CLINICAL STUDY PROTOCOL

IND 134128

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

PROTOCOL NO.: CL-0101-WS01

Sponsor:	Bio-Pharm Solutions Co., Ltd. 6F, C Bldg., Advanced Institute of Convergence Technology 145 Gwanggyo-Ro, Yeongtong-Gu Suwon, Gyeonggi-Do Korea 16229
Sponsor Contact:	[redacted]
Version of Protocol:	2.0
Date of Protocol:	15 September 2020

CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice.

Protocol Approval – Sponsor Signatory

Study Title	A Phase 2 Study to Assess the Safety, Tolerability, Exploratory Efficacy, and Pharmacokinetics of Orally Administered JBPOS0101 for Refractory Infantile Spasms Patients.
Protocol Number	CL-0101-WS01
Protocol Date	Protocol Version 2.0 – 15 September 2020

Protocol accepted and approved by:

President and CEO

Dr. Yong Moon Choi, Ph.D.
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[redacted] [redacted]

Signature Date

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A Phase 2 Study to Assess the Safety, Tolerability, Exploratory Efficacy, and Pharmacokinetics of Orally Administered JBPOS0101 for Refractory Infantile Spasms Patients" and the accompanying current version of the investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 2.0, dated 15 September 2020, the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with Bio-Pharm Solutions Co., Ltd. or implement protocol changes without institutional review board (IRB) approval except to eliminate an immediate risk to patients. I agree to administer study treatment only to patients under my personal supervision or the supervision of a subinvestigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Bio-Pharm Solutions Co., Ltd.

[redacted]

Signature of Principal Investigator Date

[redacted]

Printed Name of Principal Investigator

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Protocol Synopsis

Protocol Number:	CL-0101-WS01
Title:	A Phase 2 Study to Assess the Safety, Tolerability, Exploratory Efficacy, and Pharmacokinetics of Orally Administered JBPOS0101 for Refractory Infantile Spasms Patients
Sponsor:	Bio-Pharm Solutions Co., Ltd.
Study Phase:	Phase 2
Study Sites:	Multicenter study
Indication:	Infantile spasms (IS)
Rationale:	This open-label, multicenter study design allows JBPOS0101 (investigational product) to be given as either add-on therapy or monotherapy for patients with refractory infantile spasms. The design and choice of study population of this Phase 2 clinical study is based on the need to provide initial safety, tolerability, pharmacokinetics (PK), and efficacy outcomes of the investigational product for future clinical studies.
Objectives:	Primary Objective To evaluate the safety and tolerability of the investigational product in patients with refractory IS. Secondary Objective To characterize the PK of the investigational product in patients with refractory IS. Exploratory Objective To evaluate the efficacy of the investigational product in treating patients with refractory IS.
Study Population:	Inclusion criteria Male or female between 6 months through 36 months of age at the time of informed consent, has clinical diagnosis of IS, confirmed by video-electroencephalogram (EEG) analysis, and hypsarrhythmia on EEG at screening according to the Burden of Amplitudes and Epileptiform Discharges (BASED) scale score. As assessed by the investigator has no or partial response to at least 2 out of the 3 therapies of adrenocorticotrophic hormone (ACTH), vigabatrin, and glucocorticoids (i.e. prednisolone), or has no or partial response to at least 1 out of the 3 therapies of ACTH, vigabatrin, and glucocorticoids and is contraindicated to and/or refused by the patient's legal representative(s) for treatment with one or both other 2 therapies. Patients has general good health (defined as the absence of any clinically relevant

abnormalities as determined by the investigator) based on physical and neurological examinations, medical history, normal renal function and electrocardiogram (ECG), and clinical laboratory values completed during the Screening Period visit (Visit 1).

Exclusion criteria

Patient considered by the investigator, for any reason (including, but not limited to, the risks described as precautions and warnings in the current version of the investigator's brochure for investigational product) to be an unsuitable candidate to receive the investigational product.

Patient has known or suspected allergy to the investigational product or apple juice.

Patient has clinically significant renal impairment, defined as creatinine >1.5 mg/dL or blood urea nitrogen >2 × upper limit of normal (ULN); clinically significant liver dysfunction, defined as total bilirubin ≥2 × ULN, or aspartate aminotransferase or alanine aminotransferase ≥3 × ULN; has clinically significant abnormal laboratory values; the investigator may deem the patient eligible if he/she judges the laboratory values to be not clinically significant.

Patient has an ongoing or known history of human immunodeficiency virus infection, or chronic hepatitis B or C.

Patient has a clinically significant abnormality on ECG that, in the opinion of the investigator, increases the safety risks of participating in the study.

Patient has a neurodegenerative disorder as the underlying cause of IS.

Patient has a known history of aspiration pneumonia within the past year.

Patient has previously participated in another clinical study of the investigational product or received any investigational drug or device or investigational therapy within 30 days of study entry.

Patient has received therapy with felbamate, cannabinoids, ketogenic diet or vagus nerve stimulation within 14 days of screening.

Patient has received therapy with a medication known to be a CYP3A4 substrate and whose PK has been shown to be impacted in the presence of a CYP3A4 inhibitor within 14 days

	of screening (see Appendix 13.3 for a non-exhaustive list of CYP3A4 substrates). Patient has not remained at stables doses of all drugs used for treating epileptic seizures for at least 14 days prior to screening (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 [see Appendix 13.3 for a non-exhaustive list of CYP3A4 substrates]). Patient has a lethal or potentially lethal condition other than infantile spasms, with a significant risk of death before 18 months of age such as non-ketotic hyperglycinemia. Patient has an underlying metabolic disease associated with glucose intolerance (e.g., glucose transporter deficiencies). Patient has a body weight below 5 kg.
Study Design:	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; 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.

Estimated Study Duration:	The overall study duration is expected to be up to 84 days (± 5 days). 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). The actual length of the Screening Period is expected to be appreciably shorter than 28 days as patients who meet study entry criteria will be eligible to receive the investigational product on the 6th day after completing all screening procedures and assessments. During the Screening Period, Treatment Period 1, and Treatment Period 2, no changes to dosages of any drugs used for treating epileptic seizures will be 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 [see Appendix 13.3 for a non-exhaustive list of CYP3A4 substrates]). Changes of dosages of drugs used for treating epileptic seizures will be permitted 2 or more days after the investigational product has been discontinued.
Safety Assessments:	Safety assessments include monitoring and reporting of adverse events related to physical and neurological examination findings, vital sign measurements (blood pressure, pulse, and respiratory rate), height, weight, body mass index, ECG tracings, and clinical laboratory test results (hematology, serum chemistry, and urinalysis).
Pharmacokinetic Assessments:	Plasma concentration of the investigational product will be measured. Population PK analysis will be performed to calculate plasma PK parameters for the investigational product. The primary plasma PK parameters for the investigational product will include the area under the concentration-time curve (AUC), minimum plasma concentration (C_{min}), and maximum plasma concentration (C_{max}). Other PK parameters may be calculated, as appropriate.
Efficacy Assessments:	Efficacy assessment will include evaluation of EEG responses, responses in seizure diary, and assessment via Clinical Global Impression of Change (CGI-C). A 16-hour overnight video-EEG will be performed to look for changes from baseline, [redacted] The investigator will also review seizure counts recorded by the

