# STATISTICAL ANALYSIS PLAN

## A Phase 2 Study to Assess the Safety, Tolerability, Exploratory Efficacy, and Pharmacokinetics of Orally Administered JBPOS0101 for Refractory Infantile Spasms Patients

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for

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## LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AE | adverse event |
| AEDs | anti-epileptic drugs |
| ATC | anatomical therapeutic chemical |
| AUC | area under the plasma concentration-time curve |
| BASED | burden of amplitudes and epileptiform discharges |
| BID | twice daily |
| BLQ | Below limit of quantification |
| BMI | body mass index |
| CI | confidence interval |
| CGI-C | clinical global impression of change |
| $C_{max}$ | maximum plasma concentration |
| $C_{min}$ | minimum plasma concentration |
| CSR | clinical study report |
| CV | coefficient of variation |
| DMP | data management plan |
| EAS | efficacy analysis set |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EEG | electroencephalogram |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practices |
| GM | geometric mean |
| HR | heart rate |
| ICF | informed consent form |
| ICH | International Council for Harmonization |
| IS | infantile spasms |
| LFT | liver function tests |
| mEAS | Modified efficacy analysis set |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NONMEM | Non-linear Mixed Effects Modeling |
| OTC | over-the-counter |
| PK | pharmacokinetic(s) |
| PT | preferred term |
| Q1 | quartile 1 |

| Abbreviation | Definition |
|---|---|
| Q3 | quartile 3 |
| QTcF | QT interval from Fridericia's formula |
| SAE | serious adverse event |
| SAP | statistical Analysis Plan |
| SD | standard deviation |
| SOC | system organ class |
| SQRT | square root |
| TEAE | treatment-emergent adverse event |

**TABLE OF CONTENTS**

# 1 INTRODUCTION

This statistical analysis plan (SAP) is consistent with the statistical methods section of the final study protocol (Version 2.0, dated 15 September 2020) and includes additional detail of safety, tolerability, exploratory efficacy and pharmacokinetic (PK) summaries to be included in the clinical study report (CSR).

# 2 STUDY OBJECTIVES AND ENDPOINTS

## 2.1 Primary Objectives

- To evaluate the safety and tolerability of the investigational product in patients with refractory Infantile Spasms (IS).

## 2.2 Secondary Objective

- To characterize the PK of the investigational product in patients with refractory IS.

## 2.3 Exploratory Objective

- To evaluate the efficacy of the investigational product in treating patients with refractory IS.

## 2.4 Study Endpoints

### 2.4.1 Primary Safety Endpoints

- Incidence of Treatment emergent Adverse Events (TEAEs)
- Vital signs
- Electrocardiograms (ECGs)
- Physical and Neurological examinations
- Clinical laboratory assessments

### 2.4.2 PK Endpoints

- Primary PK endpoints include plasma PK parameters: area under the concentration-time curve (AUC), minimum plasma concentration ($C_{min}$) and maximum plasma concentration ($C_{max}$)
- Relationship between plasma investigational product levels and response

### 2.4.3 Exploratory Efficacy Endpoints

- [redacted]

[redacted]

[redacted]

# 3 STUDY DESIGN

## 3.1 General

This is an open-label, multicenter study to evaluate the safety, tolerability, PK, and exploratory efficacy of the investigational product in children aged 6 months through 36 months with IS. Patients will receive the investigational product at a dose of 6 mg/kg orally twice daily (BID); once in the morning and 12 hours following the morning dose during the first 7 days of Treatment Period 1. Starting from the PM dose on the day of Visit 3, the dose will be escalated and patients will receive the investigational product at a dose of 9 mg/kg orally twice daily. Starting on Day 15, the dose will be escalated again and patients will receive the investigational product at a dose of 15 mg/kg orally twice daily until the end of Treatment Period 1. [redacted] Table 3-1 Schedule of Event.

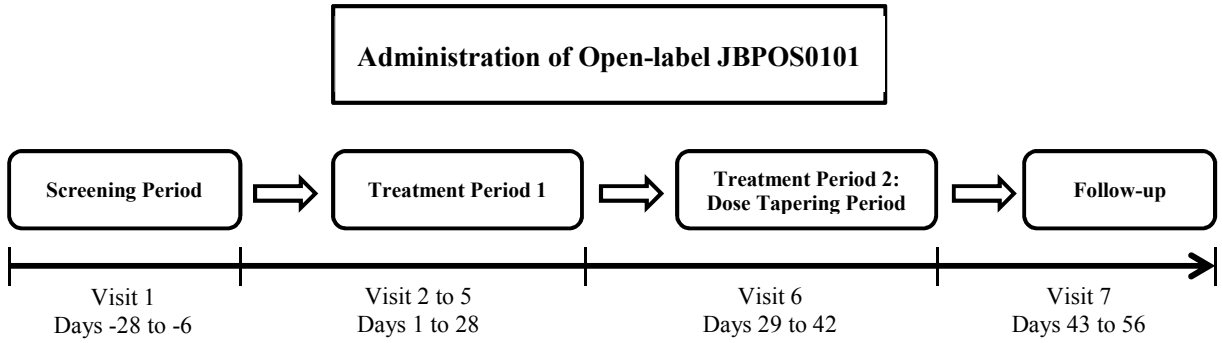
The overall study duration is expected to be up to 84 days (± 5 days). As illustrated in Figure 3-1, the study is planned to include 4 periods: Screening Period (up to 28 days), Treatment Period 1 (28 days), Treatment Period 2 (Dose Tapering Period [14 days]), and a Follow-Up Period (14 days). There will be a total of 7 study visits and 6 telephone/email contacts. Overall, the study includes 3 overnight stays: one for screening procedures, one for Day 1 (Visit 2) PK sampling and AE monitoring, and one for Day 28 (Visit 5 [± 2 days]) video-EEG recordings.

During the Screening Period, Treatment Period 1, and Treatment Period 2, no changes to dosages of any drugs used for treating epileptic seizures are permitted (except for rescue medications used for acute treatment of breakthrough seizures which are not known to be CYP3A4 substrates and whose PK has not been shown to be impacted in the presence of a CYP3A4 inhibitor). Changes of dosages of drugs used for treating epileptic seizures are permitted 2 or more days after the investigational product has been discontinued.

