Title: A PHASE 2, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF TAK-935 (OV935) AS AN ADJUNCTIVE THERAPY IN PEDIATRIC PATIENTS WITH DEVELOPMENTAL AND/OR EPILEPTIC ENCEPHALOPATHIES (ELEKTRA)

NCT Number: NCT03650452

Protocol Approve Date: 14 February 2019

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This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

PROTOCOL TAK-935-2002 (OV935)

A PHASE 2, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF TAK-935 (OV935) AS AN ADJUNCTIVE THERAPY IN PEDIATRIC PATIENTS WITH DEVELOPMENTAL AND/OR EPILEPTIC ENCEPHALOPATHIES (ELEKTRA)

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Date of Amendment 2: 14 February 2019
Date of Amendment 1: 23 April 2018
Date of Original Protocol: 16 February 2018

SPONSOR SIGNATURE PAGE

PROTOCOL TITLE: A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-935 (OV935) as an Adjunctive Therapy in Pediatric Patients with Developmental and/or Epileptic Encephalopathies (ELEKTRA)

PROTOCOL NUMBER: TAK-935-2002 (OV935) Amendment 2

PPD

02/13/2019

Date

PROTOCOL AMENDMENT 2 SUMMARY OF CHANGES

Rationale for Amendment 2

This document describes the changes in reference to the protocol incorporating Amendment No. 2. The primary reasons for this amendment are to update the study design (adding 6 weeks to the treatment duration), change the primary endpoint, change the secondary and exploratory endpoints, revise the inclusion criteria to clarify the use of benzodiazepines as antiepileptic drugs, and clarify the criteria regarding the diagnosis of Dravet syndrome and Lennox-Gastaut syndrome.

Changes Implemented by Amendment 2:

In addition to the changes described above, the following changes were also implemented:

- Clarified that for all clinical studies across the TAK-935 program, the independent Data Monitoring Committee will review the AE profiles of 12 patients aged ≥9 years completing 4 weeks of treatment of TAK-935 in the TAK-935 program before opening enrollment to younger patients
- Added history of confirmed cataract (untreated with surgery) as an exclusion criterion
- Added perampanel as a prohibited medication
- Added 2 new forms of approved contraceptive methods
- Clarified that only sexually active female patients of childbearing potential will have pregnancy tests performed
- Clarified the duration for avoidance of pregnancy and donation of sperm and ova for male and female patients, respectively
- Revised the PK sampling time points

Administrative and minor grammatical, editorial, and formatting changes were made for clarification purposes only. A detailed description of and rationale for changes implemented by Amendment 2 are provided in Appendix 5.

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for TAK-935. I have read the TAK-935-2002 (OV935) Protocol Amendment 2, dated 11 February 2019, and agree to conduct the study in accordance with this protocol, all applicable government regulations, the principles of the ICH E6 Guidelines for Good Clinical Practice, and the principles of the World Medical Association Declaration of Helsinki. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

1. SYNOPSIS

Name of Sponsor/Company:

Ovid Therapeutics, Inc.

Name of Study drug:

TAK-935

Title of Study:

A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-935 (OV935) as an Adjunctive Therapy in Pediatric Patients with Developmental and/or Epileptic Encephalopathies (ELEKTRA)

Study Number: TAK-935-2002 (OV935)	**Phase:** 2

Study Design:

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, study in pediatric patients (aged ≥2 and ≤17 years) with Dravet syndrome and Lennox Gastaut syndrome (LGS) demonstrating ≥3 convulsive or ≥4 drop seizures, respectively, per month during the 3 months immediately prior to Screening (based on historical information) and ≥3 convulsive or ≥4 drop seizures, respectively, during a minimum of 4 weeks during the prospective Baseline Period (based on the seizure diary records). Convulsive seizures include generalized tonic-clonic, focal to bilateral tonic-clonic with impaired awareness, hemi-clonic, and simultaneous bilateral clonic (generalized clonic) seizures. Drop seizures are defined as involving the entire body, trunk, or head that leads to a fall, injury, slumping in a chair, or head hitting a surface, or that could have led to a fall or injury, depending on the position of the patient at the time of the seizure or spell. Examples of seizures causing drop include, but are not limited to, atonic, clonic, and tonic seizures.

Approximately 126 patients will be randomized to ensure 112 evaluable patients. Randomization will be stratified by 2 categories: patients with Dravet syndrome with convulsive seizures and patients with LGS with drop seizures. Stratification will be performed to ensure balance of treatments within each stratum.

The study will begin with a phased enrollment based on age. Patients aged ≥9 years will be enrolled first, prior to open enrollment in the study, for assessment of safety. The independent Data Monitoring Committee (iDMC) will review the adverse event (AE) profiles of the first 12 patients aged ≥9 years completing 4 weeks of treatment across all ongoing pediatric TAK-935 studies, prior to recommending treatment for patients aged <9 years.

Study Periods:

This study consists of 2 main periods:

- 4- to 6-week Screening/Baseline Period
- 20-week Treatment Period
  - 8-week Dose Optimization Period
  - 12-week Maintenance Period

The Treatment Period consists of the Dose Optimization Period and Maintenance Period.

Dravet syndrome patients who have had on average ≥3 convulsive or LGS patients who have had on average ≥4 drop seizures per month during the 3 months immediately prior to Screening (based on the historical information) and ≥3 convulsive or ≥4 drop seizures, respectively, during a minimum of 4 weeks during the Baseline Period (based on the seizure diary records) will be eligible for entry into the study.

At the end of the 4-week Baseline Period, patients will return to the clinic (Visit 2). Seizure diaries will be reviewed by the Medical Monitor or delegated staff and if a patient did not meet the eligibility criteria, including minimum number of seizures required for the study, the patient will be discontinued from the study and considered a screen failure.

The patients who meet the entry criteria will be randomized in a 1:1 ratio to double-blind treatment with TAK-935 or matching placebo for the 20-week Treatment Period (8-week Dose Optimization Period and 12-week Maintenance Period).

Dosing and Titration Schedule

All patients will receive TAK-935 twice a day (BID) orally or via gastrostomy tube (G-tube)/ percutaneous endoscopic gastrostomy (PEG) tube with or without food (patients enrolled in clinical sites in China are not to receive study drug via G-tube/PEG tube).

For patients weighing <60 kg, the total daily dose of study drug (either placebo or TAK-935) is calculated based on body weight at Visit 1 and will be given BID (Table 1). The selected doses for the different weight groups are listed in Table 1. For patients weighing ≥60 kg at Visit 1, dosing will be 200 mg/day followed by 400 mg/day, then 600 mg/day (Table 1). Study drug can be taken with or without food. For patients aged ≥9 years at Visit 1, the total daily dose of study drug (either placebo or TAK-935) is calculated based on body weight at Visit 1 and will be given BID. Patients will receive the initial dose of study drug, Dose 1, for the first 7 days after randomization on Visit 2. In the subsequent phone call and visit (phone call 1 [Day 8] and Visit 3 [Day 15]), the study drug dose will be increased to Dose 2 and Dose 3. The maximum dose for any patient will be 600 mg/day (300 mg BID). Patients will be contacted by phone within the first 2 days following escalation to the maximum dose to assess safety and tolerability of the study drug. Study drug dose will be allowed to change in first 6 weeks of Dose Optimization Period, based on the judgment of the Investigator and with the approval of the Medical Monitor. The final dose level will be maintained until the end of the Maintenance Period; however, the dose may be decreased to the previous lower doses, for safety and tolerability issues. Patients who cannot tolerate Dose 1 will be withdrawn from the study (and will complete the early termination and safety follow-up visits).

Dosing Schedule by Weight:

Weight (kg)	Dose 1		Dose 2		Dose 3	
	(mg/day)[a]	No. Tablets/ Mini-tablets	(mg/day)[a]	No. Tablets/ Mini-tablets	(mg/day)[a]	No. Tablets/ Mini-tablets
10-14	80	0/4	160	0/8	220	0/11
15-19	120	0/6	200	0/10	260	0/13
20-24	120	0/6	240	0/12	320	0/16
25-29	120	0/6	240	0/12	360	0/18
30-34	160	0/8	280	0/14	400	0/20
35-39	160	0/8	280	0/14	440	0/22
40-44	160	0/8	320	0/16	480	0/24

45-49	200	0/10	360	0/18	480	0/24
50-54	200	0/10	360	0/18	520	0/26
55-59	200	0/10	360	0/18	560	0/28
≥60	200	2/0	400	4/0	600	6/0

[a] Total dose administered twice daily.

Pharmacokinetic Assessments:

Pharmacokinetic (PK) sample collection will start at Visit 2 (Day 1), and it is designed to investigate the PK in all patients. The first 12 randomized patients aged ≥9 years and the first 12 randomized patients aged <9 years will receive the first dose of TAK-935 or placebo in the clinic; PK blood draws will occur within 1 hour before the morning dose (pre-morning dose) and 30 min (±10 min) and 1, 2, and 4 hours (±10 min) post-morning dose. After Visit 2 (Day 1), additional PK samples will be collected within 1 hour before the morning dose (pre-morning dose) and 30 min (±10 min) post-morning dose at Visits 3, 4, 5, and 6 during the study.

The remaining randomized patients in the study will receive the first dose of TAK-935 or placebo in the clinic, with PK blood draws occurring within 1 hour before the morning dose (pre-morning dose) and 30 min (±10 min) post-morning dose at Visits 2, 3, 4, 5, and 6 during the study.

Concomitant and Prohibited Medications:

Adjunctive antiepileptic drug (AED) treatment, (medical) marijuana, cannabidiol products, vagal nerve stimulator (VNS) settings, and ketogenic diet should not be altered during the study. Concurrent treatment regimen data will be collected throughout the study.

Use of strong inducers and inhibitors of cytochrome P450 (CYP) 3A4 (prescription medications, OTC medications, or dietary supplements) within 30 days before randomization through follow-up is prohibited, except for AEDs (e.g., carbamazepine, phenobarbital, phenytoin). Refer to Appendix 4 for a list of prohibited CYP3A4 inducers and inhibitors.

Use of perampanel from screening through follow-up is prohibited.

Use of traditional Chinese medicines should be approved by the Medical Monitor at screening.

Following completion of the study, patients will have the option to enroll in a long-term (24-month), open-label extension study (under a separate protocol, TAK-935-18-001 [OV935]) or to enter a double-blind taper period (maximum 14 days). During the taper period, the study drug dose will be de-escalated to a lower dose (taper Dose 3 to Dose 2, taper Dose 2 to Dose 1) every 3 days or less frequently based on Investigator's discretion until there is no de-escalation and study drug dose is discontinued. After tapering, the patients will complete a Safety Follow-up visit approximately 15 days after the last dose of study drug and exit the study. The total study duration from Screening to the last visit in this study will be approximately 30 weeks.

An iDMC will monitor the patients' safety, in accordance with the iDMC charter.

Procedures:

Daily seizure diaries will be used to determine seizure frequency for the evaluation of efficacy.

Blood samples for clinical safety laboratory tests (5.7 mL at each sample time point), including hematology and chemistry, will be collected at Visit 1 (Screening), Visit 2 (Day 1), Visit 4 (Day 36), and at Visit 6 (Day 141). One blood sample will be collected (2 mL for PD assessment) at Visit 7 (Day 169), the follow-up visit. In addition, urinalysis will be performed at the specified visits.

