a real-world clinical setting.

2.2. Secondary Objectives

The secondary objectives are

- To evaluate the efficacy of ESL QD as a first or later adjunctive therapy based on the number of seizures reported over a 24-week maintenance period.
- To evaluate the safety and tolerability of ESL QD as a first or later adjunctive therapy.
- To evaluate the effect of treatment with ESL QD on the quality of life (QOL), behavior, and mood.

2.3. Exploratory Objectives

The exploratory objectives are

- To evaluate the accuracy of an investigational wearable watch device from Empatica in recording seizure counts.
- To evaluate the performance of an investigational electronic seizure diary in the form of a smartphone application (Empatica MATE).

2.4. Study Endpoints

2.4.1. Primary Endpoint

The primary endpoint is the proportion of subjects completing 24 weeks adjunctive therapy during Maintenance Phase (Visit 9).

2.4.2. Secondary Efficacy Endpoints

- Seizure data via the paper diary will be used to calculate the following seizure related endpoints:
  - Standard Seizure Frequency (SSF) during the first 12 weeks, the last 12 weeks, and the 24 weeks of the Maintenance Phase.
  - 50% and 75% responder rate (calculated as 50% and 75% reduction in SSF from baseline) as evaluated during the first 12 weeks, the last 12 weeks, and the 24 weeks of the Maintenance Phase.
  - Relative reduction (%) in SSF from baseline during the first 12 weeks, the last 12 weeks, and the 24 weeks of the Maintenance Phase.
  - Proportion of seizure-free subjects during the first 12 weeks, the last 12 weeks, and the 24 weeks of the Maintenance Phase.
- Time on ESL

2.4.3. Other Efficacy Endpoints

- Changes from baseline in the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E)-6-item questionnaire.
- Changes from baseline in the Profile of Mood States Short-form (POMS-SF).
- Changes from baseline in the agitation/behavioral measurements as evaluated by the Modified Overt Aggression Scale (MOAS).
- Changes from baseline in Quality of Life in Epilepsy-Patient-Weighted (QOLIE-31-P) scores.
- Change from baseline in EuroQol Five Dimensions Questionnaire (EQ-5D) scores.
- Clinical Global Impression of Improvement (CGI-I) scores at each evaluation time point.
- Patient's Global Impression of Change (PGI-C) scores at each evaluation time point

2.4.4. Safety Endpoints

- Number and percentage of subjects with AEs.
- Number and percentage of subjects with serious adverse events (SAEs).
- Number and percentage of subjects with AEs leading to discontinuation.
- Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS): Proportion (%) of events in each classification class (as completed by the subject).
- Changes from baseline in clinical laboratory parameters, including thyroid panel.
- Changes from baseline in vital signs parameters.
- Score of AED-specific AEs (by the Liverpool Adverse Event Profile [LAEP]).

2.4.5. Exploratory Endpoints

- Seizure data recorded by an investigational wearable watch device from Empatica.
- Seizure data recorded by an investigational electronic seizure diary from Empatica MATE application.

3. Study Design

3.1. General Description

This is a 31-week, multicenter, 2-arm, prospective, open-label, non-randomized, Phase 4 study of ESL as adjunctive therapy in adult subjects with a diagnosis of epilepsy with POS. Two groups of ESL-naïve subjects will be evaluated. The groups are defined as follows:

Arm 1 (ESL as first add-on): This group will include subjects who have been maintained on a regimen consisting of a stable dose of LEV or LTG for at least 1 month (28 days) prior to screening and who have not used any adjunctive treatment.

Arm 2 (ESL as later add-on): This group will include subjects who have been maintained on a regimen consisting of a stable dose of 1 - 2 anti-epileptic drugs (AEDs) (excluding oxcarbazepine [OXC]) for at least 1 month (28 days) prior to screening and who have used adjunctive treatment in the past.

The Arm 1 subjects will allow an assessment of the efficacy and safety of ESL in subjects who are early in the course of their disease and being treated with one of the most common first line AEDs. The subjects in Arm 2 are similar to the subject population in the Phase 3 adjunctive studies, treatment-resistant subjects who are later in the course of their disease. The inclusion of these subjects in the present study will provide an assessment of the efficacy and safety of ESL as a later adjunctive therapy in a real world clinical setting. In addition, this study will provide data from both Arm 1 and Arm 2 for several behavioral, mood-related, and QOL-related assessments that were not evaluated in in the Phase 3 program.

Approximately 100 subjects will be enrolled (approximately 50 subjects in Arm 1 and 50 subjects in Arm 2).

The study will consist of a Screening Phase of 1 to 2 weeks, followed by a 2-week Titration Phase, a 24-week Maintenance Phase, and a Safety Follow-up/Taper Phase of 4 weeks. The last visit in the Maintenance Phase (Visit 9) is considered the End of Study (EOS) visit.

The screening visit should take place 7 - 10 days prior to the titration visit and may be extended to 7 - 17 days if required with consent of medical monitor. Subjects of Asian ancestry who require HLA-B*1502 testing (eg do not have prior test results) may have the screening visit 7 - 17 days prior to the titration visit.

Subjects who withdraw prior to the EOS visit should have an Early Discontinuation Visit (EDV) within 72 hours.

3.2. IXRS and Dispensing of Study Drugs

An Interactive Web/Voice Response System (IXRS) will be used to register the Screening Visit (Visit 1) and assignment of the Subject Screening number. If the Subject is enrolled in the study the Screening number becomes the Subject number. The IXRS will also be utilized to register the Titration Visit (Visit 2), Maintenance Phase Visits (Visit 3 – Visit 9) and EDV. Study drug will be dispensed based on assignment by the IXRS at Visits 2 – Visit 8. At Visit 9 and EDV the IXRS will give an option to dispense an additional bottle of study drug if needed for taper. Please ensure to dispense the correct lot number(s) assigned to each Subject. In addition, the IXRS will be utilized to register Screen Failure and Acknowledgment of study drug receipt at site.

3.3. Determination of Sample Size

Sample size is determined outside of statistical consideration. Approximately 100 subjects will be enrolled, almost evenly split between Arm 1 (first add-on) and Arm 2 (later add-on). Assuming the completion rates at 24 weeks of the Maintenance Phase are 60% and 50% for Arm 1 and Arm 2 respectively, the width of 95% CI for completion rate will be approximately 14% based on normal approximation method.

3.4. Changes in the Conduct of the Study or Planned Analyses

3.4.1. Change in the Conduct of the Study

Four amendments have been incorporated into protocol since final protocol.

3.4.2. Changes from Analyses Planned in the Protocol

Since the study drug accountability data was not collected in the data source, the number of dose taken and average daily dose will not be calculated.

3.5. Schedule of Assessments

Study Period	**Screening**	**Titration[a]**	**24-Week Maintenance Phase[a]**									**EDV[a]**	**Safety Follow-up**
Visit	**V1**	**V2**	**V3**	**V4**	**TC1**	**V5**	**V6**	**TC2**	**V7**	**V8**	**V9 (EOS)**		**V10 or TC3**
Week	**-1 to -2o WKs**	**WK 1 Day 1**	**WK 3**	**WK 7**	**WK 9**	**WK 11**	**WK 15**	**WK 17**	**WK 19**	**WK 23**	**WK 27**		**WK 31**
Windows (days)	**(+3)**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**±7**
Procedures													
Informed Consent Form	X	-	-	-	-	-	-	-	-	-	-	-	-
Genetic Consent for HLA-B*1502 Characterization: Subjects of Asian Ancestry only[b,o]	X	-	-	-	-	-	-	-	-	-	-	-	-
Genetic Consent for HLA genotyping (optional)[c]	X	-	-	-	-	-	-	-	-	-	-	-	-
Review of Inclusion/ Exclusion Criteri[a]	X	X	-	-	-	-	-	-	-	-	-	-	

Study Period	**Screening**	**Titration[a]**	**24-Week Maintenance Phase[a]**									**EDV[a]**	**Safety Follow-up**
Visit	**V1**	**V2**	**V3**	**V4**	**TC1**	**V5**	**V6**	**TC2**	**V7**	**V8**	**V9 (EOS)**		**V10 or TC3**
Week	**-1 to -2o WKs**	**WK 1 Day 1**	**WK 3**	**WK 7**	**WK 9**	**WK 11**	**WK 15**	**WK 17**	**WK 19**	**WK 23**	**WK 27**		**WK 31**
Windows (days)	**(+3)**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**±7**
Procedures													
Demographics	X	-	-	-	-	-	-	-	-	-	-	-	
Medical and Neurologic History	X	-	-	-	-	-	-	-	-	-	-	-	-
Complete DISCOVER form	X	-	-	-	-	-	-	-	-	-	-	-	-
Administer HEP and Collect Seizure History Data[d]	X	-	-	-	-	-	-	-	-	-	-	-	-
Prior/Concomitant Medications[e]	X	X	X	X	-	X	X	-	X	X	X	X	X
Physical/Neurologic Examination	X	-	X	X	-	X	X	-	-	X	X	X	-
Vital Signs	X	X	X	X	-	X	X	-	X	X	X	X	-
Body Weight	X	X	X	X	-	X	X	-	X	X	X	X	-
Height	X	-	-	-	-	-	-	-	-	-	-	-	-
12-lead ECG	X	-	-	-	-	-	-	-	-	-	X	X	-
Clinical Laboratory Tests[f]	X										X	X	