	parent(s)/caregiver(s) in diaries to make certain seizure counts are not increasing. The seizure diaries will indicate whether spasms are still present. [redacted] 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".
Investigational Product, Dosage, and Route of Administration:	Investigational product is a white to off-white powder. The dosage form received at each clinical study site is a glass bottle containing a nominal quantity of 100 mg of the powder JBPOS0101 active pharmaceutical ingredient (API) for reconstitution into an oral solution.
Sample Size:	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.
Statistical Methods:	The primary endpoint is the incidence of treatment-emergent adverse events (TEAEs). Safety results will be reported using summary tables, listings, and figures, as appropriate, for all patients in the safety population. The Medical Dictionary for Regulatory Activities (latest version) will be used to classify all AEs with respect to system organ class and preferred term. Adverse event summaries will include only TEAEs. Prior and concomitant medications will be summarized according to the World Health Organization Drug Dictionary. Numerical laboratory test results, vital sign measurements, and ECG data will be summarized for observed values and change from screening/baseline. Shifts from screening/baseline will also be presented for clinical laboratory findings according to normal range criteria, physical and neurological examination findings, and overall ECG interpretation findings.

	Data listings will be provided for protocol-specified safety data. The secondary endpoints include plasma PK parameters AUC, C_{min}, and C_{max}. Other PK parameters may be calculated, as appropriate. Plasma PK parameters will be presented in a summary table, as data allow. Relationship between plasma investigational product levels and response will be studied. The efficacy analysis serves as the explorative endpoint.
Version and Date of Protocol:	Version 2.0 and 15 September 2020

List of Abbreviations

Abbreviation	Definition
ACTH	adrenocorticotrophic hormone
AE	adverse event
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
API	active pharmaceutical ingredient
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve during 24 hours
BASED	Burden of Amplitudes and Epileptiform Discharges
BID	twice daily
BMI	body mass index
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CGI-C	Clinical Global Impression of Change
CL_{tot}/F	apparent (oral) clearance
CNS	central nervous system
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
DSMB	Data Safety Monitoring Board
EAS	efficacy analysis set
eCRF	electronic case report form
ECG	electrocardiogram
EEG	electroencephalogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
hERG	human rther-à-go-go-related gene
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	institutional review board
IS	infantile spasms
LFT	liver function tests
mEAS	Modified efficacy analysis set
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
mGluR	metabotropic glutamate receptor
NMDA	N-methyl-D-aspartate
NOAEL	no observed adverse effect level
OTC	over-the-counter
PK	pharmacokinetics
PT	preferred term
Q1	Quartile 1
Q3	Quartile 3
QTcF	QT interval from Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	status epilepticus
SOC	system organ class
SOE	schedule of events
TEAE	treatment-emergent adverse event
t_{max}	time to reach maximum plasma concentration
ULN	upper limit of normal
WHODrug	World Health Organization Drug Dictionary

1 Introduction

1.1 Overview of Infantile Spasms

Infantile spasms (IS) is a rare form of epileptic encephalopathy that is specific to infancy and early childhood. This disease is associated with poor developmental outcome and results in significant disability (Eling et al 2002; Hrachovy and Frost 2013). The clinical manifestations of IS include brief tonic contractions of axial muscles which may be flexor, extensor, or mixed. They typically last 1-3 seconds each. The spasms may occur either in isolation or clusters but are more frequently observed in clusters and often occur on awakening (Hrachovy and Frost 2013). Infantile spasms carry very high mortality risks. A cohort study in the metropolitan area of Atlanta showed that by the age of 10 years there was a mortality ratio of 11.9 for IS – adjusted for the effects of age, race, and sex (Lux 2013). A long-term outcome study of patients with IS with history of infantile spasms reported mortality in 31% patients prior to early adulthood, of which 10% patients died prior to 3 years, and 19% patients died prior to 10 years of age. Infection was the leading cause of death and most of the patients died due to underlying neurological disability (Riikonen 1996).

1.2 Approved Indications and Unmet Medical Need

Infantile spasms is a devastating pediatric epilepsy syndrome with unsatisfactory treatment options. There are 2 treatments currently approved for IS: adrenocorticotrophic hormone (ACTH) and Sabril® (vigabatrin), however, none of them demonstrated a sustained cessation of IS (Nelson 2015). A large national infantile spasms consortium which followed infants with new-onset IS prospectively showed that only 46% of patients who received one of these first-line therapies responded (Knupp et al 2016a). Furthermore, of the children who failed on one first-line treatment and switched to receive the alternate first line treatment, only 55% responded (Knupp et al 2016b). Thus, that leaves nearly one third of infants who have spasms refractory to both first line agents. Importantly, the treatment with vigabatrin or high-dose steroids presents serious and potentially life-threatening adverse events (AEs) such as vision loss, sepsis or congestive heart failure (Tsao 2009; Chiron and Dulac 2015). Similarly, AEs associated with long-term use of ACTH limit their utility; physicians typically do not treat patients with ACTH for longer than 1 month. Most of the children develop Cushingoid features, obesity, and irritability. More serious AEs may include arterial hypertension, electrolyte imbalance, gastric ulcer, growth retardation, cardiomyopathy, and

immunosuppression (Shields 2006). Other treatments have been tested in uncontrolled studies but are not approved specifically for infantile spasms, including topiramate, zonisamide, valproic acid, nitrazepam, lamotrigine, levetiracetam, felbamate, high-dose pyridoxine, liposteroid, ganaxolone, intravenous immunoglobulin, ketogenic diet, and thyrotropin-releasing hormone. None of these therapies have demonstrated complete success in treating IS and are associated with adverse effects of varying severity (Nelson 2015). A large national spasms consortium which followed infants with new-onset IS prospectively, showed that only 9% of patients responded to nonstandard therapies (i.e., not ACTH and vigabatrin) (Knupp et al 2016a).

1.3 Rationale for Using JBPOS0101 (Investigational Product) for Treatment of Infantile Spasms

Infantile spasms is an epileptic encephalopathy that occurs in infancy with seizure-related developmental regression. There is increasing evidence that a longer duration of uncontrolled spasms is associated with poorer neurodevelopmental outcomes (Lux 2013). Therefore, therapies providing timely spasm suppression are critically needed.