Blood samples for PK analysis of TAK-935 and M-I will be drawn within 1 hour of the morning dose (pre-morning dose) and 30 min (±10 min) and 1, 2, and 4 hours (±10 min) post-morning dose for the first 12 patients aged ≥9 years and the first 12 patients aged <9 years. After Visit 2 (Day 1), additional PK samples will be collected within 1 hour before the morning dose (pre-morning dose) and 30 min (±10 min) post-morning dose at Visits 3, 4, 5, and 6 during the study from those patients. The remaining randomized patients in the study will receive the first dose of TAK-935 or placebo in the clinic, with PK blood draws occurring within 1 hour before the morning dose (pre-morning dose) and 30 min (±10 min) post-morning dose at Visits 2, 3, 4, 5, and 6 during the study.

The total blood volume collected during the study will be approximately 73.2 mL for patients. The maximum blood volume collected during a 30-day period will be 28.4 mL and maximum blood volume collected during a single visit will be 14.7 mL. The total blood volume limits are consistent with physiological minimal risk as specified by the WHO guidelines.[1]

Primary Objective:

To investigate the effect on the frequency of all seizures (convulsive and drop) in patients treated with TAK-935 as an adjunctive therapy compared to placebo in the Maintenance Period

Secondary Objectives:

- To investigate the effect on the frequency of all seizures (convulsive and drop) in patients treated with TAK-935 as an adjunctive therapy compared to placebo throughout the Treatment Period
- To investigate the effect on the frequency of convulsive seizure in patients with Dravet syndrome treated with TAK-935 as an adjunctive therapy compared to placebo in the Maintenance Period
- To investigate the effect on the frequency of drop seizure in patients with LGS treated with TAK-935 as an adjunctive therapy compared to placebo in the Maintenance Period
- To investigate the seizure frequency of LGS patients considered treatment responders throughout the Maintenance Period; treatment responders are defined as those with:
  - Worsening of 25% or more in drop seizures from baseline
  - Worsening of 1% to 25% in drop seizures from baseline
  - No change in drop seizures from baseline (Worsening of 1% to Reduction of 1%)
  - Reduction of 25% or more in drop seizures from baseline
  - Reduction of 50% or more in drop seizures from baseline
  - Reduction of 75% or more in drop seizures from baseline
  - Reduction of 100% in drop seizures from baseline
- To investigate the seizure frequency of Dravet patients considered treatment responders throughout the Maintenance Period; treatment responders are defined as those with:
  - Worsening of 25% or more in convulsive seizures from baseline
  - Worsening of 1% to 25% in convulsive seizures from baseline
  - No change in convulsive seizures from baseline (Worsening of 1% to Reduction of 1%)

- Reduction of 25% or more in convulsive seizures from baseline
- Reduction of 50% or more in convulsive seizures from baseline
- Reduction of 75% or more in convulsive seizures from baseline
- Reduction of 100% in convulsive seizures from baseline

- To investigate the change in Clinical Global Impression of Severity and Change assessment (CGI-S/C) responses of Investigator and Caregiver Clinical Global Impression of Change assessment (Care GI-C) in patients treated with TAK-935 as an adjunctive therapy compared to placebo
- To characterize the relationship between plasma 24S-hydroxycholesterol (24HC) levels and seizure frequency

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Safety Objectives:

- To evaluate safety and tolerability of TAK-935 as adjunctive therapy as compared to placebo
- To investigate the effect on behavior and adaptive function in patients treated with TAK-935 as adjunctive therapy compared to placebo using the Vineland Adaptive Behavioral scales (VABS) and Aberrant Behavior Checklist community questionnaire (ABC-C)
- To evaluate the occurrence of myoclonic and atypical absence-free days to determine if there is worsening of these seizure types during treatment with TAK-935

Study Population:

Pediatric patients aged ≥2 and ≤17 years with Dravet syndrome or LGS who are on background AED therapy

Number of Patients: Approximately 126 male and female patients will be randomized to ensure at least 112 eligible patients (a minimum of 46 in the Dravet stratum, and 80 in the LGS stratum).	**Number of Sites:** Estimated total: approximately 45 sites globally
Study Drug: Patients will be dosed with either TAK-935 or matching placebo	**Route of Administration:** Oral or via gastrostomy tube (G-tube)/ percutaneous endoscopic gastrostomy (PEG) tube. Note: Patients enrolled in clinical sites in China are not to receive study drug via G-tube/PEG tube. Twice daily
Duration of Treatment: 20 weeks plus 2-week taper	**Period of Evaluation:** ~30 weeks (includes 4- to 6-week Screening/Baseline period, 20-week double-blind treatment period [8-week Dose Optimization Period and 12-week Maintenance Period], 2-week taper, and 2-week safety follow-up period)

Main Criteria for Inclusion:

1. The patient and patient's legal representative (i.e., parent or legal guardian) are willing and able to read, understand, and sign the informed consent form and assent, if applicable
2. Male and female patients aged ≥2 and ≤17 years at the time of informed consent and the first dose of study drug
3. Clinical diagnosis of LGS and a history of, on average, ≥4 drop seizures per month during the 3 months immediately prior to Screening based on historical information, and the patient has ≥4 drop seizures during a minimum of 4 weeks of seizure data collection during the prospective Baseline Period
   - OR -
   Clinical diagnosis of Dravet syndrome and a history of, on average, ≥3 convulsive seizures per month during the past 3 months based on the historical information, and the patient has ≥3 convulsive seizures during a minimum of 4 weeks of seizure data collection during the prospective Baseline Period
4. Weight of ≥10 kg at the Screening visit (Visit 1)
5. Currently taking 1 to 4 AEDs at a stable dose for 4 weeks prior to the Screening visit (Visit 1); benzodiazepines used chronically (on daily frequency) to treat seizures are considered AEDs
6. If using a VNS, must have VNS placed at least 3 months prior to the Screening visit with stable settings for >1 month; VNS parameters must remain constant throughout the study (VNS will not be counted as an AED)
7. If on a ketogenic diet, must have started the ketogenic diet at least 3 months prior to the

Screening visit (Visit 1), diet should be stable for 4 weeks before the Screening visit (Visit 1); and should continue through the duration of the study (ketogenic diet will not be counted as an AED)

8. Failed to become and remain seizure free with trials of at least 2 AEDs
9. The patient and patient's legal representative (i.e., parent or legal guardian) are willing to keep the AED, VNS, and ketogenic diet regimen(s) stable throughout the study
10. The patient is able to carry out all appropriate assessment and take study drug in the opinion of the Investigator and parent/caregiver
11. The patient has a documented clinical diagnosis of Dravet syndrome or LGS:

Diagnosis of Dravet syndrome supported by:

- Onset of seizures around 6 months of age
- Initial seizures
  - Fever-induced or fever-triggered seizures
  - Hemiclonic or generalized tonic seizures
  - Prolonged seizures (approximately 15 minutes or longer, some >30 min)
- Between 1 and 5 years, other seizure types emerge:
  - Myoclonic seizures
  - Focal awareness altered
  - Absence
  - Non-convulsive status (absence or myoclonic)
  - Convulsive status epilepticus
- Development normal within 1st year of life, then intellectual disability emerges
  - May regress with recurrent status epilepticus

Diagnosis of Lennox-Gastaut syndrome supported by:

- History of abnormal EEG consistent with LGS
  - EEG with slow and/or disorganized background AND one of the following:
    - EEG with bursts of generalized 2.5 Hz (or less) spike and wave activity, OR
    - Generalized paroxysmal fast activity (GPFA)
- Greater than 1 type of generalized seizure for at least 6 months
  - At least 1 seizure type with drop seizures
- Less than 11 years of age at the onset of LGS
  - Evidence of development delay or regression OR history of special education classed OR measured IQ <70

12. Sexually active female patients of childbearing potential (defined as first menarche) must agree to use a highly effective method of birth control during the study and for 30 days following the last dose of study drug

Main Criteria for Exclusion:

Patients will be excluded from study enrollment if they meet any of the following criteria:

1. The patient has been admitted to a medical facility and intubated for treatment of status epilepticus 2 or more times in the 3 months immediately prior to the screening visit
2. Non-epileptic events that cannot be reliably distinguished from epileptic seizures (e.g., gastroesophageal reflux, muscle cramps, etc.)
3. Patients with history of confirmed cataract (untreated with surgery)
4. Unstable, clinically significant neurologic (other than the disease being studied), psychiatric, cardiovascular, ophthalmologic, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, immunologic, hematopoietic, endocrine disease, malignancy including progressive tumors, or other abnormality, which may impact the ability to participate in the study or that may potentially confound the study results. It is the responsibility of the Investigator to assess the clinical significance; however, consultation with the Medical Monitor may be warranted
5. Any history of alcohol, opioid, or other drug use disorder, as per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), within the 2 years immediately prior to the Screening visit (Visit 1)
6. Suicide attempt within the last year, at significant risk of suicide (either in the opinion of the Investigator or defined as 'yes' to suicidal ideation question 4 or 5 on the Columbia-Suicide Severity Rating Scale [C-SSRS] at Screening) or appearing suicidal per Investigator judgment
7. History of human immunodeficiency virus (HIV) infection (patient who has tested positive for human immunodeficiency virus antibodies (HIV)-1/2Ab), or history of active hepatitis B, or active hepatitis C infection. (Note that patients who have been vaccinated against hepatitis B [hepatitis B surface antibody {Ab}-positive] who are negative for other markers of prior hepatitis B infection [eg, negative for hepatitis B Core Ab] are eligible)
8. Abnormal and clinically significant ECG abnormality at Screening
    a. QT interval with Fridericia's correction method (QTcF) >450 ms (males) or >470 ms (females), confirmed with one repeat testing, at the Screening visit
9. Abnormal clinical laboratory test results at the Screening visit that suggest a clinically significant underlying disease that would compromise the well-being of the patient (if the patient has alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST] >2.5 × the upper limit of normal [ULN], the Medical Monitor should be consulted)
10. Participated in a clinical study involving another study drug in the previous month (or 5 half-lives of the study drug, whichever is longer) or currently receiving another study drug
11. Received TAK-935 in a previous clinical study or as a therapeutic agent
12. Immediate family members, or in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, child, sibling)
13. Known hypersensitivity to any component of the TAK-935 formulation
14. Currently pregnant or breastfeeding or is planning to become pregnant within 90 days of the last dose of study drug

Endpoints:

Primary Efficacy Endpoint

- Percent change from Baseline in seizure frequency per 28 days (based only on convulsive seizures for the patients in the Dravet syndrome stratum and drop seizures for the patients in the LGS stratum) in patients receiving TAK-935 as compared to placebo during the Maintenance Period