Study Period	**Screening**	**Titration[a]**	**24-Week Maintenance Phase[a]**									**EDV[a]**	**Safety Follow-up**
Visit	**V1**	**V2**	**V3**	**V4**	**TC1**	**V5**	**V6**	**TC2**	**V7**	**V8**	**V9 (EOS)**		**V10 or TC3**
Week	**-1 to -2o WKs**	**WK 1 Day 1**	**WK 3**	**WK 7**	**WK 9**	**WK 11**	**WK 15**	**WK 17**	**WK 19**	**WK 23**	**WK 27**		**WK 31**
Windows (days)	**(+3)**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**±7**
Thyroid panel (free T3, T4, and TSH)	X	-	-	-	-	-	-	-	-	-	X	X	-
Blood Sample for HLA-B*1502 testing: Subjects of Asian ancestry only[g]	X	-	-	-	-	-	-	-	-	-	-	-	-
Genetic Saliva Sample and Questionnaire (optional)[h]	-	-	-	X	-	-	-	-	-	-	-	-	-
Serum β-hCG[i]	X	-	-	-	-	-	-	-	-	-	X	X	-
Urine Pregnancy Test[i]	-	X	X	X	-	X	X	-	X	X			
Urine Drug Screen	X												
Liverpool Adverse Event Profile[j]	**-**	**X**	**X**	**X**	**-**	**X**	**X**	**-**	**X**	**X**	**X**	**X**	**-**
Adverse Events	**-**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

Study Period	**Screening**	**Titration[a]**	**24-Week Maintenance Phase[a]**									**EDV[a]**	**Safety Follow-up**
Visit	**V1**	**V2**	**V3**	**V4**	**TC1**	**V5**	**V6**	**TC2**	**V7**	**V8**	**V9 (EOS)**		**V10 or TC3**
Week	**-1 to -2o WKs**	**WK 1 Day 1**	**WK 3**	**WK 7**	**WK 9**	**WK 11**	**WK 15**	**WK 17**	**WK 19**	**WK 23**	**WK 27**		**WK 31**
Windows (days)	**(+3)**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**±7**
Procedures													
Pre-treatment Adverse Events	**X**	-	-	-	-	-	-	-	-	-	-	-	-
Dispense Study Drug	-	**X**	**X**	**X**	-	**X**	**X**	-	**X**	**X**	**X[k]**	**X[p]**	-
Collect Study Drug	-	-	**X**	**X**	-	**X**	**X**	-	**X**	**X**	**X**	**X**	-
Record Any ESL Dose Change Since Last Visit	-	-	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	-	-
Record Any AED Dose Change Since Last Visit	-	-	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	-
Distribute Empatica Watch[l]	**X**	-	-	-	-	-	-	-	-	-	-	-	-

Study Period	**Screening**	**Titration[a]**	**24-Week Maintenance Phase[a]**									**EDV[a]**	**Safety Follow-up**
Visit	**V1**	**V2**	**V3**	**V4**	**TC1**	**V5**	**V6**	**TC2**	**V7**	**V8**	**V9 (EOS**		**V10 or TC3**
Week	**-1 to -2o WKs**	**WK 1 Day 1**	**WK 3**	**WK 7**	**WK 9**	**WK 11**	**WK 15**	**WK 17**	**WK 19**	**WK 23**	**WK 27**		**WK 31**
Distribute Paper Seizure Diary[m]	**X**	**X**	**X**	**X**	-	**X**	**X**	-	**X**	**X**	**X**	**X**	-
Collect Paper Seizure Diary	-	**X**	**X**	**X**	-	**X**	**X**	-	**X**	**X**	**X**	**X**	-
Review Seizure Diaries		**X**	**X**	**X**	-	**X**	**X**	-	**X**	**X**	**X**	**X**	**X[q]**
EQ-5D	-	**X**	-	-	-	**X**	-	-	-	-	**X**	**X**	-
CGI-I			**X**	-	-	**X**	-	-	-	-	**X**	**X**	-
PGI-C			**X**	-	-	**X**	-	-	-	-	**X**	**X**	-
QOLIE-31-P	-	**X**	-	-	-	**X**	-	-	-	-	**X**	**X**	-
POMS-SF	-	**X**	-	-	-	**X**	-	-	-	-	**X**	**X**	-
NDDI-E	-	**X**	-	-	-	**X**	-	-	-	-	**X**	**X**	-
MOAS	-	**X**	-	-	-	**X**	-	-	-	-	**X**	**X**	-
eC-SSRS[n]	**X**	**X**	**X**	**X**	-	**X**	**X**	-	**X**	**X**	**X**	**X**	-
Return of watch and data collection device	-	-	-	-	-	-	-	-	-	-	**X**	**X**	-

Abbreviations: AED = Antiepileptic drug; β-hCG = Beta-human chorionic gonadotropin; CGI-I – Clinical Global Impression of Improvement; CRF = case report form; eC-SSRS = electronic Columbia-Suicide Severity Rating Scale; DISCOVER = Diagnostic Interview for Seizure Classification Outside of Video EEG Recording; ECG = Electrocardiogram; EDV = Early Discontinuation Visit; EOS = End of Study; EQ-5D = EuroQol Five Dimensions Questionnaire; ESL = Eslicarbazepine acetate; HEP = pre-Human Epilepsy Project; HLA = Human Leukocyte Antigen; MOAS = Modified Overt Aggression Scale; NDDI-E = Neurological Disorders Depression Inventory for Epilepsy; PGI-C = Patient's Global Impression of Change; POMS-SF = Profile of Mood States Short-form; QOLIE-31-P = Quality of Life in Epilepsy-Patient-Weighted (31-item); T3 = Triiodothyronine; T4 = Thyroxine; TC = telephone call; TSH = Thyroid Stimulating Hormone; US = United States; WK = Week

a Eligible subjects will begin the 2-week Titration Phase on Day 1 (Week 1), during which they will initiate treatment with ESL at 400 mg/day and remain on that dose for 1 week (Days 1 – 7). Subjects will titrate to ESL 800 mg/day the beginning of week 2 (Day 8) and will remain on that dose for 1 week up to the beginning of the maintenance phase. Subjects will maintain a minimum dose of 800 mg/day for the Maintenance Phase; however, during the Maintenance Phase, subjects may titrate in weekly increments of 400 mg/day as medically indicated at the discretion of the Investigator up to a maximum dose of 1200 mg/day (Canadian Sites) or 1600 mg/day (US sites), (based on maximum local labelled dose). Additional details are provided in Section 10.1.1. Subjects who withdraw prior to the (end of study) EOS visit should have an early discontinuation visit (EDV) within 72 hours.
b Subjects of Asian ancestry (or subjects for whom the absence of Asian ancestry cannot be confirmed) who cannot provide documentation stating that they are not carriers of HLA-B*1502 must give written informed consent for genotyping. Asian ancestry will be based on subject self-report.
c This consent for genetic saliva sample and associated questionnaire is optional.
d Record seizure history (the number and types of seizures that occurred over the longest available period up to 3 months prior to screening).
e Record all prior and concomitant medications, including over the counter medications, taken within the previous 60 days.
f Includes clinical chemistry, hematology and urinalysis. Estimated creatinine clearance using Cockcroft-Gault equation at Screening only.
g Required for subjects of Asian ancestry (or subjects for whom the absence of Asian ancestry cannot be confirmed) and who do not have documentation to show that they are not carriers of HLA-B*1502.
h Subjects who provided optional separate informed consent/assent only.
i A serum pregnancy test will be given to all female subjects of childbearing potential at screening. An on-site urine pregnancy test will be given to all female subjects of childbearing potential at Visits 1-8. Any positive urine pregnancy test will be followed up with a serum test for confirmation of pregnancy. A serum pregnancy test will be given to all females subjects of childbearing potential at Visit 9 (EOS) or at the EDV.
j The Liverpool Adverse Event Profile collects information on AEs associated with AEDs.
k Subjects who elect to continue on commercially available drug will not be dispensed additional ESL at this visit. Subjects who elect to discontinue ESL will be provided sufficient ESL to accommodate the appropriate taper regimen.
l Subjects will be provided with the Empatica watch and instructed in the use of the watch.
m Subjects will be provided a standardized paper daily seizure diary and an electronic daily seizure diary and instructed in the use of the diaries. Diaries are to be completed daily whether a seizure occurs or not.
n The “Baseline/Screening” (lifetime) version should be administered at the screening visit and the “Since Last Visit” version at all other time points.
o The screening visit should take place 7 - 10 days prior to the titration visit, and may be extended to 7 – 17 days if required with consent of medical monitor. Subjects of Asian ancestry who require HLA-B*1502 testing (eg, do not have prior test results) may have the screening visit 7 - 17 days prior to the titration visit.
p Subjects who discontinue prior to the EOS visit will be provided sufficient ESL to accommodate the appropriate taper regimen.
q At the Safety Follow-Up visit, the standardized paper daily seizure diary will not be collected; however it will be reviewed as part of the subject’s safety assessments.