Glutamate is an excitatory neurotransmitter essential in both integrative brain functions and nervous system development (Swanson et al 2005). Glutamate receptors are categorized as ionotropic or metabotropic receptors. The ionotropic receptors comprise cation-specific ion channels and are subdivided into α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and N-methyl-D-aspartate (NMDA) receptors. Very rapid neuronal excitation is a hallmark characteristic of glutamate transmission through the ionotropic receptors. The metabotropic glutamate receptors (mGluRs) having subtypes of 1-8, mediate relatively slow glutamate responses by coupling to intracellular signal transduction via G-proteins. The mGluR1 and mGluR5 belong to the Group 1 metabotropic receptor class and are localized to both pre- and post-synaptic terminals. These receptors modulate synaptic glutamate release, and antagonists of these receptors have neuroprotective effects (Bruno et al 2001). The Group 3 receptors, mGluR4 and mGluR7, are expressed primarily on presynaptic terminals, and their activation leads to decreases in glutamate release from presynaptic terminals. These modulators exhibit anticonvulsant activity and have a potential application in seizure disorders. The advantage of drugs that target the mGluRs is that they do not mediate, but rather modulate excitatory synaptic transmission, and are therefore, likely to be devoid of the undesirable effects resulting from the inhibition of excitatory synaptic

transmission, such as sedation or an impairment of learning and memory (Bruno et al 2001). JBPOS0101 has been shown to activate mGluR4 and inhibit mGluR1, mGluR5, and mGluR7, making it a promising drug for the treatment of IS.

1.4 Summary of Nonclinical and Clinical studies

1.4.1 Nonclinical Summary

The efficacy of the investigational product has been studied in numerous rodent models of seizure/epilepsy. [redacted]

Expected, pharmacologically-based, clinical signs were observed with the investigational product in various safety pharmacology studies. [redacted]

[redacted]

1.4.2 Clinical Summary

The safety, tolerability, and pharmacokinetic (PK) profile of the investigational product was evaluated in a Phase 1, double-blind, randomized, placebo-controlled, single-center study carried out in young healthy male subjects aged 18 to 45 years old, with a body mass index (BMI) within the range of 19.0 kg/m^2 to 30.0 kg/m^2, inclusive, and a minimum weight of at least 50 kg. [redacted]

[redacted]

[redacted]

Details of clinical and nonclinical studies conducted with JBPOS0101 can be found in the Investigators' Brochure.

1.4.3 Clinical versus Preclinical

[redacted]

2 Study Objectives

2.1 Primary Objective

To evaluate the safety and tolerability of the investigational product in patients with refractory 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.

3 Investigational Plan

3.1 Study Design

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 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.

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 including video-electroencephalogram (EEG) recordings, one for Day 1 (Visit 2) PK sampling (Section 6.2) and AE monitoring, and one for Day 28 (Visit 5 [± 2 days]) video-electroencephalogram (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 [see Appendix 13.3 for a non-exhaustive list of CYP3A4 substrates]). Changes of dosages of drugs used for treating epileptic seizures are permitted 2 or more days after the investigational product has been discontinued.

Screening Period (Days -28 to -6):

Eligible patients will complete all screening procedures and assessments within no more than 28 days before the start of Treatment Period 1. Refer to Appendix 13.1 for the list of tests/procedures. The actual length of the Screening Period is expected to be appreciably

shorter than 28 days as patients who meet study entry criteria will be eligible to receive the investigational product on the 6th day after completing all screening procedures and assessments. At the Screening Period visit (Visit 1), the investigator will ensure that the patient's legal representative (parent[s]/caregiver[s]) provides a written informed consent form (ICF) on behalf of the infant patient. Patient's parent(s)/caregiver(s) will receive a copy of the ICF for review and must provide the ICF prior to study participation. A 16-hour, video-EEG will be completed within the Screening Period (overnight video-EEG). Seizure diary will be distributed on the Screening Period visit (Visit 1) and families will be trained by the investigator or his/her delegate on how to log seizures. Patients will be allowed to be re-screened once with the approval of the medical monitor or sponsor.

Treatment Period 1 (Days 1 to 28):

Patients will report to the hospital/clinic on Day 1 (Visit 2) and will remain at the clinical site for the first 24 hours following the first dose of investigational product. During Day 1 (Visit 2), vital signs will be monitored. The first 2 doses of the investigational product (6 mg/kg orally) will be administered during Visit 2. Physical and neurological examinations will occur prior to the first dose on Day 1, and on Day 2 prior to discharge. The investigator or his/her delegate will contact the parent/caregiver by telephone or email during the next 5 days (from Day 2 to 6) of Treatment Period 1 to ensure that the seizure diary is being completed, to review seizure counts, and to conduct daily assessments which includes following questions:

- Have you noticed any change in seizure pattern?
- Have you noticed an evolution of new seizure type?
- Have you noticed any changes in appetite?
- Have you noticed a change in stools?
- Have you noticed excessive sedation?
- Have you noticed excessive irritability?
- Have you noticed the onset of new rash?

- Has your child experienced any possible AE?
- Did your child take all prescribed doses of the investigational product today?
- Did your child take all prescribed doses of other drugs used for treating epileptic seizures today?
- Did your child require the use of a rescue medication for the treatment of a breakthrough seizure today?
- What, if any, prescribed or over-the-counter medications is your child currently taking?

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 using the above questions.

Patients will return to the study clinic on Day 7 (Visit 3 [± 2 days]). 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.

At Visit 2 and each visit thereafter, a record of the incidence and severity of TEAEs and SAEs will be collected and this will serve as a primary outcome criterion for this study. Other safety-related parameters such as 12-lead electrocardiogram (ECG), hematology, chemistry, physical examination, and vital signs will also be assessed at specified visits. Seizure diaries will be collected to assess spasms count prior to each visit following Visit 1.

Video-EEG will be repeated at Day 28 (Visit 5 [± 2 days]) (overnight video-EEG), following Treatment Period 1 for the assessment of spasms and hypsarrhythmia.

At Visit 2 and each visit thereafter, Clinical Global Impression of Change (CGI-C) will be collected from both the investigator and the parent/caregiver.

[redacted]

[redacted]

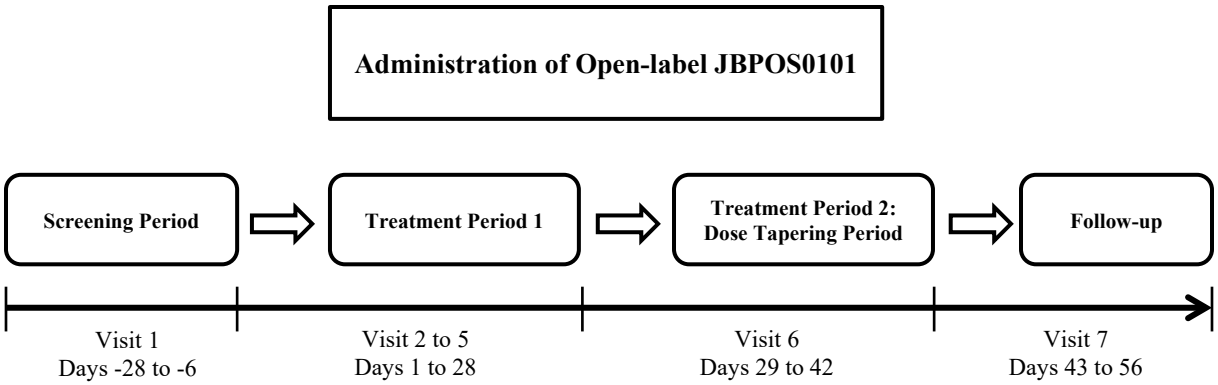
Treatment Period 2: Dose Tapering Period (Days 29 to 42):

The full dose of the investigational product will be continued until Day 28. At the start of the Dose Tapering Period on Day 29, the dose will be reduced by half. On Day 35, the dose will be reduced by half again, and on Day 42, the investigational product will be stopped. Patients will return to the study clinic on Day 42 (Visit 6 [± 5 days]). Refer to Appendix 13.1 for list of tests/procedures. [redacted]

Follow-Up Period (Day 43 to 56):

Patients will return to the study clinic on Day 56 (Visit 7 [± 5 days]). Refer to Appendix 13.1 for list of tests/procedures.