Secondary Efficacy Endpoints

- Percent change from Baseline in seizure frequency per 28 days (based only on convulsive seizures for the patients in the Dravet syndrome stratum and drop seizures for the patients in the LGS stratum) in patients receiving TAK-935 as compared to placebo during the Treatment Period
- Percent change from Baseline in convulsive seizure frequency per 28 days in patients randomized to the Dravet syndrome stratum and receiving TAK-935 as compared to placebo during the Maintenance Period
- Percent change from Baseline in drop seizure frequency per 28 days in patients randomized to the LGS stratum and receiving TAK-935 as compared to placebo during the Maintenance Period
- Proportion of patients in the LGS stratum considered treatment responders throughout the Maintenance Period; treatment responders defined as those with:
  - Worsening of 25% or more in drop seizures from baseline
  - Worsening of 1% to 25% in drop seizures from baseline
  - No change in drop seizures from baseline (Worsening of 1% to Reduction of 1%)
  - Reduction of 25% or more in drop seizures from baseline
  - Reduction of 50% or more in drop seizures from baseline
  - Reduction of 75% or more in drop seizures from baseline
  - Reduction of 100% in drop seizures from baseline
- Proportion of patients in the Dravet syndrome stratum considered treatment responders throughout the Maintenance Period; treatment responders are defined as those with:
  - Worsening of 25% or more in convulsive seizures from baseline
  - Worsening of 1% to 25% in convulsive seizures from baseline
  - No change in convulsive seizures from baseline (Worsening of 1% to Reduction of 1%)
  - Reduction of 25% or more in convulsive seizures from baseline
  - Reduction of 50% or more in convulsive seizures from baseline
  - Reduction of 75% or more in convulsive seizures from baseline
  - Reduction of 100% in convulsive seizures from baseline
- Change in CGI-S/C responses of Investigator reported impression of efficacy and tolerability of study drug
- Change in Care GI-C responses of parent/family reported impression of efficacy and tolerability of study drug
- To characterize plasma 24HC levels and change in seizure frequency in patients treated with TAK-935 as an adjunctive therapy

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Pharmacokinetic Endpoints

- To determine the plasma concentrations of TAK-935 and the TAK-935 metabolite (M-I) at multiple time points
- Estimate exposure parameters from sparse PK samples using population modelling
- Determine any potential relationship with estimated TAK-935 exposure parameters with changes in seizure frequency

Safety Endpoints

- Incidence of treatment-emergent adverse events (TEAEs)
- Change in behavioral and adaptive functional measures using the VABS
- Change in behavior measures using total scores and subscale scores of ABC-C for patients ≥6 years of age
- Incidence of abnormal values for clinical laboratory evaluations, vital signs, body weight and height, and electrocardiogram (ECG) parameters after TAK-935 treatment
- Change from Baseline in clinical laboratory evaluations, vital signs, body weight, C-SSRS, and ECG parameter values after TAK-935 treatment
- Mean percent of myoclonic- and atypical-absence free days in patients receiving TAK-935 as compared to placebo during the Maintenance Period

Safety:

An iDMC will monitor the patient safety in accordance with the iDMC charter.

Statistical Considerations:

All statistical analyses will be performed using SAS® Version 9.4 or higher. All clinical study data will be presented in patient data listings. Data summaries will be presented for all endpoints and will include descriptive statistics (number of patients [n], mean, standard deviation [SD], first quartile [Q1], median, third quartile [Q3], minimum and maximum) for continuous variables, and frequency and percentage for categorical and ordinal variables. If there are missing values, the number of missing will be presented, but without a percentage.

For all analyses, 'Baseline' refers to the prospective 4-week Baseline Period.

Modified Intent-to-Treat Analysis Set

All randomized patients who have received at least 1 dose of study drug and have been assessed for at least 1 day in the Treatment Period will be included in the modified intent-to-treat (mITT) analysis set. All mITT analyses will be based on each patient's randomized treatment assignment.

Efficacy Analysis Set

All mITT patients whose efficacy assessments are compliant with Protocol Amendment 2 will be included in the efficacy analysis set. Efficacy analyses for primary and secondary efficacy endpoints will be based on the efficacy analysis set. CCI [redacted] Efficacy analyses will be based on each patient's randomized treatment assignment.

Safety Analysis Set

All randomized patients who take at least 1 dose of study medication will be included in the Safety Analysis Set. Safety analyses will be based on the medication that was actually administered to each patient.

Stratification by Seizure Type

At Visit 2, all eligible patients will be stratified by 2 categories: Dravet syndrome patients with convulsive seizures, and LGS patients with drop seizures to ensure balance of treatments within each stratum. Note that patients with the minimum number of convulsive or drop seizures will be assigned to a stratum following the stratification rules.

Patients with Dravet syndrome:

- 46 eligible patients diagnosed with Dravet syndrome with ≥3 convulsive seizures per 28 days during the prospective Baseline period will be randomized into the Dravet syndrome stratum.

Patients with LGS (Lennox Gastaut Syndrome):

- 80 eligible patients diagnosed with LGS with ≥4 drop seizures per 28 days during the prospective Baseline period will be randomized into the LGS stratum.

If a patient does not meet any of these criteria, the patient will be considered a screen failure.

Primary Efficacy Analyses

For the patients randomized to the Dravet syndrome stratum (≥3 convulsive seizures per 28 days), convulsive seizure frequencies per 28 days for the 4-week prospective Baseline Period and the Maintenance Period will be calculated.

For the patients randomized to the LGS stratum (≥4 drop seizures per 28 days), drop seizure frequencies per 28 days for the 4-week prospective Baseline Period and the Maintenance Period will be calculated.

For each patient, percent change from Baseline to the frequency during Maintenance Period (per 28 days) will be calculated for the seizure type corresponding to the assigned stratum of that patient (convulsive for the Dravet stratum and drop for the LGS stratum). Percent change from Baseline will be compared between TAK-935 and placebo using a Mann-Whitney (Wilcoxon) test adjusting for Baseline and randomization stratum.

The null hypothesis of no treatment difference will be tested at a two-sided 0.05 level of significance. The Mann-Whitney estimator and the corresponding 95% confidence interval (CI) comparing TAK-935 with placebo will also be displayed.

Secondary Efficacy Analyses

For each patient, percent change from Baseline to the frequency during Treatment Period (per 28 days) will be calculated for the seizure type corresponding to the assigned stratum of that patient (convulsive for the Dravet stratum and drop for the LGS stratum). Percent change from Baseline will be compared between TAK-935 and placebo using a Mann-Whitney (Wilcoxon) test adjusting for Baseline and randomization stratum.

For Dravet syndrome stratum, percent change in convulsive seizure frequency from Baseline to the frequency of convulsive seizures during the Maintenance Period will be compared between TAK-935 and placebo using a Mann-Whitney test adjusting for Baseline convulsive seizure frequency and randomization stratum. For the drop seizures in LGS stratum, percent change in drop seizure frequency from Baseline to the frequency of drop seizures during the Maintenance Period will be compared between TAK-935 and placebo using a Mann-Whitney test adjusting for Baseline drop seizure frequency. For the 2 randomization strata, the null hypothesis of no treatment difference will be tested at a two-sided 0.1 level of significance. The Mann-Whitney estimator and the corresponding 95% confidence interval (CI) comparing TAK-935 with placebo will also be displayed.

The primary analysis will be repeated for the 20-week Treatment Period.

For the Dravet syndrome stratum, the proportion of treatment responders based on ≥25% worsening, <25% and >1% worsening, no change (Worsening of 1% to Reduction of 1%), ≥25% reduction, ≥50% reduction, ≥75% reduction, and 100% reduction from Baseline in convulsive seizure frequency for the Maintenance Period will be summarized for TAK-935 and placebo. The 95% CIs for the difference of proportions will be displayed for each responder category. For the LGS stratum, the proportion of treatment responders based on ≥25% worsening, <25% and >1% worsening, no change (Worsening of 1% to Reduction of 1%), ≥25% reduction, ≥50% reduction, ≥75% reduction, and 100% reduction from Baseline in drop seizure frequency for the Maintenance Period will be summarized for TAK-935 and placebo; 95% CIs for the difference of proportions will be displayed for each responder category.

Change in CGI-S/C responses of Investigator reported impression of efficacy and tolerability of study drug and change in Care GI-C responses of parent/family reported impression of efficacy and tolerability of study drug will be analyzed descriptively.

Techniques for handling missing information with respect to reporting of seizures in the treatment period (Dose Optimization and Maintenance) will be specified in detail in the statistical analysis plan (SAP).

Safety Analyses

Descriptive statistics will be used to summarize all safety endpoints, by treatment group. Two-sided 95% CIs will be presented where meaningful. Data summaries will be displayed for incidence of AEs, clinical laboratory variables, vital signs, body weight and height, ECG parameters, percent myoclonic and atypical absence-free days, as well as changes in behavioral and adaptive functioning measures using VABS and sub-scales of ABC-C, as appropriate.

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Pharmacokinetic Analyses

Plasma concentrations of TAK-935 and the metabolite of TAK-935 (M-I) will be summarized and displayed graphically per nominal time points. Mean plasma concentrations over time will be presented graphically.

The plasma concentration-time and PD (24HC) data obtained in this study will be used to estimate TAK-

935 exposure parameters, analyze target engagement in terms of 24HC reduction, and evaluate potential relationships between TAK-935 exposure or 24HC responses and clinical and safety endpoints. Full details of the relevant population PK/PD modeling work (including objectives, relevant endpoints, methodology, software, etc.) will be defined in a separate data analysis plan or the study SAP, and results will be reported separately. The actual elapsed time from dose will be used in the final PK modeling and parameter calculations.

Sample Size Justification:

The sample size calculations are based on unadjusted Mann-Whitney (Wilcoxon rank-sum) test.

The randomization will be stratified by 2 categories: Dravet syndrome stratum and LGS stratum. The primary endpoint is defined as percent change in convulsive seizures for the patients in the Dravet syndrome and percent change in drop seizures for those in the LGS stratum.

Assuming that the mean difference in percentage change from baseline between active and placebo arms is 29% for the 2 strata combined and the standard deviation is 42.3%, with 56 patients per treatment group, there will be 92% power to test the treatment difference at a two-sided 0.05 level of significance. Assuming a 10% drop-out rate, 63 patients per arm will be randomized.

Within the 2 randomization strata, hypothesis tests will be performed at levels of significance higher than 0.05 in this Phase 2 proof of concept trial and will have power of 80%. The following table shows the within stratum sample size calculations:

	Dravet Syndrome Stratum	LGS Stratum
Alpha	0.1	0.1
1-sided or 2-sided	2	2
Treatment Difference	0.30	0.28
Standard Deviation	0.35	0.45
Power	80%	80%
N per group	20	36
N per group (after 10% adjustment)	23	40
Total N	46	80

Interim Analysis:

Plasma concentrations of TAK-935 in first 12 patients within each category of aged ≥9 years and <9 years will be used to estimate PK parameters using the current population PK model. If needed, adjustment to the dose will be made. The frequency of PK sample collection may be changed based on results of interim analysis.

Overall and by-stratum (LGS and Dravet strata) futility and interim analyses may be performed. Enrollment may be stopped for one of the strata if the treatment effect is not sufficiently strong. If one stratum is discontinued, enrollment will continue with the other stratum until the total sample size is achieved. Thresholds for stopping enrollment will be pre-specified in the interim analysis plan.