The study design of the study is depicted in Figure 3-1.

**Figure 3-1**

**Figure 3-1**



## Error! Reference source not found. Table 3-1 Schedule of Events

| Procedure | Screening Period | Treatment Period 1 | | | | | | Treatment Period 2: Dose Tapering Period | Follow-Up |
|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Visit 1** | **Visit 2** | **Telephone Contact** | **Visit 3** | **Telephone Contact** | **Visit 4** | **Visit 5** | **Visit 6 / Early Termination Visit** | **Visit 7** |
| **Study Days** | **–28 to -6** | **1** | **2 to 6[a]** | **7** | **12 or 13 or 14[a]** | **21** | **28** | **42** | **56** |
| **Visit Window** | | | | **± 2 days** | | **± 2 days** | **± 2 days** | **± 5 days** | **± 5 days** |
| Informed consent | X | | | | | | | | |
| Medical history | X | | | | | | | | |
| Inclusion/exclusion criteria | X | | | | | | | | |
| Video EEG[b] | X | | | | | | X | | |
| BASED Score | X | | | | | | X | | |
| Demographics | X | | | | | | | | |
| 12-lead electrocardiogram | X | | | X | | | X | X | |
| Urine drug screen[c] | X | | | | | | | | |
| Physical and neurological examination[d] | X | X | X[e] | X | | X | X | X | X |
| Vital sign measurements[f] | X | X | | X | | X | X | X | X |
| Clinical laboratory tests[g] | X | | | X | | | X | X | |
| Investigational product administration[h] | | X | X | X | X | X | X | | |

| Procedure | Screening Period | Treatment Period 1 | | | | | | Treatment Period 2: Dose Tapering Period | Follow-Up |
|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Visit 1** | **Visit 2** | **Telephone Contact** | **Visit 3** | **Telephone Contact** | **Visit 4** | **Visit 5** | **Visit 6 / Early Termination Visit** | **Visit 7** |
| **Study Days** | **–28 to -6** | **1** | **2 to 6[a]** | **7** | **12 or 13 or 14[a]** | **21** | **28** | **42** | **56** |
| **Visit Window** | | | | **± 2 days** | | **± 2 days** | **± 2 days** | **± 5 days** | **± 5 days** |
| Dispensing of investigational product | | X | | X | | X | X | | |
| Investigational product accountability assessment | | | | X | | X | X | X | X |
| Adverse event monitoring | | X | X | X | X | X | X | X | X |
| Review of prior and concomitant medications[i] | X | X | X | X | | X | X | X | X |
| Clinical Global Impression of Change[m] | | X | | X | | X | X | X | |
| Seizure diary[j] | X | X | X | X | X | X | X | X | |
| Pharmacokinetic blood sampling[k] | | X | | | | X | | | |
| Pharmacokinetic urine sampling[l] | | X | | | | X | | | |

Abbreviations: EEG, electroencephalogram

a. The investigator or his/her delegate will follow-up by telephone or email on Day 2 to Day 6 to ensure that the seizure diary is being completed, to review seizure counts, and to conduct daily assessments. The investigator will also contact the parent/caregiver by telephone on Day 12, or Day 13 or Day 14 to review seizure counts and to assess the patient's status.

b. An overnight video-EEG will be completed within the Screening Period (Days -21 to -6), and repeated at Day 28 (Visit 5 [± 2 days]), [redacted]

c. Urine drug screen assessment to test for the presence of cannabinoids will be performed locally.

d. A complete physical examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular,

abdomen, lymph nodes, and musculoskeletal system/extremities. Where possible, a neurological examination will include mental status evaluation, examination of cranial nerves, motor examination (muscle tone, strength, and reflexes), cerebellar examination (coordination and gait), and sensory examination. Physical and neurological examination will also be conducted on Day 2 prior to discharge.

e. After physical and neurological examination is conducted on Day 2, physical and neurological examination is not scheduled to be conducted again until Day 7 (Visit 3 [± 2 days]).
f. Vital signs measurements will include blood pressures, temperature (measured rectally), pulse rate, and respiratory rate. Height, weight, and body mass index (BMI) will be measured at each clinic visit. Vital sign measurements will also be conducted on Day 2, prior to discharge.
g. Includes urinalysis. Hematology, coagulation and serum chemistry assessments will be performed by the sponsor's central laboratory; urinalysis assessment will be performed locally.
h. Investigational product will be administered orally twice daily, in the morning and 12 hours after the morning dose at a dose of 6 mg/kg after at least a 2-hour fast during the first 7 days of Treatment Period 1. Starting from the PM dose on the day of Visit 3, the dose will be escalated and patients will receive the investigational product at a dose of 9 mg/kg orally twice daily. Starting on Day 15, the dose will be escalated again and patients will receive the investigational product at a dose of 15 mg/kg orally twice daily until the end of Treatment Period 1. The first 2 doses of the investigational product (6 mg/kg orally) will be administered during Visit 2 and the remaining doses will be administered at home. Patients will receive investigational product up to Day 28 (Treatment Period 1). Following Treatment Period 1, Treatment Period 2 (Dose Tapering Period) will begin on Day 29 and the dose will be reduced by half for all patients. On Day 35, the dose will be reduced by half again, and on Day 42, the investigational product will be stopped.
i. Prior medications will be recorded during the Screening Period. All medications taken by patients after Screening Period until the completion of the final Follow-Up visit will be documented as concomitant medications.
j. Seizure diary will be distributed on the Screening Period visit (Visit 1). The investigator will ensure that the seizure diary is being completed. The investigator will also review seizure counts to make sure seizures are not increasing. [redacted]
k. Details regarding PK blood sampling are provided in Table 3–2.
l. Urine sampling for PK assessment will be collected by using a plastic urine collection bag following the morning dosing of investigational product on Day 1 and Day 21 (Visit 4 [± 2 days]).
m. The Clinical Global Impression of Change is completed by both the Investigator and the Caregiver. CGI-C on Day 1 is performed prior to dosing.