Figure 3-1 Study Design



3.1.1 Rationale of Study Design

This open-label, multicenter study design allows the investigational product to be given as either add-on therapy or monotherapy. The design and choice of study population for this Phase 2 clinical study is based on the need to provide initial safety, tolerability, PK, and efficacy outcomes of the investigational product for future clinical studies.

4 Patient Selection and Withdrawal Criteria

4.1 Selection of Study Population

Approximately 50 patients will be screened of which, approximately 35 patients will be enrolled to target at least 26 patients as study completers at the appropriate number of study sites in the United States and Republic of Korea. At least 7 of the patients enrolled must be between 6 months through 12 months of age at the time of informed consent. Patients will be assigned to study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or patient safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.1.1 Inclusion Criteria

Each patient must meet all the following criteria to be enrolled in this study:

1. Parent(s)/caregiver(s) fully comprehend and sign the ICF in accordance with applicable laws, regulations, and local requirements, understand all study procedures, and can communicate satisfactorily with the investigator and study coordinator.
2. Is a male or female from 6 months through 36 months of age at the time of informed consent.
3. Has clinical diagnosis of IS, confirmed by video-EEG analysis, and hypsarrhythmia on EEG at screening according to the Burden of Amplitudes and Epileptiform Discharges (BASED) scale score.
4. As assessed by the investigator, has no or partial response to at least 2 out of the 3 therapies of ACTH, vigabatrin, and glucocorticoids (i.e. prednisolone), or has no or partial response to at least 1 out of the 3 therapies of ACTH, vigabatrin, and glucocorticoids and is contraindicated to and/or refused by the patient’s legal representative(s) for treatment with 1 or both other 2 therapies.

5. Has general good health (defined as the absence of any clinically relevant abnormalities as determined by the investigator) based on physical and neurological examinations, medical history, normal renal function, and ECG, and clinical laboratory values completed during the Screening Period visit (Visit 1).
6. Parent(s)/caregiver(s) is willing and able to comply with the study procedures and visit schedules in the opinion of the investigator.

4.1.2 Exclusion Criteria

Patient meeting any of the following criteria will be excluded from the study:

1. Is considered by the investigator, for any reason (including, but not limited to, the risks described as precautions and warnings in the current version of the investigator's brochure for the investigational product) to be an unsuitable candidate to receive the investigational product.
2. Has known or suspected allergy to the investigational product.
3. Has known or suspected allergy to apple juice.
4. Has clinically significant renal impairment, defined as creatinine >1.5 mg/dL or blood urea nitrogen (BUN) >2 × upper limit of normal (ULN).
5. Has clinically significant liver dysfunction, defined as total bilirubin ≥2 × ULN, or aspartate aminotransferase or alanine aminotransferase ≥3 × ULN.
6. Has clinically significant abnormal laboratory values; the investigator may deem the patient eligible if he/she judges the laboratory values to be not clinically significant.
7. Has an ongoing or known history of human immunodeficiency virus infection, or chronic hepatitis B or C.
8. Has a clinically significant abnormality on ECG that, in the opinion of the investigator, increases the safety risks of participating in the study.
9. Has a neurodegenerative disorder as the underlying cause of IS.
10. Has a known history of aspiration pneumonia within the past year.
11. Has previously participated in another clinical study of the investigational product or received any investigational drug or device or investigational therapy within 30 days of study entry.

12. Has received therapy with felbamate, cannabinoids, ketogenic diet or vagus nerve stimulation within 14 days of screening.
13. Has received therapy with a medication known to be a CYP3A4 substrate and whose PK has been shown to be impacted in the presence of a CYP3A4 inhibitor within 14 days of screening (see Appendix 13.3 for a non-exhaustive list of CYP3A4 substrates).
14. Has not remained at stables doses of all drugs used for treating epileptic seizures for at least 14 days prior to screening (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 [see Appendix 13.3 for a non-exhaustive list of CYP3A4 substrates]).
15. Has a lethal or potentially lethal condition other than infantile spasms, with a significant risk of death before 18 months of age such as non-ketotic hyperglycinemia.
16. Has an underlying metabolic disease associated with glucose intolerance (e.g., glucose transporter deficiencies).
17. Has a body weight below 5 kg.

4.2 Withdrawal of Patients From the Study

4.2.1 Reasons for Withdrawal/Discontinuation

Patients may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. Every effort should be made to keep patients in the study. The reasons for patients not completing the study will be recorded. Reasons for patients being withdrawn from the study may include:

- The patient does not meet the protocol inclusion or exclusion criteria.
- The patient's safety or welfare is at risk.
- The patient is noncompliant with the protocol, defined as failure to perform any portion of scheduled assessments or procedures.
- The patient has serious or intolerable AEs that, in the investigator's opinion, require withdrawal from the study.

- The patient is lost to follow-up.
- The patient's legal representative (parent(s)/caregiver(s)) withdraws consent or the investigator or sponsor decides to discontinue the patient's participation in the study.

The investigator will also withdraw a patient if Bio-Pharm Solutions Co., Ltd. terminates the study. Upon occurrence of a serious or intolerable AE, the investigator will confer with the sponsor. If a patient is discontinued because of an AE, the event will be followed until it is resolved. The patient's legal representative (parent[s]/caregiver[s]) may withdraw his or her consent at any time.

4.2.2 Handling of Withdrawals

Patients are free to withdraw from the study or study treatment at any time upon request. Patient participation in the study may be stopped at any time at the discretion of the investigator or at the request of the sponsor.

At the discretion of the investigator, patients who withdraw from the study prematurely may receive tapered doses of investigational product before discontinuing. The tapering schedule for early withdrawal patients will be determined on a case-by-case basis and the medical monitor will be available for assistance if needed. When a patient withdraws from the study treatment or active participation in the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the electronic case report form (eCRF).

If a patient discontinues the study prematurely, investigator's assessment of efficacy and tolerability of the investigational product will be recorded on Visit 6 (± 5 days).

Whenever possible, all patients who discontinue study treatment or withdraw from the study prematurely will undergo all end-of-study (Visit 6) assessments. Patients who fail to undergo final assessments will be contacted by the study site in an attempt to have them comply with the protocol. Following a minimum of 2 documented unsuccessful telephone calls, a registered letter will be sent to the patient in a final attempt to ensure protocol compliance.

It is vital to obtain follow-up data on any patient withdrawn because of an AE or SAE. In every case, efforts must be made to undertake protocol-specified safety follow-up procedures.

4.2.3 Replacements

A total of 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. Patient screening and enrollment will be closed after 35 patients have begun Treatment Period 1. Patients who discontinue the study for any reason after dosing will not be replaced.