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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
24HC	24*S*-hydroxycholesterol
AED	antiepileptic drugs
APP/PS-1 dTg	amyloid precursor protein and presenilin-1 double transgenic
AUC	area under the plasma concentration-time curve
AUC_{24}	area under the plasma concentration-time curve from time 0 to 24 hours
$AUC_{24,ss}$	area under the plasma concentration-time curve from time 0 to 24 hours at steady state
AUC_{τ}	area under the plasma concentration-time curve during a dosing interval
BID	twice daily
CGI-S/C	Clinician's Clinical Global Impression of Severity and Change
Care GI-C	Caregiver Global Impression of Change
CH24H	cholesterol 24*S* hydroxylase
C_{max}	maximum observed plasma concentration
$C_{max.ss}$	maximum observed plasma concentration during a dosing interval, at steady state
CNS	central nervous system
C-SSRS	Columbia–Suicide Severity Rating Scale
CYP	cytochrome P-450
DEE	developmental and epileptic encephalopathy
DRF	dose range–finding
DS	Dravet syndrome
ED_{50}	median effective dose
EE	epileptic encephalopathy
EEG	Electroencephalogram
EO	enzyme occupancy
FDA	Food and Drug Administration
GABA	γ-amino butyric acid
GABAA	γ-amino butyric acid subunit A
HIE	hypoxic-ischemic-encephalopathy
I	steady state total Cmax at the highest dose of the inhibitor
IB	Investigator's Brochure.
IC50	50% inhibitory concentration
iDMC	independent Data Monitoring Committee
ILAE	International League Against Epilepsy

Term	Definition
IND	Investigational New Drug
IS	infantile spasms
KCl	potassium chloride
KO	Knockout
LGS	Lennox-Gastaut syndrome
M-I	*N*-oxide metabolite of TAK-935
NMDA	*N*-methyl-D-aspartate
OLE	open-label extension
PET	positron emission tomography
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PO	Oral
QD	once daily
SRS	spontaneous recurrent seizures
$t_{1/2z}$	terminal disposition phase half-life
t_{max}	time of first occurrence of Cmax
TMEV	Theiler's murine encephalomyelitis virus
TSC	tuberous sclerosis complex
UGT	uridine diphosphate glucuronosyltransferase
VNS	vagal nerve stimulator

3. INTRODUCTION

3.1. Background

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More information about the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) of TAK-935 may be found in the current edition of the Investigator's Brochure (IB).

3.2. Study Rationale

Epileptic encephalopathies (EE) are a group of rare disorders in which the unremitting epileptic activity contributes to severe cognitive and behavioral impairment and these can worsen overtime leading to progressive cerebral dysfunction.[4] Epileptic encephalopathies start at an early age and manifest with seizures, which are usually intractable, have aggressive electroencephalogram (EEG) paroxysmal abnormalities, and severe neurocognitive deficits. Potential to halt or improve the neurocognitive consequences of epilepsy with a successful

treatment is a fundamental concept behind clustering of these disorders. In a group of severe genetic disorders causing EE, the underlying genetic mutation also contributes to developmental delay, in addition to severe epilepsy in these patients. Hence, the International League Against Epilepsy (ILAE) expanded the concept of EE from the severe epilepsies with onset in infancy and childhood to epilepsy syndromes associated with encephalopathy including those that have a genetic etiology.[5] The revised classification now refers to DEEs. Dravet syndrome (DS) or severe myoclonic epilepsy in infancy is one of the most well-known disorders of the epileptic encephalopathies. Clinically, DS is characterized by frequent convulsive febrile seizures, followed later by nonfebrile seizures, mainly clonic and unilateral, of long duration and frequent status epilepticus (SE). Lennox Gastaut syndrome (LGS) is rare and is one of the most severe forms of childhood epilepsy. The syndrome usually has its onset between the ages of 1 and 8 years (typically between 3 and 5 years), but occasionally it occurs in children who are more than 8 years old, even into adulthood. The hallmarks of the disease include: presence of multiple seizure types: the hallmark tonic-atonic seizures; the most hazardous are drop seizures/attacks, which can lead to serious injuries and occur in about 56% of patients. Other seizure types include atypical absences, but tonic-clonic, myoclonic, and partial seizures are also frequently present.

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The current study is designed to further characterize the effects of TAK-935 on seizure frequency using a seizure diary. An additional aim is to explore the safety, tolerability, PK, and PD of multiple-dose TAK-935 administration in pediatric patients with developmental and/or epileptic encephalopathies.

4. STUDY OBJECTIVES AND ENDPOINTS

Study objectives and associated endpoints are presented in Section 4.1 and Section 4.2, respectively; the frequency and timing of study measurements is provided in the Schedule of Assessments (Table 3). Information regarding sample collection and safety data collection are presented in Section 8.

4.1. Objectives

4.1.1. Primary Objective

The primary objective of this study is to investigate the effect on the frequency of all seizures (convulsive and drop) in patients treated with TAK-935 as an adjunctive therapy compared to placebo in the Maintenance Period.

4.1.2. Secondary Objectives

- To investigate the effect on the frequency of all seizures (convulsive and drop) in patients treated with TAK-935 as an adjunctive therapy compared to placebo throughout the Treatment Period
- To investigate the effect on the frequency of convulsive seizure in patients with Dravet Syndrome treated with TAK-935 as an adjunctive therapy compared to placebo in the Maintenance Period
- To investigate the effect on the frequency of drop seizure in patients with LGS treated with TAK-935 as an adjunctive therapy compared to placebo in the Maintenance Period
- To investigate the seizure frequency of LGS patients considered treatment responders throughout the Maintenance Period; treatment responders are defined as those with:
  - Worsening of 25% or more in drop seizures from baseline
  - Worsening of 1% to 25% in drop seizures from baseline
  - No change in drop seizures from baseline (Worsening of 1% to Reduction of 1%)
  - Reduction of 25% or more in drop seizures from baseline
  - Reduction of 50% or more in drop seizures from baseline
  - Reduction of 75% or more in drop seizures from baseline
  - Reduction of 100% in drop seizures from baseline
- To investigate the seizure frequency of Dravet patients considered treatment responders throughout the Maintenance Period; treatment responders are defined as those with:
  - Worsening of 25% or more in convulsive seizures from baseline
  - Worsening of 1% to 25% in convulsive seizures from baseline

- No change in convulsive seizures from baseline (Worsening of 1% to Reduction of 1%)
- Reduction of 25% or more in convulsive seizures from baseline
- Reduction of 50% or more in convulsive seizures from baseline
- Reduction of 75% or more in convulsive seizures from baseline
- Reduction of 100% in convulsive seizures from baseline

- To investigate the change in Clinical Global Impression of Severity and Change assessment (CGI-S/C) responses of Investigator and Caregiver Clinical Global Impression of Change (Care GI-C) in patients treated with TAK-935 as an adjunctive therapy compared to placebo
- To characterize the relationship between plasma 24HC levels and seizure frequency

4.1.3. Exploratory Objectives

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4.1.4. Safety Objectives

- To evaluate safety and tolerability of TAK-935 as adjunctive therapy as compared to placebo
- To investigate the effect on behavior and adaptive function in patients treated with TAK-935 as adjunctive therapy compared to placebo using the Vineland Adaptive Behavioral scales (VABS) and Aberrant Behavior Checklist-Community questionnaire (ABC-C)
- To evaluate the occurrence of myoclonic and atypical absence-free days to determine if there is worsening of these seizure types during treatment with TAK-935

4.2. Endpoints

4.2.1. Primary Endpoint

The primary endpoint for this study is the percent change from Baseline in seizure frequency per 28 days (based only on convulsive seizures for the patients in the Dravet syndrome stratum and drop seizures for the patients in the LGS stratum) in patients receiving TAK-935 as compared to placebo during the Maintenance Period.

4.2.2. Secondary Efficacy Endpoints

- Percent change from Baseline in seizure frequency per 28 days (based only on convulsive seizures for the patients in the Dravet syndrome stratum and drop seizures for the patients in the LGS stratum) in patients receiving TAK-935 as compared to placebo during the Treatment Period
- Percent change from Baseline in convulsive seizure frequency per 28 days in patients randomized to the Dravet syndrome stratum and receiving TAK-935 as compared to placebo during the Maintenance Period
- Percent change from Baseline in drop seizure frequency per 28 days in patients randomized to the LGS stratum and receiving TAK-935 as compared to placebo during the Maintenance Period
- Proportion of patients in the LGS stratum considered treatment responders throughout the Maintenance Period; treatment responders defined as those with:
  - Worsening of 25% or more in drop seizures from baseline
  - Worsening of 1% to 25% in drop seizures from baseline
  - No change in drop seizures from baseline (Worsening of 1% to Reduction of 1%)
  - Reduction of 25% or more in drop seizures from baseline
  - Reduction of 50% or more in drop seizures from baseline
  - Reduction of 75% or more in drop seizures from baseline
  - Reduction of 100% in drop seizures from baseline
- Proportion of patients in the Dravet syndrome stratum considered treatment responders throughout the Maintenance Period; treatment responders are defined as those with:
  - Worsening of 25% or more in convulsive seizures from baseline
  - Worsening of 1% to 25% in convulsive seizures from baseline
  - No change in convulsive seizures from baseline (Worsening of 1% to Reduction of 1%)
  - Reduction of 25% or more in convulsive seizures from baseline
  - Reduction of 50% or more in convulsive seizures from baseline
  - Reduction of 75% or more in convulsive seizures from baseline
  - Reduction of 100% in convulsive seizures from baseline
- Change in CGI-S/C responses of Investigator reported impression of efficacy and tolerability of study drug

- Change in Care GI-C responses of parent/family reported impression of efficacy and tolerability of study drug
- To characterize plasma 24HC levels and change in seizure frequency in patients treated with TAK-935 as an adjunctive therapy

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4.2.4. Pharmacokinetic Endpoints

- To determine the plasma concentrations of TAK-935 and the TAK-935 metabolite (M-I) at multiple time points
- Estimate exposure parameters from sparse PK samples using population modelling
- Determine any potential relationship with estimated TAK-935 exposure parameters with changes in seizure frequency

4.2.5. Safety Endpoints

- Incidence of treatment-emergent adverse events (TEAEs)
- Change in behavioral and adaptive functional measures using the VABS
- Change in behavior measures using total scores and subscale scores of ABC-C for patients ≥6 years of age
- Incidence of abnormal values for clinical laboratory evaluations, vital signs, body weight and height, and electrocardiogram (ECG) parameters after TAK-935 treatment
- Change from Baseline in clinical laboratory evaluations, vital signs, body weight, Columbia–Suicide Severity Rating Scale (C-SSRS), and ECG parameter values after TAK-935 treatment
- Mean percent of myoclonic- and atypical-absence free days in patients receiving TAK-935 as compared to placebo during the Maintenance Period

5. INVESTIGATIONAL PLAN

5.1. Summary of Study Design

Study TAK-935-2002 (OV935) is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, study in pediatric patients (aged ≥2 and ≤17 years) with Dravet syndrome and LGS demonstrating ≥3 convulsive or ≥4 drop seizures, respectively, per month during the 3 months immediately prior to Screening (based on historical information) and ≥3 convulsive or ≥4 drop seizures, respectively, during a minimum of 4 weeks during the prospective Baseline Period (based on the seizure diary records). Convulsive seizures include generalized tonic-clonic, focal to bilateral tonic-clonic with impaired awareness, hemi-clonic and simultaneous bilateral clonic (generalized clonic) seizures. Drop seizures are defined as involving the entire body, trunk, or head that leads to a fall, injury, slumping in a chair, or head hitting a surface, or that could have led to a fall or injury, depending on the position of the patient at the time of the seizure or spell. Examples of seizures causing drop include, but are not limited to, atonic, clonic, and tonic seizures.

Approximately 126 patients will be randomized to ensure 112 evaluable patients. Randomization will be stratified by 2 categories: Dravet syndrome patients with convulsive seizures and LGS patients with drop seizures. Stratification will be performed to ensure balance of treatments within each stratum.