4. Planned Analyses

The following analyses will be performed for this study:

- Final Analysis

4.1. Data Monitoring Committee (DMC)

There will be no DMC for this study.

4.2. Interim Analysis

There will be no interim analysis for this study.

4.3. Final Analysis

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following Sponsor Authorization of this Statistical Analysis Plan, Database Lock and Sponsor Authorization of Analysis Sets.

5. Analysis Populations

5.1. Safety Population

The safety population will consist of all subjects who have taken any study medication. Safety population will be used for all analyses except efficacy analyses.

5.2. Modified Intent-to-Treat [mITT] Population

The modified intent-to-treat (mITT) population will include subjects who are in the safety population and have paper seizure data available. The mITT population will be used for efficacy analyses.

5.3. Per Protocol [PP] Population

The per protocol (PP) population will include subjects who are in the mITT population and did not have any important protocol deviations (IPDs). The per-protocol population will be used in an additional analysis of the efficacy endpoints and subject demographics and baseline characteristics. If no IPDs occurred, as determined by the review team before the database lock, analyses of PP population specified in the SAP will not performed.

6. General Considerations

6.1. General Principles

Unless stated otherwise, all continuous variables, including those assessed on a discrete scale, will be summarized using descriptive statistics, including number of subjects, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum. For categorical variables, summaries will include numbers of subjects and percentages.

All endpoints will be summarized descriptively for Arm 1 and Arm 2 separately. There will be no statistical comparisons between Arm 1 and Arm 2.

6.2. Reference Start Date and Study Day

Study Day will be calculated from the reference start date and will be used to show start/ stop day of assessments and events.

Reference start date is defined as the day of the first dose of study medication, (Day 1 is the day of the first dose of study medication) and will appear in every listing where an assessment date or event date appears.

If the date of the event is on or after the reference date then:

Study Day = (date of event – reference date) + 1

If the date of the event is prior to the reference date then:

Study Day = (date of event – reference date)

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings.

6.3. Baseline

For the seizure-related endpoints, baseline will be defined as the seizure data for the longest available period up to 3 months prior to screening from seizure history and from screening to first dose of study medication from the paper seizure diary.

Hence, the period of baseline will be calculated as the days of (1 month, 2 months or 3 months) + the number of days from Screening to the first dose from paper seizure dairy. One month will be calculated as 30.42 days.

For all other endpoints, baseline will be defined as the last non-missing measurement taken prior to the first dose of study drug.

6.4. Retests, Unscheduled Visits and Early Discontinuation Visit (EDV)

In general, for by-visit summaries, data recorded at the nominal visit will be presented including visit 9 (EOS) and EDV. Unscheduled measurements collected prior to the first dose of study medication will contribute to the derivation of the baseline value.

Unscheduled measurements collected post baseline will not be included in by-visit summaries but will contribute to the potentially clinically significant values for vital signs and labs and best/ worst case value where required (e.g. shift table).

In the case of a retest (same visit number assigned), the latest available measurement for that visit will be used for by-visit summaries.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.5. Windowing Conventions

No visit windowing will be performed for this study.

Refer to Appendix 1 for the visit convention for this study.

6.6. Statistical Tests

There will be no statistical testing performed.

6.7. Common Calculations

For quantitative measurements, change from baseline will be calculated as:

Test Value at Visit X – Baseline Value

6.8. Software Version

All analyses will be conducted using SAS version 9.4 or higher.

7. Statistical Considerations

As summaries are going to be descriptive in nature, there will not be any adjustments for covariates.

7.1. Multicenter Studies

This study will be conducted by multiple investigators at multiple centers with sites in the United States and Canada. There will be no summaries of data by site/pooled site or country.

7.2. Handling of Dropouts or Missing data

Subjects who dropped out before study completion are not to be replaced and all available information obtained from them will be included in the appropriate efficacy and safety summaries to the time of dropout. No imputation is planned for any safety measures.

If the date of the seizure is missing or incomplete and the seizure cannot be allocated to a study interval, these data will not be used in the analysis, but will be presented in the subject data listings. If the seizure diary was returned and there was no seizure data available for a day during that evaluation period, it will be assumed that the patient had missing seizure data, and the day will be excluded from the calculation of the standardized seizure frequency.

Seizure related variables will be calculated based on available data. For dropout subjects, their seizure frequency will be derived for each interval up to the last interval where the subject had data. The last interval standardized seizure frequency (SSF) will be computed based on available data prior to dropout.

7.3. Multiple Comparisons/Multiplicity

There will be no multiple comparison/multiplicity for this study.

7.4. Examination of Subgroups

Subgroup analyses will be conducted as stated in the respective primary, efficacy and safety analysis sections. The following subgroups will be assessed. Determinations of the subgroups will be based on baseline data.

Gender:

- Female
- Male

Age Groups (years):

- ≥ 18 to <= 65

- o > 65

Race Groups:

- o White
- o Black or African American
- o Asian
- o Other (American Indian/Alaska Native, Native Hawaiian or Other Pacific Islander, Multiple, Other)

Baseline AEDs:

- For Arm 1:
  - o Use of lamotrigine as baseline AED (yes/no)
  - o Use of levetiracetam as baseline AED (yes/no)
- For Arm 2:
  - o Use of lamotrigine as baseline AED (yes/no)
  - o Use of levetiracetam as baseline AED (yes/no)
  - o Use of carbamazepine as baseline AED (yes/no)
  - o Use of valproic acid as baseline AED (yes/no)
  - o Use of any other additional baseline AEDs that occur in >=15% of the subjects (yes/no)

Number of Baseline AEDs:

- For Arm 2:
  - o 1
  - o 2

Seizure Type:

- o Simple Partial
- o Complex Partial
- o Partial Evolving to Secondarily Generalized Seizures

- Other

8. Output Presentations

Appendix 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by IQVIA Biostatistics.

9. Disposition and Withdrawals

All subjects who provide informed consent will be accounted for in this study.

Subject disposition will be summarized and presented for the number and percentage of subjects, who were screened, screen-failed, entered, completed the study, and discontinued early including reasons for discontinuations such as adverse event, lack of efficacy, withdrawal by subject, withdrawal by investigator, protocol deviation, study terminated by Sponsor, death, pregnancy and Other.

Listing of subject disposition will also be provided.

10. Important protocol deviations

Prior to database lock, important protocol deviations (IPDs) will be identified in a review of all protocol deviations reported. Possible IPDs will include, but may not be limited to, subjects who:

- Did not meet inclusion/exclusion criteria or eligibility was not adequately verified
- Received any disallowed concomitant medication
- Developed withdrawal criteria but were not withdrawn

Individual IPDs will be presented in a data listing. The number and percentage of subjects with IPDs will be summarized by type of deviation as categorized above.

11. Demographic and other Baseline Characteristics

Demographics, including (age, gender, race, and ethnicity where applicable), and other baseline characteristics collected at screening, such as height, weight, body mass index, and disease conditions will be summarized using descriptive statistics. These data will be presented as a listing. Demographic data and other baseline characteristics will be presented for the safety and PP population.

11.1. Derivations

BMI (kg/ m^2) = weight (kg)/ height $(m)^2$

Duration of epilepsy (years) = (Date of first dose - date of epilepsy onset)/365.25

- Date of epilepsy onset: If the date of onset of epilepsy is partial, i.e. month and year recorded, or only year recorded, the missing component will be imputed with the last day of the month (where only day is missing) or 31 December (where the day and month are missing). If the date of onset is missing, the duration will not be calculated.

Age (years) = (date of informed consent – date of birth)/365.25

Baseline AEDs:

- An AED is considered to be used at baseline if it started at any time prior to the first dose of study treatment and continued. Subjects may appear in multiple AED use.

12. Medical and Epilepsy History

12.1. Medical History

Medical history will be coded using (MedDRA), version 13.1, and presented for the safety population by SOC and PT.

A data listing of medical history will be provided.

12.2. Epilepsy History

Epilepsy information will be collected and summarized descriptively for the safety population.

Epilepsy summary will include age at onset of epilepsy in years and years since onset of epilepsy (refer to section 11.1 for derivation). Category of possible etiology for epilepsy will also be summarized.

Listing of epilepsy history will be provided.

13. Prior and Concomitant Medications

Medications will be presented for the safety population and coded using WHO Drug version 01MAR 2017.

The number and percentage of subjects using each concomitant medication will be summarized overall according to the WHODRUG Anatomic Therapeutic Class (ATC) Level III and preferred term for concomitant AED and non-AED medication separately. Subjects with multiple uses of a concomitant medication will be counted once by the ATC level and preferred term.

See Appendix 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior, concomitant, the medication will be classified by the worst case; i.e. concomitant.

- Prior medications are medications which started and stopped prior to the first dose of study medication.
- Concomitant medications are medications which started at the same time of or after the first dose of study medication and at the same time of or before the last dose of study medication; or started prior to and ended at the same time of or after the first dose of study medication; or started at the same time of or prior to the last dose of study medication and marked as ongoing.
- Post-treatment medications are medications which started after the last dose of study medication.

Listings of concomitant AED, non-AED medications, prior, and post-treatment medications will be provided.