5 Study Treatments

5.1 Treatments Administered

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.

5.2 Identity of Investigational Product

The investigational product is a white to off-white powder. The dosage form received at each clinical study site is a glass bottle containing a nominal quantity of 100 mg of the powder JBPOS0101 active pharmaceutical ingredient (API) for reconstitution into an oral solution. Each JBPOS0101 API powder-in-glass bottle received at the clinical study site is individually enclosed in a heat-sealed aluminum foil pouch.

At the clinical study site, a pharmacist or authorized study personnel will dispense the JBPOS0101 API powder-in-glass bottle to the patient's caregiver without the heat-sealed aluminum foil pouch enclosure. Before dispensing, the pharmacist or authorized study personnel will adjust the content of the JBPOS0101 API powder-in-glass bottle to reflect the proper dose to be administered to the patient; the proper dose will be based on bodyweight and will be determined by the investigator. For the subsequent administration of the clinical material that will be performed by the patient's caregiver not at the clinical study site, the caregiver will be dispensed the customized doses of JBPOS0101 API powder-in-glass bottle in bulk packaging and will also be supplied with apple juice, an oral syringe and instructions for preparation of the solution for oral dosing. Other alternative dosing administration methods of the JBPOS0101 API powder-in-glass bottle may be permitted on a case-by-case basis with the approval of the sponsor and medical monitor.

The JBPOS0101 API powder-in-glass bottle is to be mixed with room temperature apple juice using the oral syringe supplied with the investigational product [redacted]

[redacted]

Patients will be dosed the full amount of solution using the oral syringe. Patients may also be dosed the solution via gastrostomy or nasogastric tube. Each individual dose should be prepared and used immediately. Any unused apple juice remaining in the individual packages of apple juice after making the oral solution is to be discarded. Any used or unused JBPOS0101 API powder-in-glass bottle is to be returned to the study site for reconciliation.

5.3 Management of Clinical Supplies

5.3.1 Investigational Product Packaging and Storage

Investigational product API powder-in-glass bottles will be prepared in boxes, stored and shipped by Bio-Pharm Solutions' designee. There will be no randomization scheme and the medication will be dispensed at the study site by a pharmacist or authorized study personnel.

The JBPOS0101 API powder-in-glass bottle, and JBPOS0101 API powder-in-glass bottle enclosed in the heat-sealed aluminum foil pouch, should be tightly capped and stored at room temperature (15°C – 30°C), protected from moisture and direct sunlight. The apple juice provided by the study sites should be stored at room temperature. Adequate care should be taken when handling the dosage form to avoid breakage of the glassware.

The sponsor's designee will ship adequate supplies of the investigational product to the study sites.

5.3.2 Investigational Product Accountability

The investigator will maintain accurate records of receipt of all investigational product, including dates of receipt. In addition, the investigator must be able to account for all opened and unopened investigational product and accurate records will be kept regarding when and how many bottles of investigational product is dispensed and used by each patient, returned from each patient (if applicable), and disposed of at the site or returned to the sponsor or designee. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all investigational product will be reconciled and retained or destroyed according to applicable regulations. All accountability records must be made available for

inspection by the sponsor and regulatory agency inspectors; copies must be provided to the sponsor at the conclusion of the study.

5.4 Overdose Management

An overdose is any dose of investigational product given to a patient that exceeds the dose described in the protocol. Any overdose, with or without associated AEs, must be promptly reported to the Sponsor Drug Safety Center. Overdoses without signs or symptoms do not need to be recorded as AEs; in case of any AEs associated with the overdose, these should be reported on relevant AE/SAE sections in the eCRF.

5.4.1 Treatment of Overdose

There is no known antidote for JBPOS0101. In case of suspected overdose, patients should be treated per standard medical practice based on the investigator's judgement. Dose delays and reductions may be implemented as necessary. Patients will be withdrawn from the study if persistent or unacceptable treatment-related toxicity is observed.

5.5 Blinding

This is an open-label study.

5.6 Treatment 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 eCRF.

5.7 Prior and Concomitant Medication

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 (see Appendix 13.3 for a non-exhaustive list of CYP3A4 substrates) 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. Except for drugs known to be CYP3A4 substrates and whose PK has been shown to be impacted in the presence of a CYP3A4 inhibitor, concomitant medications for treating non-epileptic seizure disorders are acceptable but changes in dose(s) are discouraged. 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.

All medications taken by patients after the Screening Period visit until the completion of the final Follow-Up visit will be documented as concomitant medications (medication, dose, treatment duration, and indication). The reported medications will be reviewed and evaluated by the investigator to determine if they will affect a patient’s eligibility to participate or continue to participate in the study.

6 Study Assessments and Procedures

Before performing any study procedures, all legal representatives (parent[s]/caregiver[s]) of potential patients will sign an ICF. Patient's legal representative (parent[s]/caregiver[s]) will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the patient's legal representative (parent[s]/caregiver[s]). The investigator or designee will also sign the ICF.

Study visits and timing of assessments and procedures are presented in the schedule of events (SOE; Appendix 13.1).

6.1 Safety and Tolerability Assessments

Safety variables will include physical and neurological examination findings, vital sign measurements (blood pressure, pulse, and respiratory rate), height, weight, BMI, ECG tracings, clinical laboratory test results (hematology, serum chemistry, and urinalysis), and reporting of AEs.

Safety assessments will be conducted as shown in the SOE (Appendix 13.1).

6.1.1 Physical and Neurological Examination

A complete physical examination will be performed at the time points indicated in the SOE (Appendix 13.1). 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 be performed at the time points indicated in the SOE (Appendix 13.1). 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.

6.1.2 Vital Sign Measurements, 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 the time points indicated in the SOE (Appendix 13.1).

Height, weight, and BMI will be measured at each clinic visit.

The investigator will determine whether any of the vital sign measurements 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 values is noted, the clinically significant value and reason for clinical significance will be documented on the AE page of the patient's 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.

6.1.3 Electrocardiograms

Single 12-lead ECGs will be obtained at the time points indicated in the SOE (Appendix 13.1). Electrocardiogram 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. In addition, measurements of the following intervals will be measured and reported: RR interval, PR interval, QRS width, QT interval, and QTcF.

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. The investigator will continue to monitor the patient with additional assessments until either 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.

6.1.4 Clinical Laboratory Tests

Blood and urine samples will be collected at the time points indicated in the SOE (Appendix 13.1). Hematology, coagulation and serum chemistry assessments will be

performed by the sponsor's central laboratory; urinalysis assessment will be performed locally.

The following hematology, coagulation, serum chemistry, and urinalysis assessments will be performed:

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).

6.1.5 Adverse Events

6.1.5.1 Definitions of Adverse Events

The investigator is responsible for reporting all TEAEs that are observed or reported during the study, regardless of their relationship to the investigational product or their clinical significance.

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.

6.1.5.2 Serious Adverse Events

An SAE is defined as any event that results in death, is immediately life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or doubling of seizure frequency compared to baseline over a period of 7 days or longer.