The study will begin with a phased enrollment based on age. Patients aged ≥9 years will be enrolled first, prior to open enrollment in the study, for assessment of safety. The independent Data Monitoring Committee (iDMC) will review the adverse event (AE) profiles of the first 12 patients aged ≥9 years completing 4 weeks of treatment across all ongoing pediatric TAK-935 studies, prior to recommending treatment for patients aged <9 years.

This study consists of 2 main periods:

- 4- to 6-week Screening/Baseline Period
- 20-week Treatment Period
  - 8-week Dose Optimization Period
  - 12-week Maintenance Period

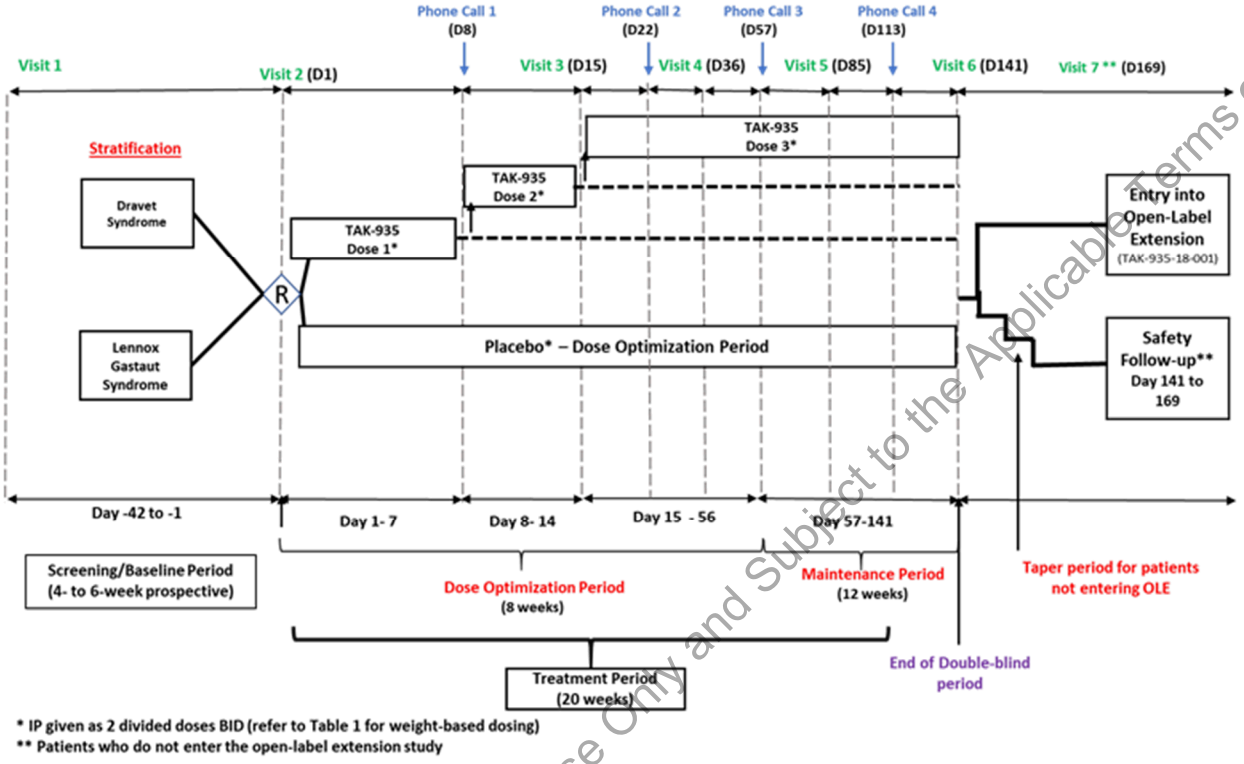
The Treatment Period consists of the Dose Optimization Period and Maintenance Period. Figure 1 illustrates the study design.

Dravet syndrome patients who have had, on average, ≥3 convulsive or LGS patients who have had on average ≥4 drop seizures per month during the 3 months immediately prior to Screening (based on historical information) and ≥3 convulsive or ≥4 drop seizures, respectively, during a minimum of 4 weeks during the Baseline Period (based on the seizure diary records) will be eligible for entry into the study.

At the end of the prospective 4- to 6-week Screening/Baseline Period, patients will return to the clinic (Visit 2). Seizure diaries will be reviewed by the Medical Monitor or delegated staff and if a patient did not meet the eligibility criteria, including minimum number of seizures required for

the study and seizure stratum, the patient will be discontinued from the study and considered a screen failure.

Figure 1: Study Design for Clinical Protocol OV/TAK-935-2002 (OV935)



Patients and/or patients' caregivers will be provided with a seizure diary and will be instructed to record seizure data daily starting at Visit 1 (screening visit) and to continue throughout the study. The seizure diary data will be collected during the prospective Baseline Period and will be used as the baseline seizure data for endpoint analyses. An external independent or Sponsor's reviewer(s) will confirm the patient's diagnosis prior to randomization.

Patients who cannot tolerate Dose 1 will be withdrawn from the study.

5.1.1. End of Study Definition

The end of the study for an individual patient is defined as the last protocol-specified contact with that patient. The overall end of the study is defined as the last protocol-specified contact with the last patient ongoing in the study.

5.1.2. Study Extension

Following completion of the study, patients will have the option to enroll in a long-term, open-label extension (OLE) study (under a separate protocol, TAK-935-18-001 [OV935]).

5.2. Selection and Timing of Doses in the Study

Preclinical data from rodent epilepsy models suggest potentially efficacious exposures, and safety data from nonclinical studies were used to determine exposure-based safety margins. Clinical safety and tolerability data from single- and multiple-dose Phase 1 studies in adult healthy volunteers were used to perform PK, PD, and enzyme occupancy (EO) analyses with allometric scaling to determine an appropriate dose of TAK-935 for pediatric patients.

5.2.1. Modeling and Simulation of Clinical Data

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6. STUDY POPULATION

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened. Refer to Section 8.1.23.4 for additional information on recording screen failures.

Individuals may be re-screened up to 2 times, after consultation with the Medical Monitor. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all the following criteria and none of the exclusion criteria:

1. The patient and patient's legal representative (i.e., parent or legal guardian) are willing and able to read, understand, and sign the informed consent form and assent, if applicable
2. Male and female patients aged ≥2 and ≤17 years at the time of informed consent and the first dose of study drug
3. Clinical diagnosis of LGS and a history of, on average, ≥4 drop seizures per month during the 3 months immediately prior to Screening based on historical information, and the patient has ≥4 drop seizures during a minimum of 4 weeks of seizure data collection during the prospective Baseline Period
   - OR -
   Clinical diagnosis of Dravet syndrome and a history of, on average, ≥3 convulsive seizures per month during the past 3 months based on the historical information, and the patient has ≥3 convulsive seizures during a minimum of 4 weeks of seizure data collection during the prospective Baseline Period
4. Weight of ≥10 kg at the Screening visit (Visit 1)
5. Currently taking 1 to 4 AEDs at a stable dose for 4 weeks prior to the Screening visit (Visit 1); benzodiazepines used chronically (on daily frequency) to treat seizures are considered AEDs
6. If using a vagal nerve stimulator (VNS), must have VNS placed at least 3 months prior to the Screening visit with stable settings for >1 month; VNS parameters must remain constant throughout the study (VNS will not be counted as an AED)
7. If on a ketogenic diet, must have started the ketogenic diet at least 3 months prior to the Screening visit (Visit 1), diet should be stable for 4 weeks before the Screening visit (Visit 1); and should continue through the duration of the study (ketogenic diet will not be counted as an AED)
8. Failed to become and remain seizure free with trials of at least 2 AEDs
9. The patient and patient's legal representative (i.e., parent or legal guardian) are willing to keep the AED, VNS, and ketogenic diet regimen(s) stable throughout the study
10. The patient is able to carry out all appropriate assessments and take study drug in the opinion of the Investigator and parent/caregiver

11. The patient has a documented clinical diagnosis of Dravet syndrome or LGS:

Diagnosis of Dravet syndrome supported by:

- Onset of seizures around 6 months of age
- Initial seizures
  - Fever-induced or fever-triggered seizures
  - Hemiclonic or generalized tonic seizure
  - Prolonged seizures (approximately 15 minutes or longer, some >30 min)
- Between 1 and 5 years, other seizure types emerge:
  - Myoclonic seizures
  - Focal awareness altered
  - Absence
  - Non-convulsive status (absence or myoclonic)
  - Convulsive status epilepticus
- Development normal within 1st year of life, then intellectual disability emerges
  - May regress with recurrent status epilepticus

Diagnosis of Lennox-Gastaut syndrome supported by:

- History of abnormal EEG consistent with LGS
  - EEG with slow and/or disorganized background AND one of the following:
    - EEG with bursts of generalized 2.5 Hz (or less) spike and wave activity, -- *OR* -
    - Generalized paroxysmal fast activity (GPFA)
- Greater than 1 type of generalized seizure for at least 6 months
  - At least one seizure type with drop seizures
- Less than 11 years of age at the onset of LGS
  - Evidence of development delay or regression OR history of special education classed OR measured IQ <70

12. Sexually active female patients of childbearing potential (defined as first menarche) must agree to use a highly effective method of birth control during the study and for 30 days following the last dose of study drug.

    Highly effective contraceptive methods are as follows:

    a. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
        - Oral
        - Intravaginal
        - Transdermal
    b. Progestogen-only hormonal contraception associated with inhibition of ovulation:
        - Oral
        - Injectable
        - Implantable
    c. Intrauterine device
    d. Intrauterine hormone-releasing system
    e. Bilateral tubal occlusion
    f. Vasectomized partner
    g. Sexual abstinence

    Sexually active male patients (post-pubertal unless permanently sterilized by bilateral orchidectomy) must agree to use male contraception (condom) during the study and for a minimum of 90 days following the last dose of study drug. Male patients must also not donate sperm during the Screening and Treatment Periods and for at least 90 days after the last dose of study drug.