14. Study Medication Exposure

The extent of exposure will be summarized descriptively: it will be calculated as the date of last dose minus the first dispensed dose date, ignoring missing days plus 1. If subject last dose is missing, subject last contact date will be used.

The date of first study medication and the date of the last dose will be taken from the Study Drug Dispensation and Disposition source, respectively.

Duration of exposure, the date of first dose, date of last dose, date of the change dose, amount, and reason for dose change will be listed.

Frequency of duration of exposure will be summarized using the following categories:

1 day - < 3 weeks

=> 3 - < 7 weeks

=> 7 - < 9 weeks

=> 9- < 11 weeks

=> 11- < 15 weeks

=> 15- < 17 weeks

=> 17- < 19 weeks

=> 19- < 23 weeks

>= 23- <27 weeks

> =27 – <= 31 weeks

> 31 weeks

14.1. Derivations

Duration of exposure (days) = date of last study medication – date of first study medication + 1.

15. Outcomes Variables

15.1. Primary Variable

15.1.1. Primary Variable & Derivation(s)

The primary outcome variable is the proportion of subjects completing 24 weeks adjunctive therapy during Maintenance Phase (Visit 9) defined as below.

$$\frac{\text{Number of subjects who completed up to and including the end of the Maintenance Phase (Visit 9/ EOS)}}{\text{Number of subjects in the safety population}} \times 100$$

15.1.2. Primary Analysis of Primary Outcome Variable

The primary analysis will be performed for the safety population.

The number and proportion (%) of subjects completing the 24 weeks of the Maintenance Phase will be provided along with a 95% confidence interval using the exact method.

It will be also summarized by age group, race group, gender, baseline AEDs and number of baseline AEDs.

15.2. Efficacy Variables

15.2.1. Efficacy Variables and Derivation

The following periods (days) are used in the efficacy analyses:

- Baseline: the duration (months) recorded for the number of seizure prior to screening from seizure history plus the days from screening to first dose of study medication via the paper seizure diary.
- Titration: date of Visit 3 (week 3) - Visit 2 (week 1)
- Each visit intervals between Visit 3 (week 3) and Visit 9 (week 27): Visit 3 to Visit 4, Visit 4 to Visit 5, Visit 5 to Visit 6, Visit 6 to Visit 7, Visit 7 to Visit 8, and Visit 8 to Visit 9
- First 12 weeks: date of week 15 (Visit 6)- the date of week 3 (Visit 3)
- Last 12 weeks: the date of week 27 (Visit 9 (EOS))- the date of week 15
- 24 weeks of the Maintenance Phase: date of week 27 (Visit 9 (EOS)) – date of week 3 (Visit 3)

For dropout subjects, if subject withdrew before the scheduled Visit 9(EOS), seizure data will be included for each interval up to the last date where the subject had data.

Seizure related efficacy endpoints will be derived based on the paper seizure diary data. Standard Seizure Frequency (SSF)

Seizure frequency from the subject's seizure diary data will be evaluated by standardizing the sum of seizures to a frequency per 4 weeks (28 days).

The standardized seizure frequency (SSF) for any given period (including baseline) will be calculated as:

$$\frac{\text{Total number of seizures reported in the diary during the interval of interest}}{\text{Number of days for the interval of interest}} \times 28 \text{ days}$$

The number of days on study for the interval of interest will be determined by:

Visit Date of last visit during the interval of interest - Visit Date of first visit during the interval of interest. Subject with missing paper seizure data in the interval of interest will not be counted toward the denominator.

15.2.1.2. Relative Reduction in SSF

Seizure frequency change from the baseline period will be evaluated by using SSF per 4 weeks (28 days).

The relative (%) change from baseline in SSF is calculated as:

$$\frac{\text{SSF for the interval of interest - SSF at baseline}}{\text{SSF at baseline}} \times 100$$

Further the relative change from baseline will be categorized into:

- 100% Decrease
- ≥ 75% - < 100% Decrease

- ≥ 50% - < 75% Decrease
- 0% to < 50% Decrease
- > 0% to < 25% Increase
- ≥ 25% to <50% increase
- ≥ 50% to <100% increase
- ≥ 100 % increase

15.2.1.3. Responder Rates

50% and 75% responder rate (≥50% and ≥75% reduction from baseline in SSF) will be calculated for the intervals of interest. The proportion will be calculated as the number of responders divided by the total number of subjects in the modified ITT population entering the period of interest.

15.2.1.4. Proportion of Seizure-Free Subjects

Subjects who did not have any seizure as per the paper seizure diary for the intervals of interest will be deemed seizure free, for the corresponding interval of interest. Subjects must complete each interval of interest without any seizures to be considered seizure-free for each interval of interest. Subject with no seizure data available during interval of interest will not be considered seizure-free for the interval of interest. However, subjects who discontinue prior to Visit 9 will be considered not seizure-free for the interval when the discontinuation takes place and all subsequent intervals (even if the subjects are seizure-free at the time of discontinuation). Anyone who drops out from the study and does not complete the 24 weeks (Visit 9), is included in the denominator for the proportion.

15.2.1.5. Time on ESL

Time on ESL will be calculated from the first dose as indicated in the Study Drug Dispensation source to the last known dose of ESL in the Disposition source. Subjects who were still on ESL at the end of study will be censored at the end of study. Subjects who dropped out of the study

while receiving treatment will be an event at the time of the last dose date. Change in dosage levels during the treatment period will be ignored.

15.2.2. Analysis of Efficacy Variables

The efficacy analyses using paper seizure data will be performed for the mITT and PP populations, and the listings of subjects will be provided.

Time on ESL analysis will be performed for the safety population only.

15.2.2.2. Standard Seizure Frequency (SSF)

The SSF will be summarized using descriptive statistics for baseline, titration, each visit intervals between Visit 3 and Visit 9, the first 12 weeks, the last 12 weeks, and the 24 weeks of the Maintenance Phase.

Additionally, the SSF will be summarized by the subgroups presented in Section 15.3.

15.2.2.3. Responder Rates

The responder rates (50% and 75%) along with 95% confidence intervals (CIs) (using the exact method) will be presented for baseline, titration, each visit intervals between Visit 3 and Visit 9.

Additionally, the number and percentage of subjects with the subgroups presented in Section 15.3 will also be presented.

15.2.2.4. Relative Reduction in SSF

Relative (%) change in SSF from baseline will be summarized using descriptive statistics for baseline, titration, each visit intervals between Visit 3 and Visit 9, the first 12 weeks, the last 12 weeks, and the 24 of the Maintenance Phase.

The number and percentage of subjects with the subgroups presented in Section 15.3 will also be presented.

15.2.2.5. Proportion of Seizure-Free Subjects

The number and proportion (%) of subject's seizure-free along with 95% confidence intervals (using the exact method) will be summarized for baseline, titration, each visit intervals between Visit 3 and Visit 9.

Additionally, the proportion of seizure free subjects will be summarized with the subgroups presented in Section 15.3.

15.2.2.6. Time on ESL

The median time on ESL in days and 95% CI will be estimated using Kaplan Meier time to event methods.

Kaplan Meier plots for the time on ESL will be provided.

15.3. Subgroup Analysis of Efficacy Variable(s)

Standardized seizure frequency (SSF), and relative change (%) from baseline in SSF, will be summarized for mITT population, by the following subgroup variables which are defined in section 7.4.

- Number of baseline AEDs
- Baseline AEDs.
- Seizure Type

Responders, and proportion of seizure-free will be summarized by number of baseline AEDs and baseline AEDs.

15.4. Exploratory Variables

15.4.1. Analysis of Exploratory Variables

The exploratory analyses will be performed for the mITT populations.

The proportions of concordance in the daily seizure frequency during the 24-weeks of the Maintenance Phase between the watch device and paper diary as well as between the Mate application and paper seizure diary for each subject will be calculated. Proportion is calculated as the number of days with concordance in daily seizure frequency between the two Empatica devices and paper seizure diary divided by the number of days with seizure frequency available in paper diary. The mean and 95% CI (exact method) of the proportion of the concordance will be provided.

In addition, the proportion of concordance in daily seizure frequency during the 24-weeks of the Maintenance Phase between the Mate application and paper seizure diary will be calculated only with the subjects who confirmed they reported all their seizures at each day (i.e. seizure compliance='Y') in the Mate application.

SSF will be calculated for the first 12 weeks, the last 12 weeks, and the 24 weeks of the Maintenance Phase using the seizure data recorded by the investigational wearable watch device, and MATE application from Empatica.

The concordance correlation coefficient (CCC)[1] with 95% confidence interval will be calculated to assess agreement in SSF during the first 12 weeks, the last 12 weeks, and the 24 weeks of the Maintenance Phase between the two Empatica devices and the paper seizure diary.

The concordance correlation coefficient, rc , for measuring agreement between continuous variables X and Y (both approximately normally distributed), is calculated as follows:

$$r_c = \frac{2S_{XY}}{S_{XX} + S_{YY} + (\bar{X} - \bar{Y})^2}$$

where Sxx = variance of X, Syy = variance of Y, Sxy=covariance of X and Y.

This is a measure of how well a set of data (Y) compares to a "gold standard" measurement or test (X). It measures both the precision (similar to Pearson's correlation coefficient), and accuracy (i.e. how far away results are from a 45-degree line through the origin, or from perfect concordance) of the association.