Source: Protocol Final Version 2.0, dated 15 September 2020.

### 3.2 Study Population

This study will enroll male and female subjects meeting the following criteria: they are between 6 months through 36 months of age at the time of informed consent, have a clinical diagnosis of IS, confirmed by video-EEG analysis, and hypsarrhythmia on EEG at screening according to the BASED scale score.

### 3.3 Evaluations at Screening and Check-in

The screening period will be a maximum of 28 days and will include Day -28 to Day -6 prior to first dose of study drug. Refer toError! Reference source not found. Table 3-1 Schedule of EventError! Reference source not found. Table 3-1 Schedule of Event for screening and check-in procedures.

### 3.4 Randomization and Treatment Assignments

This is an open-label study.

### 3.5 Study Drug Administration

Investigational product will be administered at 6 mg/kg, orally twice daily, once in the morning and 12 hours following the morning dose during the first 7 days of Treatment Period 1. Starting from the PM dose on the day of Visit 3, the dose will be escalated and patients will receive the investigational product at a dose of 9 mg/kg orally twice daily. Starting on Day 15, the dose will be escalated again and patients will receive the investigational product at a dose of 15 mg/kg orally twice daily until the end of Treatment Period 1. Each dose of the investigational product will be administered after at least a 2-hour fast. Food can be given 2 hours after dosing.

### 3.6 Compliance

Treatment compliance will be discussed with the patient's legal representative (parent[s]/caregiver[s]) by the study site staff at each visit, and noncompliance will be noted based on details the study site obtains at the patient visits. Any missed dose against the instructions will be recorded in the electronic case report form (eCRF).

### 3.7 Pharmacokinetic Sampling Schedule

PK blood sampling will be performed at time points mentioned in Table 3-2 Steady State Pharmacokinetic Sampling Time Points.

**Table 3-2 Steady State Pharmacokinetic Sampling Time Points**

| Study Period | | |
|---|---|---|
| **Visit** | **Study Days** | **Blood Sampling Time Points[a]** |
| 2[b] | 1 | • 0.5-1.5 hours post-AM dose<br>• 4-6 hours post-AM dose<br>• 8 hours post-AM dose time point and pre-PM dose |
| 4[b] | 21 | • 0.5-1.5 hours post-AM dose<br>• 4-6 hours post-AM dose<br>• 8 hours post-AM dose time point and pre-PM dose |

a. The PK blood sampling scheme may be modified on a case-by-case basis so as not to exceed a total blood draw limit of 8 mL/kg over 56 days, to a maximum blood draw of 50 mL. Note that the total blood drawn accounts for both blood draws for PK assessment as well as other assessments (i.e., clinical laboratory assessments).

b. The AM dose should be administered at the clinical site prior to the PK blood sampling on Visit 2 & 4.

Urine sampling for PK assessment will be collected for the morning dosing of investigational product on Day 1 and Day 21 (Visit 4 [± 2 days]).

Pharmacokinetic blood and urine samples may be used for future exploratory purposes outside of this study.

## 3.8 Evaluation of Treatment Safety

### 3.8.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to the investigational product. The patient's legal representative (parent[s]/caregiver[s]) will be instructed to contact the investigator at any time if any symptoms develop.

A TEAE is defined as any event not present before exposure to the investigational product or any event already present that worsens in either intensity or frequency after exposure to the investigational product.

All AEs will be reported or observed during the study will be recorded on the AE form in the eCRF. The AE and SAE reporting period begins after administration of study drug through the follow up visit. The Investigator will follow-up on all AEs observed or reported by the subject up to the end of the reporting period unless the event stabilizes and follow-up is no longer necessary. The Investigator will follow-up on SAEs until they are considered resolved or the outcome is known.

The following details will be collected for AEs: description of the AE, onset date/time, action taken with study drug (dose not changed, drug interrupted, drug withdrawn, dose increased, not applicable, or unknown), date/time of resolution, any additional treatment given, outcome

(recovered/resolved, not recovered/not resolved, recovered/resolved with sequelae, recovering/resolving, fatal or unknown), severity (mild, moderate, severe), seriousness (yes, no), relationship to study drug (unrelated, possibly, probably, definitely related or unknown), and whether the AE causes early termination of the subject.

The severity of AEs will be categorized as follows:

- Mild: These events require minimal or no treatment and do not interfere with the patient's daily activities.
- Moderate: An AE that is sufficiently discomforting to interfere with normal activities.
- Severe: These events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

### 3.8.2 Clinical Laboratory Assessments

Blood and urine samples will be collected for hematology, coagulation, serum chemistry and urinalysis at the time points on Screening and Day 7, Day 28 and on Day 42.

| | |
|---|---|
| Hematology: | Hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count, red blood cell count, and total and differential (absolute and percent) leukocyte count |
| Coagulation | International normalized ratio, partial thromboplastin time, and prothrombin time |
| Serum Chemistry: | Albumin, alanine aminotransferase, alkaline phosphatase, amylase, anion gap, aspartate aminotransferase, bicarbonate, bilirubin (total and direct), blood urea nitrogen, calcium, chloride, cholesterol (total, high-density lipoprotein, and low-density lipoprotein), creatine phosphokinase, creatinine, gamma-glutamyltransferase, globulin, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total protein, triglycerides, and uric acid |
| Urinalysis: | Appearance, bilirubin, color, glucose, ketones, leukocyte esterase, microscopy (performed if dipstick is positive; includes bacteria, casts, crystals, epithelial cells, red blood cells, and white blood cells), nitrites, occult blood, pH, protein, specific gravity, turbidity, and urobilinogen |

Abnormal clinical laboratory values will be flagged as either high or low (or normal or abnormal) based on the reference ranges for each laboratory parameter. The investigator will determine whether any of the abnormally high or low results are clinically significant or not clinically significant. Clinical significance is defined as any variation in results that has medical relevance and may result in an alteration in medical care (e.g., active observation, diagnostic measures, or therapeutic measures). If a clinically significant change from the screening value is noted, the clinically significant value and reason for clinical significance will be documented on the AE page of the eCRF. The investigator will continue to monitor the patient with additional assessments until the value has reached the reference range, or the value at the Screening Period visit, or until the investigator determines that follow-up is no longer medically necessary.