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria:

1. The patient has been admitted to a medical facility and intubated for treatment of status epilepticus 2 or more times in the 3 months immediately prior to the screening visit
2. Non-epileptic events that cannot be reliably distinguished from epileptic seizures (e.g., gastroesophageal reflux, muscle cramps, etc.)
3. Patient with history of confirmed cataract (untreated with surgery)
4. Unstable, clinically significant neurologic (other than the disease being studied), psychiatric, cardiovascular, ophthalmologic, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, immunologic, hematopoietic, endocrine disease, malignancy including progressive tumors, or other abnormality, which may impact the ability to participate in the study or that may potentially confound the study results. It is the

responsibility of the Investigator to assess the clinical significance; however, consultation with the Medical Monitor may be warranted

5. Any history of alcohol, opioid, or other drug use disorder, as per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), within the 2 years immediately prior to the Screening Visit (Visit 1)
6. Suicide attempt within the last year, at significant risk of suicide (either in the opinion of the Investigator or defined as 'yes' to suicidal ideation question 4 or 5 on the Columbia-Suicide Severity Rating Scale [C-SSRS] at Screening) or appearing suicidal per Investigator judgment
7. History of human immunodeficiency virus (HIV) infection (patient who has tested positive for human immunodeficiency virus antibodies (HIV)-1/2Ab), or history of active hepatitis B, or active hepatitis C infection. (Note that patients who have been vaccinated against hepatitis B [hepatitis B surface antibody {Ab}-positive] who are negative for other markers of prior hepatitis B infection [e.g., negative for hepatitis B Core Ab] are eligible)
8. Abnormal and clinically significant ECG abnormality at Screening:
    a. QT interval with Fridericia's correction method (QTcF) >450 ms (males) or >470 ms (females), confirmed with 1 repeat testing, at the Screening visit
9. Abnormal clinical laboratory test results at the Screening visit that suggest a clinically significant underlying disease that would compromise the well-being of the patient (if the patient has alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST] >2.5 × the upper limit of normal [ULN], the Medical Monitor should be consulted)
10. Participated in a clinical study involving another study drug in the previous month (or 5 half-lives of the study drug, whichever is longer) or currently receiving another study drug
11. Received TAK-935 in a previous clinical study or as a therapeutic agent
12. Immediate family members, or in a dependent relationship with a study site employee who is involved in the conduct of this study (e.g., child, sibling)
13. Known hypersensitivity to any component of the TAK-935 formulation
14. Currently pregnant or breastfeeding or is planning to become pregnant within 90 days of the last dose of study drug

6.3. Discontinuations

6.3.1. Discontinuation of Patients

The criteria for enrollment must be followed explicitly. If the investigative site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the Sponsor must be notified immediately. If the Sponsor identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the Investigator site will be notified immediately. A discussion must occur between the Sponsor and the Investigator to determine whether the patient may continue in the study, with or without study drug. Inadvertently enrolled patients may be

maintained in the study and on study drug when the Sponsor agrees with the Investigator that it is medically appropriate for that patient. The patient may not continue in the study with or without study drug if the Sponsor does not agree with the Investigator's determination it is medically appropriate for the patient to continue. The Investigator must obtain documented approval from the Sponsor to allow the inadvertently enrolled patient to continue in the study with or without study drug.

In addition, patients will be discontinued from the study drug (and/or from the study) in the following circumstances:

- Liver Function Test (LFT) Abnormalities
  Study drug should be discontinued immediately with appropriate clinical follow up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status, see Section 8.1.11), if the following circumstances occur at any time during study drug treatment:
  - ALT or AST >8 × ULN, or
  - ALT or AST >5 × ULN and persists for >2 weeks, or
  - ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or
  - ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- QTcF interval >500 ms that is confirmed with a repeat ECG
  Study drug should be discontinued immediately with appropriate clinical follow up (including repeat ECG)
- Greater than a 100% increase in 28-day seizure frequency from the 4-week prospective Baseline Period (see formula in Section 8.1.7) and considered by the Investigator to be clinically significant worsening of the seizure frequency
- Not tolerating Dose 1 (the lowest dose) for their weight category
- Enrollment in any other clinical study involving a study drug or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Depression and/or Suicidal Ideation
  - Study staff trained in the administration of the C-SSRS will assess patient suicidality using the C-SSRS (see Section 8.1.14), eliciting answers from the patient or the patient's caregiver. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the clinical judgment of the investigator

- Investigator Decision (Physician Decision)
  - The Investigator decides that the patient should be discontinued from the study
  - If the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
- Patient Decision (Withdrawal by Patient or Withdrawal by Patient's Legal Representative [Parent or Legal Guardian])
  - The patient or the patient's legal representative (i.e., parent or legal guardian) requests to be withdrawn from the study
- Sponsor Decision
  - The Sponsor or its designee discontinues the study or discontinues the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
  - The Sponsor or its designee stops the clinical study at a particular site
- Adverse Event
  - If the Investigator decides that the patient should be withdrawn because of an SAE or a clinically significant laboratory value, the study drug is to be discontinued and appropriate measures are to be taken. The Sponsor or its designee is to be alerted immediately (refer to Section 8.3)

Patients who discontinue the study drug and/or study early will have early termination procedures performed as shown in the Schedule of Assessments (Table 3).

6.3.2. Discontinuation of Study Sites/Site Terminated by Sponsor

Study site participation may be discontinued if the Sponsor or its designee, the Investigator, or the institutional review board/independent ethics committee (IRB/IEC) of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

6.3.3. Discontinuation of the Study/Study Terminated by Sponsor

The study will be discontinued if the Sponsor or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

7. TREATMENT

7.1. Materials and Supplies

The Sponsor will supply the study sites with TAK-935 100 mg tablets/20 mg mini-tablets and matching placebo tablets. TAK-935 tablets/mini-tablets and matching placebo tablets are manufactured by SPERA Pharma Inc. (Osaka, Japan) previously named as Takeda Pharmaceutical Co. Ltd. Each bottle will contain a label that includes pertinent study information and caution statements.

Clinical study materials will be labeled according to the country's regulatory requirements.

If a patient is unable to come for a clinic visit to obtain study drug, the study drug will be shipped via a courier service.

7.1.1. Storage

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7.2. Treatments Administered

All patients will receive TAK-935 BID orally or via gastrostomy tube (G-tube)/percutaneous endoscopic gastrostomy (PEG) tube with or without food (patients enrolled in clinical sites in China are not to receive study drug via G-tube/PEG tube).

For patients weighing <60 kg at Visit 1, the total daily dose of study drug (either placebo or TAK-935) is calculated based on body weight at Visit 1 and will be given twice a day (BID). The selected doses for the different weight groups are listed in Table 1. For patients weighing ≥60 kg at Visit 1, dosing will be 200 mg/day followed by 400 mg/day, then 600 mg/day (Table 1). Study drug can be taken with or without food.

Patients weighing <60 kg will be dispensed 20 mg mini-tablets or matching placebo, and patients weighing ≥60 kg will be dispensed 100 mg tablets or matching placebo. If patients are unable to swallow tablets or mini-tablets, formulation can be changed. No change in formulations will be made after Visit 4 (Day 36).

Patients will receive the initial dose of study drug, Dose 1, for the first 7 days after randomization at Visit 2. In the subsequent phone call and visit (phone call 1 [Day 8] and Visit 3 [Day 15]), the study drug dose will be increased to Dose 2 and Dose 3. The maximum dose for any patient will be 600 mg/day. Patients will be contacted by phone within first 2 days following escalation to the maximum dose to assess safety and tolerability of the study drug. Study drug dose will be allowed to change in first 6 weeks of the Dose Optimization Period based on the judgment of the Investigator and with the approval of the Medical Monitor. The final dose level will be maintained until the end of the Maintenance Period; however, the dose may be decreased to the previous lower doses, for safety and tolerability issues. For example, Dose 3 may be

reduced to Dose 2 and Dose 2 may be reduced to Dose 1 during Maintenance Period. If Dose 1 is not tolerated, the patient will be withdrawn from the study.

The dose may be increased per Investigator's discretion with approval of the Sponsor's Medical Monitor to a maximum of Dose 3 level. All dose changes must be made during the Dose Optimization Period; dose changes during the Maintenance Period must be discussed and approved by the Sponsor.

Table 1 Dosing Schedule by Weight

Weight (kg)	Dose 1		Dose 2		Dose 3	
	(mg/day)[a]	No. Tablets/ Mini-tablets	(mg/day)[a]	No. Tablets/ Mini-tablets	(mg/day)[a]	No. Tablets/ Mini-tablets
10-14	80	0/4	160	0/8	220	0/11
15-19	120	0/6	200	0/10	260	0/13
20-24	120	0/6	240	0/12	320	0/16
25-29	120	0/6	240	0/12	360	0/18
30-34	160	0/8	280	0/14	400	0/20
35-39	160	0/8	280	0/14	440	0/22
40-44	160	0/8	320	0/16	480	0/24
45-49	200	0/10	360	0/18	480	0/24
50-54	200	0/10	360	0/18	520	0/26
55-59	200	0/10	360	0/18	560	0/28
≥60	200	2/0	400	4/0	600	6/0

[a] Total dose administered twice daily.

Two days after each dose titration or taper, patients will be contacted by phone to monitor study drug compliance, concomitant medication use, and AEs. Any change in dose will be documented in the patient's clinic chart and dosing card. On Days 22, 57, and 113, patients will be contacted by phone to monitor compliance with study drug and seizure diary and to monitor AEs.

Tablets/mini-tablets may be crushed and mixed well in applesauce or thick liquid, for taste masking, prior to dosing. The amount of applesauce or liquid needed is dependent upon the number of tablets/mini-tablets the patient is taking. One-half teaspoon or 2.5 mL of applesauce or thick liquid is needed for each mini-tablet taken and 2 teaspoons or 10 mL is needed for each tablet taken.

For patients receiving study drug via G-tube/PEG tube, study drug will be crushed, suspended in water, and the suspension will be administered via the G-tube/PEG tube using a syringe. Complete instructions will be provided to patients/caregivers in a document provided outside of the protocol. Other medications or enteral feeds should not be given concurrently with TAK-935. Patients enrolled in clinical sites in China are not to receive study drug via G-tube/PEG tube.

If a patient misses a dose, the missed dose should be skipped, and the patient should continue with his/her normal dosing schedule. Skipped doses should be reported as missed doses.

Following completion of the study, patients will have the option to enroll in an OLE study (under a separate protocol; see Section 5.1) or to enter a double- blind taper period (maximum 14 days). During the taper period, the study drug dose will be de-escalated to a lower dose (taper Dose 3 to Dose 2, taper Dose 2 to Dose 1) every 3 days or less frequently based on Investigator's discretion until there is no de-escalation and study drug dose is discontinued. After tapering, patients will complete a Safety Follow-up visit approximately 15 days after the last dose of study drug and exit the study.

The Investigator or his/her designee is responsible for the following:

- Explaining the correct use of the investigational agent(s) to the patient/site personnel/legal representative
- Verifying that instructions are followed properly
- Maintaining accurate records of study drug dispensing and accountability
- Returning or destroying all unused medication to the Sponsor or its designee at the end of the study

Patients or the patient's legal representative (i.e., parent or legal guardian) will be instructed to contact the Investigator as soon as possible if he or she has a complaint or problem with the study drug so that the situation can be assessed.

All clinical trial material provided to the Investigator will be stored in a secure and locked place and allocated and dispensed by the interactive web-response system (IWRS). The allocation and dispensing of the study drugs will be fully documented. Detailed records of the amounts of the study drug received, dispensed, and remaining at the end of the study will be maintained.

TAK-935 or placebo tablets/mini-tablets should be administered at approximately the same times on each day. The actual time of all dose administrations prior to PK sample collection will be recorded in the patient's source documents and transcribed into electronic case report form (eCRFs).

7.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be randomized to double-blind treatment at Visit 2. Assignment to treatment groups will be determined by a computer-generated random sequence using an IWRS. The IWRS will be used to assign tablets/mini-tablets containing double-blind study drug to each patient.

To achieve between-group comparability, randomization will be stratified.

At Visit 2, all eligible patients will be stratified by 2 categories: patients with Dravet syndrome with convulsive seizures, and LGS patients with drop seizures to ensure balance of treatments within each stratum.

Note that patients with the minimum number of convulsive or drop seizures will be assigned to a stratum following these stratification rules:

Patients with Dravet syndrome:

- 46 eligible patients diagnosed with Dravet syndrome with ≥3 convulsive seizures per 28 days during the prospective Baseline Period will be randomized into the Dravet syndrome stratum

Patients with LGS (Lennox Gastaut Syndrome):

- 80 eligible patients diagnosed with LGS with ≥4 drop seizures per 28 days during the prospective Baseline period will be randomized into the LGS stratum

If a patient does not meet any of these, the patient will be considered a screen failure.