. Similar to the other correlation coefficient, the concordance correlation satisfies $-1 \leq rc \leq +1$. A value of $rc = +1$ corresponds to perfect agreement. A value of $rc = -1$ corresponds to perfect negative agreement, and a value of $rc = 0$ corresponds to no agreement.

Scatter plots of the above SSFs using the seizure data recorded by the watch device as well as Mate application and by those from the paper seizure diary will be presented to evaluate agreement graphically.

15.5. Quality of Life Analysis

Quality of Life (QoL) analyses will be performed for the safety population.

15.5.1. Variables & Derivations

15.5.1.1. EuroQol Five Dimensions Questionnaire (EQ-5D) scores

The EQ-5D is made up of two components, health state description and overall health evaluation.

In the description part, health status is measured in terms of five dimensions (5D):

1. Mobility dimension asks about the person's walking ability
    1. I have no problems walking
    2. I have slight problems walking
    3. I have moderate problems walking
    4. I have severe problems walking
    5. I am unable to walk
2. Self-care dimension asks about the ability to wash or dress by oneself
    1. I have no problems washing or dressing myself
    2. I have slight problems washing or dressing myself
    3. I have moderate problems washing or dressing myself
    4. I have severe problems washing or dressing myself
    5. I am unable to wash or dress

3. Usual activities dimension measures performance in “work, study, housework, family or leisure activities”
    1. I have no problems doing my usual activities
    2. I have slight problems doing my usual activities
    3. I have moderate problems doing my usual activities
    4. I have severe problems doing my usual activities
    5. I am unable to do my usual activities

4. Pain/discomfort dimension, it asks how much pain or discomfort they have
    1. I have no pain or discomfort
    2. I have slight pain or discomfort
    3. I have moderate pain or discomfort
    4. I have severe pain or discomfort
    5. I have extreme pain or discomfort

5. Anxiety/depression dimension, it asks how anxious or depressed they are
    1. I am not anxious or depressed
    2. I am slightly anxious or depressed
    3. I am moderately anxious or depressed
    4. I am severely anxious or depressed
    5. I am extremely anxious or depressed

The respondents self-rate their level of severity for each dimension using a 5-level scale: no problems, slight problems, moderate problems, severe problems and extreme problems.

In addition, the respondents evaluate their overall health status using the visual analogue scale. This scale is numbered from 0 to 100. 0 means the worst health you can imagine and 100 means the best health you can imagine.

15.5.1.2. Clinical Global Impression (CGI) – Improvement

The CGI-I scale is a 7-point scale that requires an approved rater to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention and rated as:

1. Very Much Improved
2. Much Improved
3. Minimally Improved
4. No Change
5. Minimally Worse
6. Much Worse
7. Very Much Worse

15.5.1.3. Patient Global Impression of Change (PGIC)

The PGI-C is a 7-point scale that requires the subject to assess the change (if any) in activity limitations, symptoms, emotions and overall quality of life.

The subject responses include:

1. No change (or condition has gotten worse)
2. Almost the same, hardly any change at all
3. A little better, but no noticeable change
4. Somewhat better, but the change has not made any real difference
5. Moderately better, and a slight but noticeable change
6. Better, and a definite improvement that has made a real and worthwhile difference
7. A great deal better, and a considerable improvement that has made all the difference

15.5.1.4. Quality of Life in Epilepsy-Patient-Weighted (QOLIE-31-P)

The QOLIE-31-P contains seven multi-item scales that investigate the following health concepts:

1. Emotional Well-Being

2. Social Functioning
3. Energy/Fatigue
4. Cognitive Functioning
5. Seizure Worry
6. Medication Effects
7. Overall Quality of Life (QOL)

The QOLIE-31-P overall score is obtained by using a weighted average of the multi-item scale scores. The QOLIE-31-P also includes a single item that assesses overall health on a visual analogue scale. The recorded responses will be converted to 0 -100-point scales as described in Table 3. The mean of the individual item scores in each subgroup are then calculated, with higher converted scores reflecting better quality of life. If one item within a scale score is missing, it will be replaced by the mean value of the other items. If more than one item is missing, the scale score will not be calculated.

The QOLIE-31-P overall score is obtained by using a weighted average of the 7 scale scores according to the following formula:

Overall score = Seizure worry * 0.08

+ Overall quality of life * 0.14

+ Emotional well-being * 0.15

+ Energy/fatigue * 0.12

+ Cognitive functioning * 0.27

+ Medication effects * 0.03

+ Social functioning * 0.21

Table 3: QOLIE-31 Response Conversions

Scale	Response	Formula

Item Numbers	1	2	3	4	5	6	
Seizure Worry							
11.	0	20	40	60	80	100	((Resp-1)/(Max-1)*100
21.	0	33.3	66.7	100	-	-	((Resp-1)/(Max-1)*100
22.	0	50	100	-	-	-	((Resp-1)/(Max-1)*100
23.	0	33.3	66.7	100	-	-	((Resp-1)/(Max-1)*100
25.	100	75	50	25	0	-	100-((Resp-1)/(Max-1))*100
Overall Quality of Life							
1.	Multiply response by 10						
14.	100	75	50	25	0	-	100-((Resp-1)/(Max-1))*100
Emotional Well-being							
3.	0	20	40	60	80	100	((Resp-1)/(Max-1)*100
4.	0	20	40	60	80	100	((Resp-1)/(Max-1)*100
5.	100	80	60	40	20	0	100-((Resp-1)/(Max-1))*100
7.	0	20	40	60	80	100	((Resp-1)/(Max-1)*100

9.	100	80	60	40	20	0	100-((Resp-1)/(Max-1))*100
Energy/Fatigue							
2.	100	80	60	40	20	0	100-((Resp-1)/(Max-1))*100
6.	100	80	60	40	20	0	100-((Resp-1)/(Max-1))*100
8.	0	20	40	60	80	100	((Resp-1)/(Max-1)*100
10.	0	20	40	60	80	100	((Resp-1)/(Max-1)*100
Cognitive Functioning							
12.	0	20	40	60	80	100	((Resp-1)/(Max-1)*100
15.	0	33.3	66.7	100	-	-	((Resp-1)/(Max-1)*100
16.	0	20	40	60	80	100	((Resp-1)/(Max-1)*100
17.	0	20	40	60	80	100	((Resp-1)/(Max-1)*100
18.	0	20	40	60	80	100	((Resp-1)/(Max-1)*100
26.	100	75	50	25	0	-	100-((Resp-1)/(Max-1))*100
Medication Effects							
24.	0	33.3	66.7	100	-	-	((Resp-1)/(Max-1)*100
29.	100	75	50	25	0	-	100-((Resp-1)/(Max-1))*100

30.	100	75	50	25	0	-	100-((Resp-1)/(Max-1))*100
Social Functioning							
13.	0	20	40	60	80	100	((Resp-1)/(Max-1)*100
19.	0	25	50	75	100	-	((Resp-1)/(Max-1)*100
20.	0	25	50	75	100	-	((Resp-1)/(Max-1)*100
27.	100	75	50	25	0	-	100-((Resp-1)/(Max-1))*100
28.	100	75	50	25	0	-	100-((Resp-1)/(Max-1))*100

Resp=Response, Max=Maximum possible response for the respective item.

15.5.1.5. Profile of Mood States Short-form (POMS-SF)

The POMS-SF is an instrument designed to assess transient, distinct mood states and consists of a list of 37 adjectives. Respondents indicate the degree to which each adjective describes themselves during the last week using a 5-point Likert scale:0= not at all, 1=a little, 2=moderately, 3=quite a bit, and 4=extremely. This format yields both an overall Total Mood Disturbance score as well as scores for each of the six subscales contained in the original POMS:

The items included in 6 subscales are

1. Fatigue-Inertia: worn-out, fatigued, exhausted, weary, bushed
2. Vigor-Activity: lively, active, energetic, cheerful, full of pep, vigorous
3. Tension-Anxiety: Tense, on edge, uneasy, restless, nervous, anxious
4. Depression-Dejection: unhappy, sad, blue, hopeless, discouraged, miserable, helpless, worthless

5. Anger-Hostility: angry, peeved, grouchy (written as grovely in some versions), annoyed, resentful, bitter, furious
6. Confusion-Bewilderment: confused, unable to concentrate, bewildered, forgetful, uncertain about things

Each subscale will be calculated by summing the point for items. The total mood disturbance score will be calculated by summing the total for the negative subscales and then subtracting the total for the positive subscale: Depression-Dejection + Tension-Anxiety + Anger-Hostility + Fatigue-Inertia + Confusion-Bewilderment -Vigor-Activity + 100. A constant (e.g. 100) will be added to total mood score in order to eliminate negative scores.

15.5.1.6. Neurological Disorders Depression Inventory for Epilepsy (NDDI-E)

The NDDI-E is a 6-item questionnaire validated to screen for depression in people with epilepsy. The NDDI-E consists of the following items:

1. Everything is a struggle
2. Nothing I do is right
3. Feel guilty
4. I'd be better off dead
5. Frustrated
6. Difficulty finding pleasure

Each item is rated on a 4-point Likert scale (1=never, 2=rarely, 3=sometimes, 4=always or often) with higher scores indicating a more severe response. Total Score is defined as the summation of all individual item scores. NIDDI-E scores ≥16 are considered positive for depression[2].