6.1.5.3 Eliciting and Documenting Adverse Events

Adverse events will be assessed from the time the patient's legal representative (parent[s]/caregiver[s]) signs the ICF until and including the Follow-Up visit, 14 days after the last dose of the investigational product.

Serious AEs that occur more than 14 days after the last dose of the investigational product need not be reported unless the investigator considers them related to the investigational product.

At every study visit, the patient's legal representative (parent[s]/caregiver[s]) will be asked a standard nonleading question to elicit any medically-related changes in the patient's well-being. They will also be asked if the patient has been hospitalized, had any accidents, taken any new medications, or changed concomitant medication regimens (both prescription and OTC medications).

In addition to patient observations, AEs identified from any study data (e.g., laboratory values, physical examination findings, and ECG changes) or identified from review of other documents (e.g., seizure diaries) that are relevant to patient safety will be documented on the AE page in the eCRF.

6.1.5.4 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF. Information to be collected includes drug treatment, dose, event term, time of onset, investigator-specified assessment of severity and relationship to the investigational product, time of resolution of the event, seriousness, any required treatment or evaluations, and outcome. Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the patient is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

6.1.5.5 Reporting Serious Adverse Events

Any AE that meets SAE criteria (Section 6.1.5.2) must be reported to Bio-Pharm Solutions Co., Ltd., immediately (i.e., within 24 hours) after the time that the study site personnel first learns about the event. The following contact information is to be used for SAE reporting:

ICON Pharmacovigilance and Safety Services

[redacted]

[redacted]

6.1.5.6 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the patient's daily activities. The intensity of the AE will be rated as mild, moderate, or severe using the following criteria:

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.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of the onset and duration of each episode.

6.1.5.7 Assessment of Causality

The investigator's assessment of an AE's relationship to the investigational product is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the investigational product in causing or contributing to the AE will be characterized using the following classification and criteria:

Unrelated:	This relationship suggests that there is no association between the investigational product and the reported event.
Possible:	This relationship suggests that treatment with the investigational product caused or contributed to the AE, i.e., the event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the investigational product but could also have been produced by other factors.
Probable:	This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the investigational product seems likely. The event disappears or decreases on cessation or reduction of the dose of investigational product.
Definite:	This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the investigational product is re-administered.

6.1.5.8 Follow-up of Patients Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and followed to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant, or until the patient is considered to be stable.

6.2 Pharmacokinetic Assessments

6.2.1 Pharmacokinetic Blood and Urine Samples

Blood for the analysis of the investigational product in plasma will be collected on Day 1 (Visit 2) and Day 21 (Visit 4 [± 2 days]) at the time points/intervals described in Table 13–2. Collections can be performed at any time during the collection intervals. The PK blood sampling scheme may be modified on a case-by-case 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). 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]). Pharmacokinetic blood and urine samples may be used for future exploratory purposes outside of this study.

6.2.2 Pharmacokinetic Parameters

Population PK analysis will be performed to calculate plasma PK parameters for the investigational product. The primary plasma PK parameters for the investigational product will include the AUC, minimum plasma concentration (C_{min}), and C_{max}. Other PK parameters may be calculated, as appropriate. Details regarding population PK analysis and PK parameters will be found in the statistical analysis plan (SAP) or Population PK modeling plan.

6.3 Exploratory Efficacy Assessments

Efficacy assessments will be performed as presented in the SOE (Appendix 13.1).

6.3.1 Electroencephalogram

A 16-hour overnight video-EEG will be performed to look for changes from baseline, [redacted] (Table 13–1). The 16-hour video-EEG will be conducted according to the current American Clinical Neurophysiology Society guidelines 1, 2, 4 and 5. The international 10/20 system (using all 21 electrodes) will be utilized for this study. Less than 21 electrodes may be used only in cases that there is clinical justification to do so (e.g. the presence of a scalp wound). [redacted]

6.3.2 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 will be assessed by the investigator as presented in the SOE (Appendix 13.1). 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]

6.3.3 Clinical Global Impression of Change

The CGI-C assessment will be performed by the investigator as presented in the SOE (Appendix 13.1). Additionally, the patient's legal representative (parent[s]/caregiver[s]) will perform the CGI-C assessment at each visit. 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." The following 7-point scale (Spearing et al 1997) will be used to evaluate the patient's condition after initiating the medication:

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

6.4 Safety Monitoring Committee

An unblinded, independent Data Safety Monitoring Board (DSMB) will be established to provide an ongoing, independent review and assessment of safety data, to safeguard the interests and safety of the patients participating in the study.

After 5 patients have completed Treatment Period 1, patient screening and enrollment will be halted and available safety data will be reviewed and assessed by the DSMB. Patient screening and enrollment can continue again following the DSMB's review and assessment of the safety data.

The frequency of DSMB data review meetings will be based on patient accruals. The first DSMB data review meeting will be held after 5 patients have completed Treatment Period 1. The second DSMB data review meeting will be held after 5 additional patients have completed Treatment Period 1 (after a total of 10 patients have completed Treatment Period 1). The third DSMB data review meeting will be held after 10 additional patients have completed Treatment Period 1 (after a total of 20 patients have completed Treatment Period 1), and the fourth DSMB data review meeting will be held after 10 additional patients have completed Treatment Period 1 (after a total of 30 patients have completed Treatment Period 1).

The committee may request additional meetings if it is deemed appropriate based on trends identified within the current data. The sponsor's designee will be responsible for scheduling this type of meeting.

The DSMB will adhere to a prospectively determined charter, which will be written by the sponsor and approved by the DSMB. The charter will define the responsibilities of the DSMB and sponsor, describe the conduct and frequency of the meetings and define the data sets to be reviewed. In addition, a special DSMB meeting will be convened if the safety-related study stopping rules are met and all serious TEAEs, TEAEs leading to investigational product discontinuation, and TEAEs leading to death will be reviewed.

6.5 Sample Collections

Blood and urine samples will be collected at the time points indicated in the SOE (Appendix 13.1). Blood and urine samples will be collected for PK assessment for the investigational product as described in Section 6.2.1.

6.6 Unscheduled Visits

All attempts should be made to keep the patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

7 Statistical and Analytical Plan

A detailed SAP will be created and finalized prior to the database lock. The SAP will provide a detailed description of the statistical methods and expand on the summary provided in the protocol. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed as deemed appropriate and included in the SAP.

7.1 Primary Safety Endpoints

The safety endpoints are the incidence of TEAEs, vital sign measurements, physical and neurological examination findings, 12-Lead ECG findings, and clinical laboratory test results.

7.2 Pharmacokinetic Endpoints

- Primary PK endpoints include plasma PK parameters: AUC, C_{min}, and C_{max} for the investigational product. Other PK parameters may be calculated, as appropriate.
- Relationship between plasma investigational product levels and response.

7.3 Exploratory Efficacy Endpoints

[redacted]

7.4 Sample Size Calculations

[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.

7.5 Analysis Sets

The following analysis sets will be used in the statistical analyses.

Safety analysis set: The safety analysis set will include all patients who were treated with at least one dose of the investigational product. The safety analysis set will be used for all safety assessments.

Efficacy analysis set (EAS): The efficacy analysis set 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.