Liver enzymes/LFTs will be assessed in accordance with the guidelines presented in the US Food and Drug Administration (FDA) Guidance for Industry–Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009).

Urine drug screen assessment will be performed locally at screening time point.

### 3.8.3 Vital Signs, Height, Weight, and Body Mass Index

Vital signs measurements will include blood pressure, temperature (measured rectally), pulse rate, and respiratory rate. Vital signs will be measured at Screening, Treatment Period 1 on Day 1, Day 2 prior to discharge, Day 7, Day 21 and Day 28, Treatment Period 2 on Day 42 and Follow-Up visit on Day 56. Height, weight, and body mass index (BMI) will be measured at each clinic visit..

### 3.8.4 Electrocardiograms

The 12-lead ECG will be measured at following time points: Screening, Treatment Period 1 on Day 7 and 28, and Treatment Period 2 on Day 42.

ECG parameters will include RR interval, PR interval, QRS width, QT interval, and QT interval from Fridericia's formula (QTcF). Subjects with ECG assessments will be interpreted locally and will include comments on whether the tracings are normal or abnormal; rhythm, presence of arrhythmia or conduction defects; morphology, any evidence of myocardial infarction, or ST segment, T Wave, and U Wave abnormalities.

The investigator will determine whether any of the 12-lead ECG results are normal or abnormal, and if abnormal results are clinically significant or not clinically significant. Clinical significance

is defined as any variation in results that has medical relevance and may result in an alteration in medical care (e.g., active observation, diagnostic measures, or therapeutic measures). If a clinically significant change from screening values is noted, the clinically significant value and reason for clinical significance will be documented on the AE page of the patient's eCRF and a pediatric cardiology consultation will be prompted.

### 3.8.5 Physical and Neurological Examinations

Subjects with complete physical and neurological examination will be documented at Screening, Day 1, Day 2 prior to discharge, Day 7, Day 21 and Day 28 of Treatment Period 1, Day 42 of Treatment Period 2 and Follow-Up visit on Day 56.

A complete physical examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities.

A neurological examination will include mental status evaluation, examination of cranial nerves, motor examination (muscle tone, strength, and reflexes), cerebellar examination (coordination and gait), and sensory examination.

### 3.8.6 Concomitant Medications

Use of all concomitant medications will be recorded in the patient's eCRF. This will include all prescription drugs, herbal products, vitamins, minerals and over-the-counter (OTC) medications. The minimum requirement is that the medication name and the dates of administration are to be recorded. Any changes in concomitant medications will also be recorded in the patient's eCRF. Use of drugs known to be CYP3A4 substrates and whose PK has been shown to be impacted in the presence of a CYP3A4 inhibitor will not be allowed during the Screening Period, Treatment Period 1, and Treatment Period 2; use of drugs known to be CYP3A4 substrates and whose PK has been shown to be impacted in the presence of a CYP3A4 inhibitor will not be allowed until 2 or more days after the investigational product has been discontinued.

Concomitant drugs used for treating epileptic seizures will be allowed during the study (excluding felbamate, cannabinoids, and drugs used for treating epileptic seizures known to be CYP3A4 substrates and whose PK has been shown to be impacted in the presence of a CYP3A4 inhibitor) if the doses remain stable during the Screening Period, Treatment Period 1, and Treatment Period 2 (with the exception that rescue medications used for acute treatment of breakthrough seizures which are not known to be CYP3A4 substrates and whose PK has not been shown to be impacted in the presence of a CYP3A4 inhibitor may be administered at any

time during the study). Changes of dosages of drugs used for treating epileptic seizures are permitted 2 or more days after the investigational product has been discontinued. Ketogenic diet and vagus nerve stimulation therapies will not be allowed during the Screening Period, Treatment Period 1, and Treatment Period 2; ketogenic diet and vagus nerve stimulation therapies will not be allowed until 2 or more days after the investigational product has been discontinued.

Prior/concomitant medications will be assessed throughout the study for all patients. Information recorded will include start and stop dates and times, dose, frequency, route of administration, and indication.

### 3.8.7 Protocol Deviation Reporting

A protocol deviation is defined as any intentional or unintentional change to, or noncompliance with, the approved protocol procedures or requirements. Deviations may result from the action or inaction of the subject or investigator.

The following lists of protocol deviations of data may include the following:

Data deviations (captured in the database):

- The patient does not meet the protocol inclusion or exclusion criteria.
- Failure to comply with dispensing or dosing requirements (eg, dosing not administered within the timeframe specified in the protocol
- Missed visits
- Test requirements, including vital signs, lab tests, physical assessments, PK blood draws, and medical history not followed – either tests not done, incorrect tests done, or not done within the timeframe specified in the protocol
- Failure to obtain consent prior to beginning the study
- The patient is noncompliant with the protocol, defined as failure to perform any portion of scheduled assessments or procedures

Major deviations leading to exclusion from PK population:

- PK data collected during the affected treatment period will be excluded from the study results.
- Inaccurate dosing on the day of PK sampling.
- Missed blood sample or deviations from blood collection times.

Major deviations leading to exclusion from EAS:

- Patients with missing or incomplete/unreadable Day 28 EEG data.

# 4 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS

There are no changes in the study conduct or analysis plans relative to the study protocol.

# 5 QUALITY CONTROL AND QUALITY ASSURANCE METHODS FOR DATA ANALYSIS

Case report forms will be monitored and collected by ICON. All monitored eCRFs will be sent to the Data Management group at ICON and processed according to the ICON Study Specific Procedure SSP DM-45080001.01 Data Management Plan (DMP). The DMP describes eCRF data processing, edit checks, data query management, medical dictionary coding, SAE reconciliation, data transfers, and data quality review through database lock or any necessary reopening of the database. After database lock, the data will be retrieved from the database using SAS® 9.4 or higher version.

# 6 PHARMACOKINETIC AND EFFICACY ASSESSMENTS

## 6.1 Pharmacokinetic Assessments

### 6.1.1 Pharmacokinetic Analysis

Pharmacokinetic analyses will be based on the PK population.