15.5.1.7. Modified Overt Aggression Scale (MOAS)

The MOAS is divided in four domains: 1. verbal aggression, 2. aggression against objects, 3 aggression against self, and 4 aggression against other people. A score from 0 to 4 is assigned to each act: 0 indicates no aggressive behavior and higher scores indicate increasing severity.

Section scores are weighted as follows: Scores from the "Verbal Aggression" section multiplied by 1; Scores from the "Aggression Against Property" section multiplied by 2; Scores from the "autoaggression" section multiplied by 3; Scores from the "physical aggression" section multiplied by 4. Weighted scores are then added together to get the total score. Total scores on the MOAS range from 0 to 40, with a higher score indicating more aggressive behavior.

Verbal Aggression:

0. No verbal aggression
1. Shouts angrily, curses mildly, or makes personal insults
2. Curses viciously, is severely insulting, has temper outbursts
3. Impulsively threatens violence toward others or self
4. Threatens violence toward others or self repeatedly or deliberately (e.g., to gain money or sex)

Aggression Against Property:

0. No aggression against property
1. Slams door angrily, rips clothing, urinates on floor
2. Throws objects down, kicks furniture, defaces walls
3. Breaks objects, smashes windows
4. Sets fires, throws objects dangerously

Autoaggression:

0. No autoaggression
1. Picks or scratches skin, pulls hair out, hits self (without injury)
2. Bangs head, hits fists into walls, throws self on floor

3. Inflicts minor cuts, bruises, burns or welts on self
4. Inflicts major injury on self or makes a suicide attempt

Physical Aggression:

0. No physical aggression
1. Makes menacing gestures, swings at people, grabs at clothing
2. Strikes, pushes, scratches, pulls hair of others (without injury)
3. Attacks others, causing mild injury (bruises, sprains, welts, etc.)
4. Attacks others, causing serious injury (fracture, loss of teeth, deep cuts, loss of consciousness, etc.)

15.5.2. Analysis of QOL Variables

15.5.2.2. Analysis of EuroQol Five Dimensions Questionnaire (EQ-5D)

The EQ-5D overall health status, visual analogue scale (VAS) scores, observed and changes from baseline for each evaluation time point will be summarized descriptively by arm.

The number and percentage of subjects for each health state description will be summarized by each evaluation timepoint and Arm. In addition shift table for each evaluation time point will be summarized by arm.

Figure of the mean (+/-SD) change from baseline for overall health (VAS) scores will be provided.

Listing of EQ-5D scores including score of each individual item will be provided.

15.5.2.2. Analysis of Clinical Global Impression of Improvement (CGI-I)

Frequency and percentage of Clinical Global Impression of Improvement (CGI-I) scores at each evaluation time point will be summarized by arm.

Listing of CGI-I scores will also be provided.

15.5.2.3. Analysis of Patient's Global Impression of Change (PGI-C)

Frequency and percentage of Patient's Global Impression of Change (PGI-C) scores for each evaluation time point will be summarized by arm.

Listing of PGI-C scores will also be provided.

15.5.2.4. Analysis of Quality of Life in Epilepsy-Patient-Weighted (QOLIE-31-P)

The QOLIE-31-P overall scores, global assessment and subscale scores, observed and changes from baseline in the score for each evaluation time point will be summarized descriptively by arm.

Figure of the mean (+/-SD) change from baseline for the total score by time point and arm will be provided.

Listing of QOLIE-31-P scores including each individual scoring item will be provided.

15.5.2.5. Analysis of Profile of Mood States Short-form (POMS-SF)

The POMS-SF total mood disturbance scores and subscale scores, observed and changes from baseline in the score of each evaluation time point will be summarized descriptively.

Figure of the mean (+/-SD) change from baseline for the total mood disturbance score by time point and arm will be provided.

Listing of POMS-SF scores including score of each individual item will be provided.

15.5.2.6. Analysis of Neurological Disorders Depression Inventory (NDDI-E)

The NDDI-E total scores and individual item scores, observed and changes from baseline in the score of each evaluation time point will be summarized descriptively.

The number of subjects with total score<16 and ≥16 will be presented by time point and arm.

Figure of the mean(+/-SD) change from baseline for the total score by time point and arm will be provided.

Listing of NDDI-E scores will also be provided.

15.5.2.7. Analysis of Modified Overt Aggression Scale (MOAS)

The MOAS total scores and domain scores, observed and changes from baseline for each evaluation time point will be summarized descriptively by arm.

Figure of the mean (+/-SD) change from baseline for the total score by time point and arm will be provided.

Listing of MOAS scores including score of each individual item will be provided.

16. Safety Outcomes

All outputs for safety outcomes will be based on the safety population.

16.1. Pre-treatment and Adverse Events

Pre-treatment events will be monitored from the time informed consent form (ICF) is provided up until the date of first ESL dose.

AEs will be monitored from the date of first ESL dose.

Serious adverse events will be monitored from the time informed consent/assent is obtained.

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 13.1.

AEs are untoward medical occurrences:

- that occurred on or after the first dose of study medication.
- with a missing start date and a stop date on or after the first dose of study medication, OR
- with both a missing start and stop date.

See Appendix 2 for handling of partial dates for AEs.

16.1.1. All AEs

Incidence of AEs and number of events will be presented by arm, System Organ Class (SOC) and Preferred Term (PT). AEs will be presented by maximum severity and relationship to study medication as specified in the sections below.

For subject incidence summaries, each subject will be counted only once within each SOC and within each PT. All AEs will be summarized overall and by age group, race group, gender, baseline AEDs and number of baseline AEDs.

Listing of all AEs and pre-treatment AEs will be provided.

16.1.2. Severity

Severity is classed as mild/ moderate/ severe (increasing severity). AEs starting after the first dose of study medication with a missing severity will be classified as severe. If a subject reports an AE more than once within that SOC/ PT, the AE with the highest known severity will be used in the corresponding severity summaries.

16.1.3. Relationship to Study Medication

Relationship, as indicated by the Investigator, is classed as “not related”, “possible”, “probable” (increasing severity of relationship) or “definite”.

For summaries by relationship to the study medication, AEs will be grouped as “related” or “not related.”

- AE Related: AEs with relationship to study medication assessed as “possible,” “probable,” or “definite”
- AE not Related: AEs with relationship to study medication assessed as “not related”
- AEs with a missing relationship to study medication will be regarded as related

If a subject report the same AE more than once within that SOC/ PT, the AE with the worst-case relationship to study medication will be used in the corresponding relationship summaries.

16.1.4. AEs Leading to Discontinuation of Study Medication

For AEs leading to discontinuation of study medication, summaries of incidence (numbers and percentages) by SOC and PT will be provided.

Listing of AEs leading to discontinuation will be provided.

16.1.5. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as” Serious” on the Adverse Events source.

Incidence of SAEs and number of events will be presented by arm, SOC and PT.

All SAEs will be summarized overall and by age group, race group, gender, baseline AEDs and number of baseline AEDs.

Additionally, listing of SAEs will be provided.

16.1.6. Non-Serious Adverse Events

Incidence of non-SAEs and number of events will be presented by arm, System Organ Class (SOC) and Preferred Term (PT).

16.1.7. Adverse Events Leading to Death

AEs leading to Death are those events which are recorded with outcome of" Fatal" on the Adverse Events source. A summary of AEs leading to death by SOC and PT will be prepared.

Listing of deaths will be provided.

16.2. Laboratory Evaluations

Results from the central laboratory will be included in the reporting of this study for Hematology, Blood Chemistry, Urinalysis, Thyroid Panel, Renal Functioning, Urine Drug Screening, Serum Pregnancy and Urine Pregnancy Test. A list of laboratory assessments to be included in the outputs is included in Appendix 1 of the protocol, Section 20.

All laboratory summaries will be used on the safety population and presentations will use SI Units.

Quantitative laboratory measurements reported as "< X", will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings. The following summaries and listings will be provided for laboratory data:

- For laboratory parameters with continuous outcomes (e.g. blood chemistry, hematology, urinalysis data, thyroid panel), descriptive statistics for the actual values and for changes from baseline will be presented by arm for each evaluation time point.
- For laboratory parameters with categorical outcomes (e.g. urinalysis data), the number and percentage of subjects with each outcome will be presented by arm at each evaluation time point.
- Overall summary of the post-bassline PCS will be presented. The number and percentage of subjects with PCS criteria will be summarized by arm . This summary will be also

presented by age group, race group, gender, baseline AEDs and number of baseline AEDs.

- Shifts from baseline by arm for each evaluation time point will be produced to show the percentage of subjects with laboratory test values below, within, and above the normal range.
- Data listing of all clinical laboratory measurements (hematology, blood chemistry, urinalysis, thyroid, and renal function) will be provided. Results outside of the reference range will be flagged.
- Listing of clinically significant out of range laboratory measurements, urine drug screen and serum pregnancy test results will be provided.
- A listing of PCS laboratory findings (e.g. blood chemistry, hematology, urinalysis data, and thyroid function) will be presented for all laboratory parameters with PCS criteria defined in Appendix 3.