7.4. Continued Access to Study drug

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7.5. Blinding

This is a double-blind study.

Emergency unblinding for AEs may be performed through an IWRS. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment.

All calls resulting in an unblinding event are recorded and reported by the IWRS.

If an Investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study. In cases where there are ethical reasons to have the patient remain in the study, the Investigator must obtain specific approval from the Sponsor Medical Monitor for the patient to continue in the study.

Unblinding should only be considered for the safety of the patient. If unblinding is deemed necessary by the Investigator, the Investigator can unblind the patient's treatment allocation using IWRS. The Investigator must note the date, time, and reason for unblinding.

The Investigator should inform the Sponsor that the patient was unblinded, however they are not required to reveal to the Sponsor the patient's treatment allocation.

When an AE is an unexpected related SAE, the blind will be broken by the Sponsor only for that specific patient. The blind will be maintained for persons responsible for the ongoing conduct of the study (such as the monitors, Investigators, etc.) and those responsible for data analysis and interpretation of results at the conclusion of the study, such as biometrics personnel. Unblinded information will only be accessible to those who need to be involved in the safety reporting to Health Authorities, Ethics Committees, and/or IRBs.

Investigators will receive only blinded information unless unblinded information is judged necessary for safety reasons.

7.6. Concomitant Medications and Non-Pharmacologic Therapies and Procedures

Adjunctive antiepileptic drug (AED) treatment, (medical) marijuana, cannabidiol products, VNS settings, and ketogenic diet should not be altered during the study. Concurrent treatment regimen data will be collected throughout the study.

All medication including vitamin supplements, over-the-counter medications, and herbal preparations including (medical) marijuana and cannabidiol products will be collected throughout the study.

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Use of perampanel from screening through follow-up is prohibited.

Use of traditional Chinese medicines should be approved by the Medical Monitor at screening.

7.7. Treatment Compliance

Patient compliance with study medication will be assessed at each visit. On in-clinic dosing days, after administration of study drug, appropriate mouth and/or hand checks will be performed to ensure that the dose is swallowed and noted in the source document. If a site visit is not possible during the morning hours, the patient should take their morning dose prior to attending the visit during the afternoon hours. The date and time of dose given in the clinic will be recorded in the source documents and on the eCRFs.

Patients and/or patients' caregivers will be required to bring study drug/unused study drug and the daily recording in the dosing card to each dispensing site visit. All patients and/or patients' caregivers should be re-instructed about the dosing requirements during study contacts. The authorized study personnel conducting the re-education must document the process in the patient source records.

Patients who are significantly noncompliant will be discontinued from the study. A patient will be considered significantly noncompliant if he or she intentionally misses more than 20% of study medication during the study. Similarly, a patient will be considered significantly noncompliant if he or she is judged by the Investigator to have intentionally or repeatedly taken more than the prescribed amount of medication.

8. STUDY ASSESSMENTS

The following sections describe the study procedures to be performed and data to be collected. For each procedure, patients are to be assessed by the same Investigator or site personnel whenever possible. Study procedures and their timing (including tolerance limits for timing) are summarized in the Schedule of Assessments (Appendix 1, Table 3).

Appendix 2 lists the laboratory tests that will be performed for this study.

Appendix 3 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

8.1. Study Procedures

8.1.1. Informed Consent Procedure

The requirements of the informed consent are described in Section 11.1.

8.1.1.1. Study Informed Consent Procedure

Informed consent must be obtained before the patient enters into the study, and before any protocol-directed procedures are performed.

The informed consent form must be signed by the patient's legally authorized representative. A verbal or written patient assent should be obtained from the patient, if applicable, in the event the patient is not capable of providing an informed consent. If the patient is not capable of providing an assent, the reason should be documented by the Investigator.

A unique patient identification (ID) number (patient number) will be assigned to each patient and will be used throughout the study.

8.1.2. Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include year of birth (as allowed per local regulations), gender, ethnicity, and race as described by the patient/caregiver. Height and weight will be collected at Screening (Visit 1).

Medical history to be obtained will include determining whether the patient has any significant conditions or diseases relevant to the disease under study that resolved at or before signing of informed consent. Ongoing conditions are considered concurrent medical conditions.

Medication history information to be obtained includes any medication relevant to eligibility criteria and the efficacy or safety evaluations stopped at or within 28 days before signing of informed consent. AED history will be collected as part of the medication history information.

8.1.3. Physical Examination Procedure

The physical examination will consist of the following body systems: (1) head, eyes, ears, nose, and throat; (2) cardiovascular system; (3) respiratory system; (4) gastrointestinal system; (5) dermatologic system; (6) extremities; (7) musculoskeletal system; (8) lymph nodes; (9) psychiatric status; and (10) other. All examinations are to be performed by the Investigator or

a qualified site staff member. The physical examination must be captured in the source document and eCRF.

8.1.4. Neurological Examination Procedure

A separate neurological examination will be performed and collected in the eCRF. This will include testing mental status, gait, cerebellar function, cranial nerves, motor function, and sensation.

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8.1.5. Weight and Height

Weight and height are to be measured while the patient is wearing indoor clothing and with shoes off. If unable to obtain height or weight, data may be collected from other sources (e.g., medical records or the patient's caretaker). The Investigator must document in the source document the reason for not obtaining height or weight (e.g., the patient is in a wheelchair).

8.1.6. Vital Signs Procedure

Vital signs to be measured are temperature, blood pressure, heart rate (beats per minute), and respiratory rate.

Vital signs should be measured at the same time of day across visits, if possible. When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 15 minutes before or after the scheduled blood draw, if possible.

All vital signs data collected at study visits will be recorded on the source documents and in the eCRF.

8.1.7. Seizure Diary Procedure

The seizure diary is an observer-reported clinical outcome assessment measure that captures the total number of motor seizures (i.e., drop seizures, tonic-clonic, tonic, bilateral clonic, atonic, myoclonic-atonic, myoclonic-tonic-clonic, focal seizures with bilateral hyperkinetic motor features) by type, in accordance with the new seizure classification system.[7] Patients and/or patients' caregivers will be the observers and reporters in the current study. Patients and/or patients' caregivers may record seizures throughout the day and must ensure that the daily diary assessment is completed each evening, even if no seizures occurred.

Drop seizures are defined as a seizure involving the entire body, trunk, or head that leads to a fall, injury, slumping in a chair, or head hitting the surface, or could have led to a fall or injury, depending on the position of the patient at the time of the attack or spell. Drop seizures will be counted separately for patients enrolled in LGS stratum (e.g., tonic seizures or generalized tonic clonic seizures leading to a drop will be captured as a drop). Convulsive seizures include

generalized tonic-clonic, focal to bilateral tonic-clonic with impaired awareness, hemi-clonic and simultaneous bilateral clonic (generalized clonic) seizures.

At the Screening visit (Visit 1) and at every clinic visit, the patient and/or patient's caregiver will be given a seizure diary and specific instructions to ensure compliance with the seizure recording. The seizure events will be recorded starting at the Screening/Baseline Period up until the Follow-up Visit. At each clinic visit, the diary will be collected and reviewed by the Investigator with the patient and/or patient's caregiver for proper recording.

For the prospective Baseline Period, the seizure frequency will be calculated as

(# of seizures) / (# of days seizures were assessed) × 28

Seizure frequency calculated through this method will be used to confirm the eligibility.

8.1.8. Documentation of Study Drug

A dosing card will be provided to the patient and/or caregiver at each clinic visit to record actual time of the last 2 dose administrations prior to PK sample collection, to record exact time of the last meal relative to dosing prior to PK or PD sample collection, and to record any changes in dosing regimen that may occur between visits and during the de-escalation period of the study; these will be recorded in the patient's source documents and transcribed into electronic case report forms (eCRFs).

8.1.9. Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the patient over the counter. Concomitant medication is not provided by the Sponsor. At each study visit, patients and/or caregivers will be asked whether patients have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and herbal preparations, must be recorded in the source document and eCRF. Documentation will include generic medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

AED treatment, VNS settings, and ketogenic diet should not be altered during the study.

8.1.10. Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. These include clinically significant laboratory, ECG, or physical examination abnormalities noted at Screening (Visit 1), according the judgment of the Investigator. The condition (i.e., diagnosis) should be described and recorded on the Medical History form.

8.1.11. Procedures for Clinical Laboratory Samples

Blood and urine samples are to be collected at the time points stipulated in the Schedule of Assessments (Table 3). Samples will be collected in accordance with acceptable laboratory procedures. Details of these procedures and required safety monitoring will be given in the laboratory manual.

The clinical laboratory tests to be performed are listed in Appendix 2.

For an individual patient, the maximum volume of blood collected over the course of the study will be 73.2 mL (Appendix 3). As this is a pediatric study, blood volume limitations will sometimes preclude the collection of all samples in a particular study visit. Appendix 3 enumerates the priorities for blood collection.

In general, existing guidelines for blood sample volume limits (ranging from 1% to 5% of total blood volume within 24 hours and up to 10% of total blood volume over 8 weeks) are consistent with the limited evidence available on "minimal risk" to children. Examples of guidelines for blood draw limits in pediatrics can be found at: http://www.who.int/bulletin/volumes/89/1/BLT-10-080010-table-T2.html.

The central laboratory will perform laboratory tests for hematology, serum chemistry, and urinalysis. The results of clinical laboratory tests will be returned to the Investigator, who is responsible for reviewing and filing these results. The Investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

If patients experience ALT or AST >3 × ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed preferably within 48 to 72 hours and no later than 5 days after the abnormality was noted. Please refer to Section 6.3.1 for discontinuation criteria and Section 8.3.3.1 for reporting requirements related to ALT or AST >3×ULN in conjunction with total bilirubin >2×ULN.

If the ALT or AST remains elevated >3 × ULN on these 2 consecutive occasions, the Investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, and discussion of the relevant patient details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 8.3.3.1 for reporting requirements).

If urine cannot be collected due to the patient's cooperation or because the patient is wearing a diaper, the reason should be documented in the source document and, for sexually active female patients, the results of the serum pregnancy test obtained at Visit 1 must be confirmed to be negative by the Investigator prior to randomization.

8.1.12. Contraception and Pregnancy Avoidance Procedure

Please refer to Section 6.1 for detailed contraception requirements.

Patients will be provided with information on acceptable methods of contraception as part of the patient informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study and for 90 days after the last dose of study drug. This may be signed by the legally authorized representative of the patient.

All sexually active female patients of childbearing potential must have a negative serum/urine hCG pregnancy test at Screening (Visit 1) and a negative urine hCG pregnancy test on Day 1 (Visit 2), before receiving any dose of study drug. If urine cannot be collected at Visit 2, the reason should be documented in the source document, the results of the serum pregnancy test obtained at Visit 1 must be confirmed to be negative by the Investigator prior to randomization, and results of a serum pregnancy test at Visit 2 must be confirmed to be negative before the

patient can receive the first dose of study drug. During the course of the study, patients will receive continued guidance with respect to the avoidance of pregnancy and ova or sperm donation as part of the study procedures. An additional serum/urine hCG pregnancy test will be performed at the Final Visit.