Plasma PK concentrations for the investigational product will be presented in a data listing and summarized in tabular and graphical formats, as data allow. Overlay individual concentration-time plasma PK profiles may also be presented.

Population PK analysis using non-linear mixed-effects modelling will be performed given the sparse nature of the PK sampling. Appropriate PK exposure metrics will be derived from the population PK model (AUC, $C_{min}$ and $C_{max}$). The relationship between plasma investigational product levels/exposure metrics and response will be explored graphically and a formal exposure-response model may be developed.

A separate Modelling & Simulation Analysis Plan will be prepared to describe the data and methods to be used in the population PK analysis. The analysis will be performed using NONMEM v7.4 or higher version. The results of the population PK analysis will be reported separately to the CSR.

## 6.2 Efficacy Assessments

Efficacy endpoints will include the following parameters: EEG, seizure diary and CGI-C.

### 6.2.1 Electroencephalogram

A 16-hour overnight video-EEG will be performed at screening and Day 28 of Treatment Period 1 to look for changes from baseline [redacted]

[redacted]

[redacted].

### 6.2.2 Seizure Diary

The patient's legal representative (parent[s]/caregiver[s]) will be provided with a seizure diary at the Screening Period visit (Visit 1) to record the number of seizures daily starting from the day after Visit 1 until the patient discontinues the investigational product. The seizure diaries for each patient will be assessed at Screening, Day 1, Day 2 to 6, Day 7, Day 12 or 13 or 14, Day 21 and 28 of Treatment Period 1, and Day 42 of Treatment Period 2.

The investigator will ensure that the seizure diary is being completed. The investigator will also review seizure counts to ensure the number of seizures is not increasing. The seizure diaries will indicate whether spasms are still present. [redacted]

### 6.2.3 Clinical Global Impression of Change

The CGI-C assessment will be collected from both the investigator and the parent/caregiver on Day 1, Day 7, Day 21 and Day 28 of Treatment Period 1 and Day 42 of Treatment Period 2. The CGI-C is a validated instrument that allows the investigator to rate the change in a patient's condition on a 7-point scale ranging from "very much improved since the initiation of treatment" to "very much worse since the initiation of treatment." [redacted]

**Table 6-1 Clinical Global Impression of Change Scale**

| Scale # | Impression |
|---|---|
| 1 | very much improved |
| 2 | much improved |
| 3 | minimally improved |
| 4 | no change |
| 5 | minimally worse |
| 6 | much worse |
| 7 | very much worse |

# 7 STATISTICAL METHODS

## 7.1 General

All statistical analysis will be conducted following the principles specified in the International Conference on Harmonization (ICH) Topic E9 Statistical Principles for Clinical Trials (CPMP/ICH/363/96).

All statistical analyses will be performed using the statistical software SAS, Version 9.4 or newer and any exceptions will be detailed in the CSR.

All results collected in the database will be presented in listings. Both absolute values and change-from-baseline values for each subject will be given where applicable. All continuous data will be listed with the same precision as presented in the database. Data listings will be sorted by subject ID, and time point.

Unless otherwise noted, continuous variables will be summarized using the number of non-missing observations (n), arithmetic mean (mean), standard deviation (SD), median, minimum, maximum, Quartile 1 (Q1), and Quartile 3 (Q3); categorical variables will be summarized using the frequency count and the percentage of subjects in each category. Time to event data will be summarized using median, 25%, and 75% percentiles.

In the data listings, study day relative to first dose of treatment may be presented. Study day relative to first dose will be calculated as: event date – first dose date (+1 if event date ≥ first dose date).

Baseline will be the last non-missing available measurement prior to first dose of the study drug.

For safety summaries, the unscheduled and repeat assessments will not be summarized; however, all results will be included in the data listings.

All PK parameters will be summarized by the overall treatment group using descriptive statistics to include, as appropriate, n, mean, SD, coefficient of variation (CV), minimum, median, maximum, geometric mean (GM), and geometric CV.

Disposition, demographics and baseline characteristics, all safety parameters and adverse events will be summarized overall.

## 7.2 Handling of Dropouts or Missing Data

Missing data will not be imputed.

### 7.2.1 Handling of incomplete dates for AE

Imputation rules for missing or partial AE start date are defined below:

**If only Day of AE start date is missing:**

If the start date has month and year but day is missing, the first day of the month will be imputed

- If this date is earlier than the first dose date, then the first dose date will be used instead.
- If this date is later than the stop date (possibly imputed), then the stop date will be used instead.

**If Day and Month of AE start date are missing:**

If the start date has year, but day and month are missing, the 1st of January will be imputed

- If this date is earlier than the first dose date, then the first dose date will be used instead.
- If this date is later than the stop date (possibly imputed), then the stop date will be used instead.

**If Year of AE start date is missing:**

If the year of AE start is missing or AE start date is completely missing then query site with no imputation. Also compare the full (or partial) AE end date to the first dose date. If the AE end date is before the first dose date then the AE should be considered as a pre-treatment AE. Otherwise, the AE will be considered as TEAE.

### 7.2.2 Handling missing or partial Prior/Concomitant Medication Dates

Missing or partial medication start date:

a. If only DAY is missing, the first day of the month will be assumed.
b. If DAY and Month are both missing, the first day of the year will be assumed.
c. If DAY, Month and Year are all missing, the day before the first dose date will be assumed.

Missing or partial medication stop date:

a. If only DAY is missing, the last day of the month will be assumed.
b. If DAY and Month are both missing, the last day of the year will be assumed.
c. If DAY, Month and year are all missing, ‘continuing’ status to stop date will be assigned.

### 7.3 Examination of Subgroups

Additional subgroup summaries will be performed to determine whether differences exist in primary safety and efficacy endpoint results between subgroups.

The list of potential subgroups (with applicable definitions in parentheses) includes, but is not necessarily limited to, the following:

- Sex (Female vs. Male)
- Age (6-12 months; >12-24 months; >24-36 months)
- Concomitant anti-epileptic drugs (AEDs) (Specific categories to be finalized prior to database lock. The categories will be determined based upon which AEDs or combinations of AEDs the subjects take during the course of the study)

For each subgroup variable, the frequency and percentage will be displayed.