16.2.1. Blood Sodium Levels

In addition to descriptive summaries of blood sodium levels and changes from baseline for each assessment time point, the number and percentage of subjects with normal baseline sodium level (i.e. >135 mEq/L) reaching ≤ 135 mEq/L but > 130 mEq/L, ≤ 130 mEq/L but > 125 mEq/L, ≤ 125 mEq/L, and > 10 mEq/L reduction (ie, < -10 mEq/L) from baseline will be summarized by arm for each evaluation time point and overall post-baseline.

16.2.2. Laboratory Reference Ranges and Potentially Clinically Significant (PCS)

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

Low: Below the lower limit of the laboratory reference range.

Normal: Within the laboratory reference range (upper and lower limit included).

High: Above the upper limit of the laboratory reference range.

Similarly, sponsor defined- PCS laboratory results will be identified using the criteria in Appendix 3.

16.3. ECG Evaluations

The number and percentage of subjects with ECG results will be presented as Normal, Abnormal and Not Evaluable. A subject will be counted in the worst result for the post-baseline value.

ECG results will be presented in a data listing.

16.4. Vital Signs

Vital signs (supine systolic and diastolic blood pressures, respiratory rate, pulse rate, and oral temperature) and weight will be summarized using descriptive statistics at baseline and each evaluation visit. Change from baseline will be included in this presentation as well. In addition, the number and percentage of subjects with vital sign PCS criteria in Table 4 will be presented.

Data listings of vital signs and PCS criteria will be provided.

Table 4. Vital Signs Potentially Clinically Significant (PCS) Criteria

Variable	Unit	Low	High
Supine SBP	mmHg	< 90 mmHg AND change from baseline ≤ -20 mmHg	> 180 mmHg AND change from baseline ≥ 20 mmHg
Supine DBP	mmHg	< 50 mmHg AND change from ≤ -15 mmHg	> 105 mmHg AND change from baseline ≥ -15 mmHg
Supine Pulse rate	beats/min	< 50 bpm AND change from baseline ≤ -15 bpm	> 120 bpm AND change from baseline ≥ 25 bpm

Variable	Unit	Low	High
Weight	Kg	percentage change from baseline ≤ -7.0 %	percentage change from baseline ≥ 7.0 %

16.5. Physical/Neurological Examination

All physical and neurological exam findings at screening will be captured in the medical history and summarized together with the other medical history events. Clinically significant changes from the screening visit will be captured as AEs as appropriate and summarized together with the other AEs. A listing displaying whether a physical examination was performed for each subject and the date of the physical examination will be provided.

16.6. Other Safety Assessments

16.6.1. Electronic Columbia Suicide Severity Rating Scale (eC-SSRS)

The eC-SSRS is a tool designed to systematically assess and track suicidal behavior and suicidal ideation for life time prior to the screening visit, and throughout the study. The strength of this suicide classification system is in its ability to comprehensively identify suicidal events while limiting the over-identification of suicidal behavior. The eC-SSRS Baseline/Screening Version is used at the screening visit and the eC-SSRS Since Last Visit Version is used from Visit 2 onward.

Subjects with complete and incomplete eC-SSRS records in the same visit, both records will be included in the listing.

Subjects who have complete and incomplete eC-SSRS records in the same visit, only complete records will be included in the summary tables. otherwise the incomplete record will be included in the tables.

eC-SSRS includes four sections: Suicidal Ideation, Intensity of Ideation, Suicidal Behavior, and Answer for Actual Suicide Attempts.

The following outcomes are eC-SSRS categories and have binary responses (yes/no). The categories are re-ordered from the scale to facilitate the definitions of the eC-SSRS endpoints, and to provide clarity in the presentation of the results.

Suicidal ideation is measured by 5 categories, representing 5 subtypes of suicidal ideation with increasing severity:

1. Category 1: Wish to be Dead
2. Category 2: Non-specific Active Suicidal Thoughts
3. Category 3: Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
4. Category 4: Active Suicidal Ideation with Some Intent to Act, without Specific Plan
5. Category 5: Active Suicidal Ideation with Specific Plan and Intent

Suicidal behavior is measured by 5 categories, representing 5 subtypes of suicidal behavior:

1. Category 6: Preparatory Acts or Behavior
2. Category 7: Aborted Attempt
3. Category 8: Interrupted Attempt
4. Category 9: Actual Attempt (non-fatal)
5. Category 10: Completed Suicide

The 10 categories above are not mutually exclusive. Subjects will be counted in each category for which they have an event.

Self-injurious behavior without suicidal intent is a non-suicide-related eC-SSRS outcome, and has a binary response (yes/no).

For eC-SSRS analysis, “baseline” and “post-baseline” are defined as follows.

Time point	Study Visit	eC-SSRS Version	Derivation Rule
Baseline	Screening/Visit 1	Baseline/Screening – life time, past one months and past two years	Most severe outcome
	Titration/Visit 2	Since Last Visit	

Post-baseline	All post-baseline visits up to and including Week 27/Visit 9, including unscheduled visits	Since Last Visit	Most severe outcome

eC-SSRS composite endpoints will be derived for each time point of interest (i.e. baseline, post baseline, and each study visit) as follows:

Any suicidal ideation: A "yes" answer to any one of the 5 suicidal ideation questions on eC-SSRS (Categories 1-5).

Any suicidal behavior: A "yes" answer to any one of the 5 suicidal behavior questions on the eC-SSRS (Categories 6-10).

Any suicidality: A "yes" answer to any one of the 10-suicidal ideation and behavior questions on the eC-SSRS (Categories 1-10).

For each subject, the suicidal ideation score at each time point of interest (i.e. baseline, post baseline, and each study visit) is defined as the maximum suicidal ideation category (1-5) present for the time of interest. If no ideation is present a score of 0 is assigned. A suicidal ideation score of 4 or 5 is considered serious.

The number and percentage of subjects with any suicidality, any suicidal ideation and subtypes of ideation, any suicidal behavior and subtypes of behavior, and any non-suicidal self-injurious behavior will be presented for:

- Baseline (as defined above)
- Post-baseline (as defined above)
- Each scheduled study visit: Screening (lifetime), Titration/Visit 2, Week 3/Visit 3, Week 7/Visit 4, Week 11/Visit 5, Week 15/Visit 6, Week 19/Visit 7, Week 23/Visit 8, Week 27/Visit 9, EDV.

Shift in suicidal ideation score from baseline to the post-baseline time point and to each the following study visit will be presented: Week 3/Visit 3, Week 7/Visit 4, Week 11/Visit 5, Week 15/Visit 6, Week 19/Visit 7, Week 23/Visit 8, Week 27/Visit 9, EDV.

Intensity of ideation for the most severe ideation subtype is measured in terms of frequency, duration, controllability, deterrents, and reasons for ideation. Each is measured with responses ranging from 0 to 5 for frequency and duration, and from 1 to 5 for controllability, deterrents, and reasons for ideation. The ideation intensity total score is the sum of responses to the five items and can range from 2 to 25 for subjects with endorsed suicidal ideation. If one or more of these five items are missing at an assessment, the total score will be set to missing. If a subject did not endorse any suicidal ideation, a score of 0 for the ideation intensity total score will be given.

Actual lethality associated with actual attempts is rated on a 6-point scale from 0 = 'No physical damage or very minor physical damage' to 5 = 'Death'. Potential lethality of actual attempts (if actual lethality = 0) is rated on a 3-point scale from 0 = 'Behavior not likely to result in injury' to 2 = 'Behavior likely to result in death despite available medical care.

The ideation intensity total score and the actual lethality and potential lethality of actual attempts will be presented in data listings.

16.6.2. Score of AED-specific AEs (by the Liverpool Adverse Event Profile [LAEP]).

The LAEP is designed as a patient self-report scale to assess the frequency of AED side effects. It includes 19 items rated on a 4-point Likert scale with 1, never a problem; 2, rarely a problem; 3, sometimes a problem; and 4, always or often a problem. Total scores range from 19 to 76, with high scores indicating more-frequent symptom reporting.

The LAEP is introduced to the participants in the questionnaire with the heading "Here are a few questions about your health generally." The recommended preamble to the scale followed with the words, "During the last 4 weeks, have you had any of the problems listed." The problems include unsteadiness, tiredness, restlessness, feelings of anger or aggression to others, nervousness and/or agitation, headache, hair loss, problems with skin (eg, acne, rash), double or

blurred vision, upset stomach, difficulty in concentrating, trouble with mouth or gums, shaky hands, weight gain, dizziness, sleepiness, depression, memory problems, and disturbed sleep.

The following summaries and listings will be provided for LAEP data:

- The individual LAEP scores and changes from baseline for each evaluation time point will be summarized for each symptom descriptively.
- The total score and change from baseline will be also summarized.
- A listing of LAEP will be provided.

Figure of the mean (+/-SD) change from baseline for the total score by time point and arm will be provided.