Pharmacokinetic (PK) analysis set: The PK analysis set 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 analysis set will be used for all PK assessments.

Modified efficacy analysis set (mEAS): To evaluate the influence of COVID-19 on the efficacy results, a modified EAS will be considered which, in addition to the original EAS, 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 in the EAS will also be performed for the mEAS. 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.

Other additional listings due to COVID-19 may be described in the SAP.

The major protocol deviations leading to exclusion from the EAS and PK analysis set will be specified in the SAP and finalized prior to the database lock.

7.6 Description of Subgroups to Be Analyzed

Details will be provided in the SAP for any proposed subgroup analyses.

7.7 Statistical Analysis Methodology

Summary statistics will be provided for all study endpoints. For continuous endpoints, the number of patients included, mean, standard deviation (SD), median, minimum, maximum, Quartile 1 (Q1), and Quartile 3 (Q3) will be provided. For categorical endpoints, the number and frequency in each category will be provided. Time to event endpoints will be summarized using median, 25%, and 75% percentiles. Statistical analysis system v9.3 (or higher) will be used throughout.

Further details of the statistical analyses, methods, and data conventions are described in the SAP.

No formal significance testing will be performed.

7.7.1 Analysis of Primary Safety Endpoint

Investigational Product Administration and Exposure: Investigational product administration and exposure will be summarized and listed. Further details on the investigational product administration and exposure calculation will be given in the SAP.

Medical History: Medical history details recorded at screening will be summarized and listed according to the coded MedDRA (latest version) by system organ class (SOC) and preferred term (PT).

Prior and Concomitant Medications: Prior and concomitant medications will be summarized according to the World Health Organization Drug Dictionary (WHODrug). The number and percentage of patients will be presented for previous and concomitant medications.

Adverse Events: AEs will be coded according to the coded MedDRA (latest version). Treatment-emergent AEs will be tabulated by SOC and PT. The following summary tables will be produced:

- 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 AEs recorded during the study (including non-treatment-emergent AEs) will be listed.

Physical and Neurological Examination: Descriptive summaries of change in examination findings from baseline to post-baseline visits will be presented by test in a shift table (normal, abnormal [not clinically significant], and abnormal [clinically significant]).

Vital Signs: Descriptive by-visit summaries of vital signs data will be presented (including raw values and change from baseline). Vital signs will include blood pressures, temperature, pulse rate, and respiratory rate.

Height, Weight, and BMI: Baseline height, weight, and BMI will be summarized and listed.

ECGs: Descriptive summaries of change in overall assessment from baseline to post-baseline visits will be presented in a shift table (normal, abnormal [not clinically significant], and abnormal [clinically significant]). In addition, descriptive by-visit summaries of ECG data will be presented (including raw values and change from baseline). ECG data will include all of the following intervals: RR interval, PR interval, QRS width, QT interval, and QT interval from Fridericia's formula (QTcF).

Laboratory Safety Tests: Hematology, coagulation, serum chemistry, and urinalysis safety tests will be summarized by visit. Post-baseline visits will include change from baseline.

7.7.2 Pharmacokinetic Analyses

Pharmacokinetic analyses will be based on the PK analysis set.

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 will be performed to calculate plasma PK parameters for the investigational product. Plasma PK

parameters for the investigational product will be listed and presented in a summary table, as data allow.

7.7.3 Analysis of Exploratory Efficacy Endpoints

[redacted]

Descriptive analysis by-visit summaries of CGI-C assessment will be provided. Description of the CGI-C assessment is documented in the study reference manual.

7.7.4 Interim Analyses

No interim analyses are planned.

8 Data Quality Assurance

Actions to ensure the accuracy and reliability of data will include the selection of qualified investigators and appropriate study centers; the review of protocol procedures with the investigator and associated study personnel prior to study start; the design of suitable source documents with appropriate instructions for use; the internal audit of source data according to Good Clinical Practice (GCP) and internal procedures to ensure their accuracy, completeness, and verifiability; as well as periodic study site monitoring by the sponsor. Written instructions will be provided for collection, preparation, and shipment of blood, plasma, and urine samples.

The sponsor or its designee will review source documents for accuracy and completeness during on-site monitoring visits and after their return to the sponsor; any discrepancy will be resolved with the investigator or designee, as appropriate. The sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, and reliability of the study data presented to the sponsor lies with the investigator generating the data. The data will be recorded into the clinical study database and verified for accuracy using the study-specific data verification plan.

8.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include seizure diary, laboratory reports, ECG strips, etc.

Study site personnel will enter patient data into an electronic data capture system. The analysis data sets will be a combination of these data and data from other sources (e.g., laboratory data).

Clinical data management will be performed in accordance with applicable sponsor name standards and data cleaning procedures to ensure the integrity of the data (e.g., removing errors and inconsistencies in the data). Adverse event terms will be coded using MedDRA, an

internal validated medical dictionary, and concomitant medications will be coded using WHODrug.

After database lock, each study site will receive a CD-ROM containing all of their site-specific eCRF data as entered into Oracle Clinical Remote Data Capture for the study, including full discrepancy and audit history. Additionally, a CD-ROM copy of all of the study site's data from the study will be created and sent to the sponsor for storage. Sponsor will maintain a duplicate CD-ROM copy for their records. In all cases, patient initials will not be collected or transmitted to the sponsor.

9 Ethics

9.1 Institutional Review Board

Federal regulations and the International Council for Harmonisation (ICH) guidelines require that approval be obtained from an institutional review board (IRB) before participation of human patients in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study patients, and any other written information regarding this study to be provided to the patient's legal representative must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with ICH harmonised tripartite guideline E6(R2): GCP will be maintained by the study site and will be available for review by the sponsor or its designee.

All IRB approvals should be signed by the IRB chairman or designee and must identify the IRB name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB. The investigator must promptly supply the sponsor or its designee, the IRB, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to patients.

9.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH, GCP, the protocol, and all applicable regulations.

9.3 Patient Information and Consent

A written informed consent in compliance with US Title 21 Code of Federal Regulations (CFR) Part 50 shall be obtained from each patient's legal representative (parent[s]/caregiver[s]) before entering the study or performing any unusual or nonroutine procedure that involves risk to the patient. An ICF template may be provided by the sponsor to study sites. If any institution-specific modifications to study-related procedures are proposed or made by the study site, the consent should be reviewed by the sponsor or its designee or both before IRB submission. Once reviewed, the consent will be submitted by

the investigator to his or her IRB for review and approval before the start of the study. If the ICF is revised during the study, all patient's legal representatives (parent[s]/caregiver[s]) must sign the revised form.

Before recruitment and enrollment, each prospective patient's legal representative (parent[s]/caregiver[s]) will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the patient's legal representative (parent[s]/caregiver[s]) understands the implications of participating in the study, the patient's legal representative (parent[s]/caregiver[s]) will be asked to give consent on behalf of the patient to participate in the study by signing the ICF.

The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the patient's legal representative (parent[s]/caregiver[s]).

10 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB but will not result in protocol amendments.