### 7.4 Analysis Populations

The following populations will be analyzed for overall treatment group (JBPOS0101):

- All Enrolled Population: The Enrolled Population will include all patients who signed informed consent.
- Safety Population: The safety population will include all patients who were treated with at least one dose of the investigational product. The safety population will be used for all safety assessments.
- Efficacy Population (EAS): The efficacy population will include all patients, without any major protocol deviation affecting the efficacy endpoint analysis, who were treated with the investigational product for at least 26 days and completed the Day 28 (Visit 5 [± 2 days]) overnight video-EEG. The EAS will be used for all efficacy assessments.
- Modified Efficacy Population (mEAS): To evaluate the influence of COVID-19 on the efficacy results, a modified EAS will be considered which, in addition to EAS population, includes also those patients with major protocol deviations affecting the efficacy endpoint analysis which can be attributed to COVID-19. The same efficacy analyses as for EAS population will also be performed for the mEAS population.
- PK Population: The PK population will include all patients, without any major protocol deviation affecting the secondary endpoint analysis, who were treated with at least one dose of the investigational product and have at least one measurable PK concentration. The PK Population will be used for all PK assessments.

### 7.5 Subject Accountability

Summaries of analysis populations and subject disposition will be presented by overall treatment (JBPOS0101) and will contain the following information:

- Number of subjects enrolled
- Number and percent of subjects with screen failure
- Number and percent of subjects with screen failure reason
- Number and percent of subjects who were dosed
- Number and percent of subjects who completed the study
- Number and percent of subjects who discontinued early and reason for early discontinuation
- Number and percent of subjects in the Safety, EAS, mEAS and PK Populations.

This summary will be based on the All Enrolled Population.

Subject disposition data, exclusions from the analysis populations, eligibility criteria satisfaction and consent information will be presented in listings.

### 7.6 Protocol Deviation Reporting

Major protocol deviations will be identified prior to database lock and may include, but are not limited to, significant violations of inclusion/exclusion criteria, noncompliance with trial treatment taken, conditions such as vomiting and diarrhea or use of prohibited medications, and not following clinical trial protocol procedures.

All Protocol deviations will be listed.

### 7.7 Subject Demographics and Baseline Characteristics

Subject demographic data and baseline characteristics will be summarized using descriptive statistics by overall treatment and will include the following parameters: sex, age, race, ethnicity, concomitant anti-epileptic drugs, height, weight, and body mass index (BMI). Demographic data and baseline characteristics will also be listed for safety population.

### 7.8 Medical and Surgical History

Medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 22.0 or later) and listed.

Medical history will be listed and summarized for safety population by System Organ Class (SOC) and Preferred Term (PT) for overall treatment.

## 7.9 Extent of Exposure

Exposure data will be presented in a listing and summarized by overall treatment.

Total exposure [mg] of a patient will be defined as the cumulative dose of study drug that a patient received during the course of the study. The extent (duration) of exposure will be derived in days as Date of last dose – Date of first dose + 1.

## 7.10 Analysis of Exploratory Efficacy Data

Exploratory Efficacy endpoints will be listed and summarized for following parameters: EEG, Seizure Diary and CGI-C.

The same efficacy analyses as in the EAS will also be performed for the mEAS population. If both populations coincide (i.e., there are no major protocol violations attributable to COVID-19 which affect the efficacy endpoint analysis) only the analyses in the EAS will be performed.

### 7.10.1 EEG

[redacted]

| Situations | Date of censoring/event |
|---|---|
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |

[redacted]

[redacted]

In addition, the overall result of the video EGG at Day 28 (Visit 5 [± 2 days]) will be summarized for overall treatment.

#### 7.10.2 Seizure Diary

Seizure diary data will be presented in a listing and summarized by overall treatment for the following assessments and for the data captured in the eCRF under Seizure Diary Review Form:

- Number of seizures
- Seizure type

[redacted]

#### 7.10.3 CGI-C

CGI-C assessment will be listed and summarized by visit using descriptive statistics for overall treatment.

### 7.11 Analysis of Pharmacokinetic Data

Concentrations data will be summarized in tables and figures when at least 3 subjects for overall treatment have non-missing data at the time point being summarized. Within individual subject concentration versus time profiles, whether graphical or tabular, all assayed concentrations will be presented, even when not summarized elsewhere.

Concentration summaries and corresponding figures/listing will be presented using PK Population. PK concentration data for blood and urine samples and volume of urine samples will be summarized for overall treatment by descriptive statistics of n, arithmetic mean, standard deviation (SD), coefficient of variation (CV), geometric mean, geometric CV, median, minimum, and maximum. Geometric CV is calculated as the square root of the exponentiated variance of the natural log transformed data minus 1 (SQRT (exp($SD^2$)-1)) where appropriate.

## 7.12 Analysis of Safety Data

### 7.12.1 Adverse Events

All AEs will be coded to SOC) and PT using Medical Dictionary for Regulatory Activities (Version 22.0 or later) and presented by subject in data listings.

A treatment-emergent adverse event (TEAE) is defined as any AE that began or worsened following the start of dosing of Treatment Period 1, Day 1 to Follow-Up.

A treatment-related AE is defined as any TEAE that is assessed by the Investigator as possibly, probably or definitely related to study drug.

Adverse event analyses will be conducted using the Safety Population.

The overall incidence of TEAEs (number and percentage of subjects) as well as the number of events will be summarized for mild TEAEs, moderate TEAEs, severe TEAEs, TEAEs assessed as at least possibly related, SAEs, TEAEs leading to study or drug discontinuation, SAEs related to study drug, life-threatening SAEs and SAEs resulting in death. All AE reports will also include the action taken as a result of the AE such as dose not changed, drug interrupted, drug withdrawn, dose increased, not applicable, or unknown.

The following TEAEs summaries will be presented (where applicable the number of patients (%) and number of events will be summarized) by SOC and PT for overall treatment group:

- TEAEs
- Treatment-related TEAEs
- TEAEs leading to investigational product discontinuation
- Treatment-related TEAEs leading to investigational product discontinuation
- Serious TEAEs
- Treatment-related serious TEAEs
- TEAEs leading to death
- Treatment-related TEAEs leading to death.