17. References

1. A Concordance Correlation Coefficient to Evaluate Reproducibility, L. Lin, Biometrics, Vol. 45, No. 1 (Mar., 1989), 255-268
2. Identifying depression in epilepsy in a busy clinical setting is enhanced with systematic screening, D. Friedman et al, Seizure, 18, 2009, 429-433.
3. SAS Institute Inc. 2009. Base SAS® 9.2 Procedures Guide. Cary, NC: SAS Institute Inc.
4. Base SAS® 9.2 Procedures Guide. Copyright © 2009 by SAS Institute Inc., Cary, NC, USA.

Appendix 1. Programming Conventions for Outputs

Dates & Times

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

Presentation of Arm

For outputs, group will be represented as follows and in that order:

Group	For Tables, Listings and Graphs
Arm 1	Arm 1
Arm 2	Arm 2

Presentation of Visits

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name
Screening (Visit 1)	Scr (V1)
Baseline (Visit 2)	BL (V2)
Week 3 (Visit 3)	W3 (V3)
Week 7 (Visit 4)	W7(V4)
---	---
Week 23 (Visit 8)	W23 (V8)
Week 27 (Visit 9)	W27 (V9/EOS)
Early Discontinuation Visit	EDV
Week 31 (Visit 10)	W31 (V10)

Listing Order

All listings will be ordered by the following (unless otherwise indicated in the template):

- Center-subject ID,
- Date (where applicable)

Appendix 2. Partial Date Conventions

Imputed dates will NOT be presented in the listings.

Algorithm for Adverse Events:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not AE If start date >= study med start date, then AE
	Partial	If start date < study med start date, then not AE If start date >= study med start date, then AE
	Missing	If start date < study med start date, then not AE If start date >= study med start date, then AE
Partial, but known components show that it cannot be on or after study med start date	Known	Pre-treatment events
	Partial	Pre-treatment events
	Missing	Pre-treatment events
Partial, could be on or after study med start date	Known	If stop date < study med start date, then Pre-treatment events If stop date >= study med start date, then AE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then Pre-treatment events If stop date >= study med start date, then AE
	Missing	Assumed AE
Partial, and known components show that it	Known	AE
	Partial	AE
	Missing	AE

START DATE	STOP DATE	ACTION
is on or after 361-201 study med start date		
Missing	Known	If stop date < study med start date, then Pre-treatment events If stop date >= study med start date, then AE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not AE If stop date >= study med start date, then AE
	Missing	Assumed AE

Algorithm for Prior / Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Partial	Impute stop date as latest possible date: • If only day unknown, impute as the earlier of (last day of month, end date of the last study visit) • If month and day unknown, impute as the earlier of (31st December, end date of the last study visit). Then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
Partial	Known	Impute start date as earliest possible date: Source questions: 'started prior to start of study?' = Yes; 'Started after last dose of study medication?' = No. • If only day unknown, impute as the later of (first day of the month). • If month and day unknown, impute as the later of (1st January). Source questions: 'Started prior to study?' = No; 'Started after last dose of study medication?' = Yes. • If only day unknown, impute as the later of (first day of the month; end of treatment + 1). • If month and day unknown, impute as the later of (1st January; end of treatment + 1). Source questions: 'Started prior to study?' = No; 'Started after last dose of study medication?' = No. • If only day unknown, impute as the later of (first day of the month; date of ICF). • If month and day unknown, impute as the later of (1st January; date of ICF). Then: If stop date < study med start date, assign as prior. If stop date >= study med start date and start date <= end of treatment, assign as concomitant. If stop date >= study med start date and start date > end of treatment, assign as post treatment.
		treatment, assign as concomitant. If stop date >= study med start date and start date > end of treatment, assign as post treatment.
	Partial	

START DATE	STOP DATE	ACTION
		Impute start date as earliest possible date: Source questions: 'Started prior to study?' = Yes; 'Started after last dose of study medication?' = No. • If only day unknown, impute as the later of (first day of the month; date of birth). • If month and day unknown, impute as the later of (1st January). Source questions: 'Started prior to study?' = No; 'Started after last dose of study medication?' = Yes. • If only day unknown, impute as the later of (first day of the month; end of treatment + 1). • If month and day unknown, impute as the later of (1st January; end of treatment + 1). Source questions: 'Started prior to study?' = No; 'Started after last dose of study medication?' = No. • If only day unknown, impute as the later of (first day of the month; date of ICF). • If month and day unknown, impute as the later of (1st January; date of ICF). Impute stop date as latest possible date: • If only day unknown, impute as the earlier of (last day of the month; end date of the last study visit). assign as prior. If stop date >= study med start date and start date <= end of treatment, assign as concomitant. If stop date >= study med start date and start date > end of treatment, assign as post treatment.

START DATE	STOP DATE	ACTION
		• If month and day unknown, impute as the earlier of (31st December; end date of the last study visit). Then: If stop date < study med start date, assign as prior. If stop date >= study med start date and start date <= end of treatment, assign as concomitant. If stop date >= study med start date and start date > end of treatment, assign as post treatment.
	Missing	Impute start date as earliest possible date: Source questions: 'Started prior to study?' = Yes; 'Started after last dose of study medication?' = No. • If only day unknown, impute as the later of (first day of the month; date of birth). • If month and day unknown, impute as the later of (1st January). Source questions: 'Started prior to study?' = No; 'Started after last dose of study medication?' = Yes. • If only day unknown, impute as the later of (first day of the month; end of treatment + 1). • If month and day unknown, impute as the later of (1st January; end of treatment + 1). Source questions: 'Started prior to study?' = No; 'Started after last dose of study medication?' = No. • If only day unknown, impute as the later of (first day of the month; date of ICF). • If month and day unknown, impute as the later of (1st January; date of ICF). Then: If stop date is missing could never be assumed a prior medication. If start date <= end of treatment, assign as concomitant. If start date > end of treatment, assign as post treatment.

START DATE	STOP DATE	ACTION
Missing	Known	If stop date < study med start date, assign as prior. If stop date >= study med start date and Source question 'Started after last dose of study medication?' = No, assign as concomitant. If Source question 'Started after last dose of study medication?' = Yes, assign as post treatment.
	Partial	Impute stop date as latest possible date: • If only day unknown, impute as the earlier of (last day of the month; end date of the last study visit). • If month and day unknown, impute as the earlier of (31st December; end date of the last study visit). Then: If stop date < study med start date, assign as prior. If stop date >= study med start date and CRF question 'Started after last dose of study medication?' = No, assign as concomitant. If Source question 'Started after last dose of study medication?' = Yes, assign as post treatment.
	Missing	If Source question 'Started after last dose of study medication?' = No, assign as concomitant. If Source question 'Started after last dose of study medication?' = Yes, assign as post treatment.

Appendix 3. PCS Criteria for Laboratory Parameters

Category Parameter Name Gender Restriction, if any	PCS Low	PCS High
Hematology		
WBC	≤ $2.8x10^9$/L	≥ $16x10^9$/L
Neutrophils	< $1.5 x10^9$/L	> $13.5 x10^9$/L
Lymphocytes	N/A	> $12.0x10^9$/L
Monocytes	N/A	> $2.5x10^9$/L
Eosinophils	N/A	> $1.6 x10^9$/L
Basophils	N/A	> $1.6 x10^9$/L
Hemoglobin Female Male	 ≤ 95 g/L ≤ 115 g/L	 ≥ 175 g/L ≥ 190 g/L
Hematocrit Female Male	 ≤ 0.32(fraction of 1) ≤ 0.37(fraction of 1)	 ≥ 0.54(fraction of 1) ≥ 0.60(fraction of 1)
RBC	≤ $3.5 x 10^{12}$/L	≥ $6.4 x 10^{12}$/L
Platelet Count	≤ $75 x 10^9$/L	≥ $700 x 10^9$/L
Blood Chemistry		
Sodium	≤ 126 mmol/L	≥ 156 mmol/L
Potassium	≤ 3 mmol/L	≥ 6 mmol/L
Chloride	≤ 90 mmol/L	≥ 118 mmol/L
Bicarbonate	≤ 16 mmol/L	≥ 35 mmol/L
Calcium	< 2.05 mmol/L	≥ 3 mmol/L
Magnesium	<0.6 mmol/L	> 1.15 mmol/L
Phosphate	0.65 mmol/L	1.65 mmol/L
AST	N/A	≥ 3 x ULN
ALT	N/A	≥ 3 x ULN

Category **Parameter Name** **Gender Restriction, if any**	**PCS Low**	**PCS High**
Alkaline Phosphatase	N/A	≥ 3 x ULN
Creatinine	N/A	≥ 177 umol/L
BUN	N/A	≥ 10.71 mmol/L
Total bilirubin	N/A	≥ 34.2 umol/L
Direct bilirubin	N/A	≥ 17.1 umol/L
Indirect bilirubin	N/A	≥ 34.2 umol/L
Total protein	≤ 45 g/L	≥ 100 g/L
Albumin	≤ 25 g/L	N/A
Uric Acid Female Male	 N/A N/A	 ≥ 506 umol/L ≥ 625 umol/L
Glucose	≤2.22 mmol/L	≥ 9.71 mmol/L
Urinalysis		
Ketones	N/A	> 4+
Glucose	N/A	> 4+
Thyroid Function		
Free T4	< 9.65 pmol/L	> 22.5 pmol/L
Free T3	< 3.07 pmol/L	> 6.38 pmol/L
TSH	0 mIU/L	> 10 mIU/L