10.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of patient's legal representative (parent[s]/caregiver[s]), except as necessary for monitoring and auditing by the sponsor, its designee, the US FDA, or the IRB.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

The sponsor is not financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, the sponsor is not financially responsible for further treatment of the patient's disease.

10.3 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the CFR by providing essential documents, including but not limited to the following:

- IRB approval.
- Original investigator-signed investigator agreement page of the protocol.
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572.
- Curriculum vitae for the investigator and each subinvestigator listed on Form FDA 1572.
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IRB-approved ICF, samples of study site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the legal representative (parent[s]/caregiver[s]).
- Laboratory certifications and normal ranges for any local laboratories used by the study site, in accordance with 42 CFR 493.

10.4 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of patients begins.

10.5 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

10.6 Adverse Events and Study Report Requirements

By participating in this study, the investigator agrees to submit reports of SAEs to the sponsor and/or IRB according to the timeline and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB as appropriate.

10.7 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

10.8 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10.9 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor.

11 Study Management

11.1 Monitoring

11.1.1 External Data Monitoring Committee

An unblinded, independent DSMB will periodically review safety data. The frequency of data review and DSMB processes are outlined in the DSMB charter. The charter will define the responsibilities of the DSMB and sponsor, describe the conduct and frequency of the meetings, and define the data sets to be reviewed.

11.1.2 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and personnel.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

11.1.3 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency (e.g., FDA) access to all study records.

The investigator should promptly notify the sponsor of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

11.2 Management of Protocol Amendments and Deviations

11.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent immediate hazard to the patient, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the Investigator's IRB for approval before patients can be enrolled into an amended protocol.

11.2.2 Protocol Deviations

The investigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study patients without prior IRB approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the patient or investigator that results in a significant additional risk to the patient. Significant deviations can include nonadherence to inclusion or exclusion criteria or nonadherence to FDA regulations or ICH GCP guidelines and will lead to the patient being withdrawn from the study (Section 4.2).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal investigators will be notified in writing by the monitor of deviations. The IRB should be notified of all protocol deviations in a timely manner.

11.3 Study Termination

Although Bio-Pharm Solutions Co., Ltd. has every intention of completing the study, Bio-Pharm Solutions Co., Ltd. reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last patient completes the last visit (includes the Follow-Up Visit).

11.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agency as required by the applicable regulatory requirements. The sponsor will also ensure that the clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study report, the sponsor will provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the patient’s legal representative, as appropriate. The study results will be posted on publicly available clinical trial registers.

12 Reference List

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13 Appendices

13.1 Appendix: Schedule of Events

Table 13–1 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 -28 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. The seizure diaries will indicate whether spasms are still present. [redacted].
k. Details regarding PK blood sampling are provided in Table 13–2.
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.

13.2 Appendix: Pharmacokinetic Sampling

Table 13–2 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 • 4-6 hours post-AM dose • 8 hours post-AM dose time point and pre-PM dose
4[b]	21	• 0.5-1.5 hours post-AM dose • 4-6 hours post-AM dose • 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.

13.3 Appendix: List of Excluded Medications

- alfentanil
- alprazolam
- amlodipine
- aprepitant
- aripiprazole
- astemizole
- atorvastatin
- avanafil
- boceprevir
- budesonide
- buspirone
- carbamazepine
- cafergot
- cerivastatin
- chlorpheniramine
- cilostazol
- cisapride
- clarithromycin
- codeine-N-demethylation
- colchicine
- conivaptan
- cyclosporine
- dapsone

- darifenacin
- darunavir
- dasatinib
- dexamethasone
- dextromethorphan
- diazepam
- diltiazem
- docetaxel
- domperidone
- dronedarone
- ebastine
- eletriptan
- eliglustat
- eplerenone
- erythromycin
- estradiol
- everolimus
- felodipine
- fentanyl
- finasteride
- gleevec
- haloperidol
- hydrocortisone
- ibrutinib
- indinavir

- irinotecan
- lercanidipine
- levo-α-acetylmethadol
- lidocaine
- lomitapide
- lovastatin
- lurasidone
- maraviroc
- methadone
- midazolam
- naloxegol
- nateglinide
- nelfinavir
- nevirapine
- nifedipine
- nisoldipine
- nitrendipine
- ondansetron
- pimozide
- prednisolone
- prednisone
- progesterone
- propranolol
- quetiapine
- quinidine

- quinine
- rilpivirine
- risperidone
- ritonavir
- rivaroxaban
- romidepsin
- salmeterol
- saquinavir
- sildenafil
- simvastatin
- sirolimus
- sorafenib
- sunitinib
- tacrolimus
- tadalafil
- tamoxifen
- taxol
- telaprevir
- telithromycin
- terfenadine
- testosterone
- ticagrelor
- tipranavir
- tolvaptan
- torisel

- trazodone
- triazolam
- vardenafil
- vemurafenib
- verapamil
- vincristine
- zaleplon
- ziprasidone
- zolpidem

13.4 Appendix: Summary of Changes to Protocol CL-0101-WS01

SUMMARY OF CHANGES OF PROTOCOL CL-0101-WS01 2.0

PRODUCT: JBPOS0101

Revision: **2.0**

Date of Revision: **September 15, 2020**

This Version Replaces Revision: **1.3 (April 9, 2020)**

13.4.1 Regulatory History and Overview

This revision is effective on 15 September 2020, and will be submitted to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and Regulatory Authorities.

Table 13-3: Summary of Protocol CL-0101-WS01 Revision History

[redacted] **Version and Date**	**Reason for Revision**
Revision 1.0 March 1, 2019	Initial protocol to support Phase 2 study entitled: *A Phase 2 Study to Assess the Safety, Tolerability, Exploratory Efficacy, and Pharmacokinetics of Orally Administered JBPOS0101 for Refractory Infantile Spasms Patients* (Protocol Number CL-0101-WS01).
Revision 1.1 May 15, 2019	[redacted]
Revision 1.2 September 19, 2019	[redacted]
Revision 1.3 April 9, 2020	[redacted]
Revision 2.0 September 15, 2020	[redacted]

13.4.2 Summary of Changes

The following changes have been made to the protocol entitled *A Phase 2 Study to Assess the Safety, Tolerability, Exploratory Efficacy, and Pharmacokinetics of Orally Administered JBPOS0101 for Refractory Infantile Spasms Patients* (Protocol Number CL-0101-WS01), Revision 1.3, dated 9 April 2020:

Protocol Section	Description of Change
General	• Version and date updated throughout the document from Version 1.3, 9 April 2020 to Version 2.0, 15 September 2020
Protocol Synopsis	[redacted]
List of Abbreviations	• [redacted]
3.1 Study Design	[redacted]
4.1.1 Inclusion Criteria	[redacted]
4.1.2 Exclusion Criteria	[redacted]

Protocol Section	Description of Change
5.3.1 Investigational Product Packaging and Storage	[redacted]
6.2.1 Pharmacokinetic Blood and Urine Samples	[redacted]
6.4 Safety Monitoring Committee	[redacted]
7.4 Sample Size Calculations	[redacted]
7.5 Analysis Sets	[redacted]
13.1 Appendix: Schedule of Events	[redacted]