All TEAEs will be summarized by SOC and PT using frequency counts and percentages (i.e., number and percentage of patients with an event); also the number of events will be presented

Tabulations will include an overall incidence of subjects reporting at least one AE, an overall incidence of TEAEs, and incidence within SOC and PT. Each patient may only contribute once (i.e., most severe occurrence) to each of the incidence rates, regardless of the number of occurrences.

For the incidence at the subject level by SOC, PT and relationship to study drug; if a subject experiences more than 1 event within the same SOC and PT, only the most related occurrence (in

descending order of definitely related, probably related, and possibly related) will be included in the incidence.

Listings of AEs, TEAEs, SAEs, TEAEs leading to death and TEAEs leading to study drug discontinuation will also be presented.

#### 7.12.2 Clinical Laboratory Assessments

Observed values and change from baseline for each parameter of continuous clinical laboratory values (hematology, coagulation, serum chemistry and urinalysis) will be summarized by overall and visit using descriptive statistics.

Shift from screening/baseline to post-baseline laboratory findings in normal range criteria will also be summarized.

A listing of all clinical laboratory data for each subject at each visit will be presented. Clinical laboratory values that are outside the normal ranges will be presented in a separate listing. The normal ranges will also be listed.

#### 7.12.3 Vital Signs, Height, Weight, and Body Mass Index

Observed values and change from baseline for each parameter of continuous vital sign parameters (blood pressure, temperature, pulse rate and respiratory rate) and height, weight, and BMI will be summarized by overall treatment and visit using descriptive statistics.

All vital signs and height, weight, and BMI data will be listed individually by each subject. Abnormal values will be flagged in the listing.

#### 7.12.4 Electrocardiograms

Continuous ECG parameters including RR interval, PR interval, QRS width, QT interval, and QTcF interval will be summarized by overall treatment and scheduled timepoints in terms of absolute values and change from baseline using descriptive statistics.

Shift tables will be presented that summarize the overall ECG interpretation as normal, abnormal not clinically significant, or abnormal clinically significant at baseline and each post-baseline time point.

ECG data will be listed by subject at each visit and time point collected with indicated clinically significant results.

ECG results meeting pre-specified criteria are listed and summarized. The following reference range ECG criteria by age range will be used.

| Age Range | ECG Parameters | Lower Limit of Normal | Upper Limit of Normal |
|---|---|---|---|
| 6-12 Months (including 12th Month) | QT Interval | 381 msec | 449 msec |
| | QTcF Interval | 350 msec | 440 msec |
| >12-24 Months | QT Interval | 381 msec | 455 msec |
| | QTcF Interval | 350 msec | 440 msec |
| >24-36 Months | QT Interval | 381 msec | 455 msec |
| | QTcF Interval | 350 msec | 440 msec |

7.12.5 Physical and Neurological Examinations

Physical and neurological examination abnormalities will be listed.

Shift tables will be presented that summarize the change in examination findings as normal, abnormal not clinically significant, or abnormal clinically significant at baseline and each post-baseline visit.

7.12.6 Prior and Concomitant Medications

Prior medications are defined as those medications that started and stopped prior to the first dose of study drug. Concomitant medications are defined as those medications with a start date on or after the first dose of study drug or started prior to the first dose of study drug and were continued after the first dose of study drug.

Prior and concomitant medications are coded using World Health Organization Drug Dictionary (WHO Drug) (Version March 2019 or later) and classified according to anatomical therapeutic chemical code (ATC) levels 2 (therapeutic sublevel) and 3 (pharmacological sublevel). Prior and concomitant medication data will be summarized and listed by ATC sublevels and preferred name.

A separate listing will be provided for concomitant procedures.

7.12.7 COVID-19

Impact of COVID-19 on various visits will be collected. This data will be listed and summarized for Safety Population.

### 7.13 Sample Size

[redacted]

Approximately 50 patients will be screened of which around 35 patients will be enrolled to provide at least 26 completers. At least 7 of the patients enrolled must be between 6 months through 12 months of age at the time of informed consent. Patients who are screened and not dosed will be replaced. Patients who discontinue the study for any reason after dosing will not be replaced.

### 7.14 Interim Analysis

No interim analyses are planned.

### 7.15 General Conventions for Tables, Listings and Figures

For summary tables, unless otherwise specified, the number of decimal places provided in the SAS output will be based on the accuracy of the least accurate value in the raw data as follows:

| | |
|---|---|
| n | integer |
| Arithmetic mean | 1 decimal place more than the least accurate number in the raw data |
| SD | 2 decimal place more than the least accurate number in the raw data |
| CV | 2 decimal places |
| Geometric mean | 1 decimal place more than the least accurate number in the raw data |
| Geometric CV | 2 decimal places |
| Median | 1 decimal place more than the least accurate number in the raw data |
| Minimum | same number of decimal places as raw data |
| Maximum | same number of decimal places as raw data |
| Q1 | same number of decimal places as raw data |
| Q3 | same number of decimal places as raw data |
| Confidence interval | same number of decimals as the associated statistic |
| Percentage | 1 decimal place |

# 8 TABLES, FIGURES, AND LISTINGS

| Table/Figure Number | Table/Figure Name |
|---|---|
| **Section 14.1** | **Demographic and Subject Characteristics Data Summaries** |
| Table 14.1.1 | Summary of Subject Disposition (All Enrolled Population) |
| Table 14.1.2 | Analysis Populations (All Enrolled Population) |
| Table 14.1.3 | Summary of Demographic and Baseline Characteristics (Safety Population) |
| Table 14.1.4 | Summary of Medical History (Safety Population) |
| Table 14.1.5 | Summary of Prior & Concomitant Medications (Safety Population) |
| Table 14.1.6 | Summary of Exposure (Safety Population) |
| **Section 14.2** | **Pharmacokinetic and Efficacy Data Summaries** |
| Table 14.2.1.1 | Summary of Electroencephalogram Responses (EAS Population) |
| Table 14.2.1.2 | Summary of Electroencephalogram Responses (mEAS Population) |
| Table 14.2.2.1 | Descriptive Summary for Time to Relapse, Resolution of Spasms and Hypsarrhythmia during Dose Tapering Period (EAS Population) |
| Table 14.2.2.2 | Descriptive Summary for Time to Relapse, Resolution of Spasms and Hypsarrhythmia during Dose Tapering Period (mEAS Population) |
| Table 14.2.3.1.1 | Summary of Seizure Diary Card (EAS Population) |
| Table 14.2.3.1.2 | Summary of Seizure Diary Card (mEAS Population) |
| Table 14.2.3.2.1 | Summary of Seizure Diary Review (EAS Population) |
| Table 14.2.3.2.2 | Summary of Seizure Diary Review (mEAS Population) |
| Table 14.2.4.1 | Summary of CGI-C Assessments Results (EAS Population) |

| | |
|---|---|
| Table 14.3.1.8 | Summary of TEAEs Leading to Death by System Organ Class and Preferred Term (Safety Population) |
| Table 14.3.1.9 | Summary of Treatment-related TEAEs Leading to Death by System Organ Class and Preferred Term (Safety Population) |
| **Section 14.3.2** | **Listings of Deaths, Other Serious and Certain Significant Adverse Events** |
| Table 14.3.2.1 | Listing of Deaths, Other Serious Adverse Events, and Significant Adverse Events (Safety Population) |
| **Section 14.3.4** | **Laboratory Summaries** |
| Table 14.3.4.1 | Listing of Abnormal Laboratory Results (Safety Population) |
| Table 14.3.4.2 | Observed and Change from Baseline for Clinical Laboratory Parameters (Safety Population) |
| Table 14.3.4.3 | Shift Assessment of Categorical Change of Laboratory Results from Baseline to each Post-Baseline Visit (Safety Population) |
| **Section 14.3.5** | **Additional Safety Data Summaries** |
| Table 14.3.5.1 | Observed and Change from Baseline Vital Signs, Height, Weight, and Body Mass Index (Safety Population) |
| Table 14.3.5.2 | Observed and Change from Baseline ECG (Safety Population) |
| Table 14.3.5.3 | Shift Assessment of Overall ECG Interpretation at Baseline and Each Post-Baseline Time-point (Safety Population) |
| Table 14.3.5.4 | Shift Assessment of Physical and Neurological Examination at Baseline and Each Post-Baseline Time-point (Safety Population) |
| Table 14.3.5.5 | Summary of COVID-19 Data (Safety Population) |
| **Listing Number** | **Listing Name** |
| **Section 16.2.1** | **Discontinued Subjects** |
| Listing 16.2.1 | Subject Disposition (All Enrolled Population) |
| **Section 16.2.2** | **Protocol Deviations** |

| | |
|---|---|
| Listing 16.2.2 | Protocol Deviations (Safety Population) |
| **Section 16.2.3** | **Subjects Excluded from Analysis** |
| Listing 16.2.3 | Exclusions from Analysis Populations (All Enrolled Population) |
| **Section 16.2.4** | **Demographic Data** |
| Listing 16.2.4.1 | Demographics and Baseline Characteristics (Safety Population) |
| Listing 16.2.4.2 | Eligibility Criteria Satisfaction (All Enrolled Population) |
| Listing 16.2.4.3 | Consent Information (All Enrolled Population) |
| Listing 16.2.4.4 | Medical History (Safety Population) |
| Listing 16.2.4.5 | Prior and Concomitant Medications (Safety Population) |
| Listing 16.2.4.6 | Concomitant Procedures (Safety Population) |
| **Section 16.2.5** | **Compliance and/or Drug Concentration Data** |
| Listing 16.2.5.1 | Study Drug Dosing Record (Safety Population) |
| Listing 16.2.5.2 | Individual Plasma JBPOS0101 Concentrations (PK Population) |
| Listing 16.2.5.3 | Individual Urine JBPOS0101 Concentrations (PK Population) |
| Figure 16.2.5.1 | Individual Plasma JBPOS0101 Concentrations vs Time for Day 1 (PK Population) *(For each subject, present the individual concentration in linear and semi-log scale.)* |
| Figure 16.2.5.2 | Individual Plasma JBPOS0101 Concentrations vs Time for Day 21 (PK Population) *(For each subject, present the individual concentration in linear and semi-log scale.)* |
| **Section 16.2.6** | **Individual Pharmacokinetic and Efficacy Response Data** |
| Listing 16.2.6.1 | EEG Responses (EAS Population) |
| Listing 16.2.6.2 | Seizure Diary Responses (EAS Population) |
| Listing 16.2.6.3 | CGI-C Assessment Results (EAS Population) |

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|---|---|
| **Section 16.2.7** | **Adverse Event Listings** |
| Listing 16.2.7.1 | All Adverse Events (Safety Population) |
| Listing 16.2.7.2 | Serious Treatment-Emergent Adverse Events by Subject (Safety Population) |
| Listing 16.2.7.3 | Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug by Subject (Safety Population) |
| Listing 16.2.7.4 | Treatment-Emergent Adverse Events Leading to Death by Subject (Safety Population) |
| **Section 16.2.8** | **Individual Laboratory Measurements by Subject** |
| Listing 16.2.8.1 | Normal Ranges for Laboratory Data |
| Listing 16.2.8.2 | Clinical Laboratory Data by Category (Safety Population) |
| Listing 16.2.8.3.1 | Vital Signs (Safety Population) |
| Listing 16.2.8.3.2 | Weight, Height and BMI (Safety Population) |
| Listing 16.2.8.4 | Electrocardiogram Results (Safety Population) |
| Listing 16.2.8.5 | Electrocardiogram Results Meeting Prespecified Criteria (Safety Population) |
| Listing 16.2.8.6 | Physical and Neurological Examination Findings (Safety Population) |
| Listing 16.2.8.7 | COVID-19 Data (Safety Population) |
| **Section 16.2.9** | **General Comments** |
| Listing 16.2.9.1 | Investigator Comments (Safety Population) |