Sexually active male patients (post-pubertal unless permanently sterilized by bilateral orchidectomy) must agree to use male contraception (condom) during the study and for a minimum of 90 days following the last dose of study drug. Male patients must also not donate sperm during the Screening and Treatment Periods and for at least 90 days after the last dose of study drug.

8.1.13. ECG Procedure

A 12-lead ECG will be recorded at Screening (Visit 1) and at 30 min (±10 min) after the morning dose at other visits. If the patient cannot tolerate being supine, a sitting ECG may be obtained. The Investigator (or a qualified observer at the study site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The interpretation of the ECG will be recorded in the source documents and in the eCRF. The time that the ECG was performed will be recorded. The following parameters will be recorded on the eCRF from the patient's ECG trace: heart rate, RR interval, PR interval, QT interval, QRS interval with QTcF and corrected QT interval. ECG traces recorded on thermal paper will be photocopied to avoid degradation of trace over time.

8.1.14. Clinical Assessment of Suicidal Ideation and Behavior

Suicidal ideation and behavior will be assessed in children aged ≥6 years by the use of the C-SSRS. The C-SSRS is a 3-part scale that measures suicidal ideation (e.g., patient endorses thoughts about a wish to be dead or has other thoughts of suicide), intensity of ideation (frequency), and suicidal behavior (actually, interrupted, and aborted attempts at suicide).[8]

Two versions of the C-SSRS will be used in this study, the Screening/Baseline C-SSRS Lifetime and the Since-Last-Visit C-SSRS.

Study staff trained in the administration of the C-SSRS will assess patient suicidality using the C-SSRS, eliciting answers from the patient or the patient's caregiver. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the clinical judgment of the investigator.

If a patient exhibits signs of suicidal ideation, the patient may be discontinued as described in Section 6.3.1.

8.1.15. Aberrant Behavior Checklist

Behavior will be assessed by the use of the ABC-C questionnaire, which is a rating scale that measures the severity of a range of problem behaviors commonly observed in individuals with intellectual and developmental disabilities.[9] It is completed by the caregiver. It is an empirically developed scale designed to measure psychiatric symptoms and behavioral disturbance exhibited by individuals across 5 domains with 58 items: irritability, agitation, and crying (15 items); lethargy, social withdrawal (16 items); stereotypy (7 items); hyperactivity/noncompliance (16 items); and inappropriate speech (4 items).

If the patient is unable to comply with the ABC-C, for example due to the language barrier (e.g., unavailability of validated test in patient's language), the Investigator may also use clinical judgment to assess for behavior.

8.1.16. Vineland Adaptive Behavior Scale

The Vineland Adaptive Behavior Scales, 3rd Edition, Parent Caregiver Form (VABS-3 Parent Caregiver Form), is a parent-report questionnaire of adaptive functioning or how an individual behaves in their day-to-day life at home and in the community.[10] It assesses adaptive functioning across 4 domains: problem behavior, communication, daily living, and socialization. The questionnaire takes about 20 minutes to complete.

If the patient is unable to comply with the VABS, for example due to the language barrier (e.g., unavailability of validated test in patient's language), the Investigator may also use clinical judgment to assess for adaptive function and behavior.

8.1.17. Quality of Life in Childhood Epilepsy

The Quality of Life in Childhood Epilepsy is a parent-reported questionnaire that evaluates health related quality of life in children ages 4 to 18 years old. It contains 76 items with 16 subscales covering 7 domains of life function: physical activities, social activities, cognition, emotional wellbeing, behavior, general health, and general quality of life.

8.1.18. Sleep Disruption Numerical Rating Scale

The patient's caregiver will be asked:

> "On a scale of '0 to 10', please circle the number that best describes your child's sleep disruption in the last week."

The markers range from 0 (slept extremely well) to 10 (unable to sleep at all). If the main caregiver is not available at the appropriate visit then this information can be captured over the telephone, ideally on the day of the visit or otherwise within 3 days.

8.1.19. Caregiver Global Impression of Change (Care GI-C)

At Visit 2 (prior to administration of the first dose of study drug), the caregiver will be asked to write a brief description of the patient's overall condition as a memory aid for the Care GI-C at subsequent visits.

The Care GI-C comprises the following question to be rated on a 7-point scale:

> Since your child started treatment, please assess the status of your child's overall condition (comparing their condition now to their condition before treatment) using the scale below.

- Very Much Improved
- Much Improved
- Slightly Improved
- No Change
- Slightly Worse

- Much Worse
- Very Much Worse

If the main caregiver is not available at the appropriate visit then this information can be captured over the telephone, ideally on the day of the visit or otherwise within 3 days.

8.1.20. Clinician's Clinical Global Impression of Severity and Change (CGI-S/C)

CGI-Severity (CGI-S) is used to obtain an assessment of symptoms severity. The CGI-S focuses on clinicians' observations of the patient's cognitive, functional, and behavioral performance since the beginning of the study. The CGI-S/C measures improvement from the first assessment.

The CGI-S is rated on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (amongst the most severely ill patients).

For the CGI-Change (CGI-C) treatment response ratings should take account of both therapeutic efficacy and treatment-related AEs and range from 0 (marked improvement and no side-effects) and 4 (unchanged or worse and side-effects outweigh the therapeutic effects). Each component of the CGI is rated separately; the instrument does not yield a global score.

The PI or designee will complete the CGI-S/C at the timepoints specified in Table 3.

8.1.21. Early Termination

Early Termination/Exit survey will be conducted at Visit 6 and takes approximately 2 minutes. The survey captures the parent's (and caregiver's) experiences with TAK-935 including impact of treatment with TAK-935 on daily life/functioning and on most important bothersome symptoms.

8.1.22. Pharmacokinetic Sample Collection and Analysis

8.1.22.1. Collection of Plasma Samples for TAK-935 and M-I PK Evaluation

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8.1.22.2. Bioanalytical Methods for TAK-935 and M-I

Plasma concentrations of TAK-935 and M-I will be measured by high-performance liquid chromatography with tandem mass spectrometry.

8.1.22.3. Pharmacokinetic Parameters

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8.1.23. Pharmacodynamic Sample Collection and Analysis

8.1.23.1. Collection of Plasma Samples for Pharmacodynamic Evaluation

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[redacted]

CCI

[redacted]

8.1.23.2. Bioanalytical Methods for 24HC

CCI

[redacted]

8.1.23.3. Pharmacodynamic Parameters

The PD parameter of change from Baseline in plasma 24HC levels will be summarized. Additional PD parameters may be calculated, as appropriate.

8.1.23.4. Documentation of Screen Failure

Investigators must account for all patients with a signed informed consent. If the patient is found to be ineligible for the study at this visit, the Investigator will enter the reason in the IWRS. The IWRS should be contacted as a notification of screen failure.

The primary reason for screen failure is to be recorded in the IWRS. Patients may be re-screened after consultation with the Medical Monitor.

Patient ID numbers assigned to patients who fail screening should not be reused. If a patient fails screening, but is later successfully rescreened, the data for the patient will be entered as if these were 2 separate patients. Therefore, the data should be entered as follows:

1. The screen failure data should be entered as a screen failure patient.
2. Rescreened patients should be assigned a new patient ID number and treated as a stand-alone patient.

8.1.23.5. Documentation of Study Entrance

Only patients who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the study.

If the patient is found to be not eligible, the Investigator should record the primary reason for failure on the applicable IWRS.

8.2. Sample Collection and Testing

Appendix 1 lists the schedule for sample collections in this study.

Appendix 2 lists the laboratory tests that will be performed for this study.

Appendix 3 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

8.2.1. Optional Blood Samples for Storage: CCI

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Samples for research purposes are optional and will be collected as specified in the Schedule of Assessments (Table 3).

The optional blood samples will be coded with the patient number and stored for up to a maximum 15 years after the last patient visit for the study at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the patient by the Investigator or site personnel. The duration allows the sponsor to respond to regulatory requests related to the study drug.

Samples will be destroyed according to a process consistent with local regulation. Patients may request to have their samples destroyed at any time.

8.3. Safety Evaluations

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting the Sponsor or designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The Investigator is responsible for the appropriate medical care of patients during the study. The Investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to the study treatment or the study, or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the Investigator.

8.3.1. Adverse Events

An AE is any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (for example, an abnormal

laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether considered related to this medicinal product.

The definition of an AE also covers medication errors and uses outside what is foreseen in the protocol only if an AE results from the error, including intentional misuse, abuse, and overdose of the product. Adverse events (including SAEs) associated with overdose should be reported according to the procedure outlined in Section 8.3.1.5. In the event of drug overdose, the patient should be treated symptomatically.

Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital) and anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen are not AEs.

Ovid has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish drug effect.

Cases of pregnancy that occur during maternal or paternal exposures to study drug are to be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

Study site personnel will record the occurrence and nature of each patient's pre-existing conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

Seizures in this patient population will be measured using the seizure diary and seizure frequency as a primary study endpoint (see Section 8.1.7). For the purpose of this study, reporting of seizures should meet the AE/SAE reporting requirements. As seizures are considered a baseline condition, seizures should be reported as an AE/SAE if: 1) there is a clear increase in the frequency of seizures compared to the patient's baseline, 2) there is an emergence of a new seizure type, or 3) the patient experiences status epilepticus, and 4) any other time the Investigator feels the seizure should be captured as an AE/SAE, in which case the Investigator should document his/her reasoning. All seizures will be captured in the seizure diary collected at the site during the study and will be analyzed by the Sponsor along with the reportable SAEs in evaluating risk:benefit. The Sponsor will report the SAE events of seizure that meet these criteria in an aggregated unblinded report at the conclusion of the study.

After the informed consent form (ICF) is signed, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs. If a patient experiences an AE after signing informed consent, but prior to receiving study drug, the event will be reported, but will be included in the patient's medical history unless the event is serious, or the Investigator feels the event may have been caused by a protocol procedure.

In addition, all AEs occurring after the patient receives the first dose of study drug must be reported to Ovid or its designee via the eCRF.

8.3.1.1. Severity Assessment

Investigators will be instructed to rate the severity of AEs using the following criteria:

Mild	Events require minimal or no treatment and do not interfere with the patient's daily activities.
Moderate	Events result in a low level of inconvenience or concerns with the therapeutic measures. Moderate events may cause some interference with functioning.
Severe	Events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Change in severity of an AE should be documented based on specific guidelines in the eCRF Completion Guidelines.

Severity and seriousness must be differentiated: severity describes the intensity of an AE, while the term seriousness refers to an AE that has met the criteria for an SAE.

8.3.1.2. Causality Assessment

Investigators will be instructed to report to Ovid or its designee their assessment of the potential relatedness of each AE to protocol procedure and/or study drug via the CRF.

An Investigator causality assessment (unrelated or related) must be provided for all AEs (both serious and non-serious). This assessment must be recorded in the CRF and any additional forms as appropriate.

Relationship of AEs to the defined study treatment (TAK-935 [after the start of TAK-935 on Day 1]), will be determined by the Investigator according to the following criteria. Please note that not all criteria must be present to be indicative of a particular relationship.

Not Related	Exposure to the defined study treatment did not occur, or the occurrence of the AE is not reasonably related in time
Unlikely Related	The AE occurred in a reasonable time after the defined study treatment and is doubtfully related to the investigational agent/procedure
Possibly Related	The defined study treatment and the AE were reasonably related in time, and the AE could be explained equally well by causes other than exposure to the defined study treatment
Related	The defined study treatment and the AE were reasonably related in time, and the AE was more likely explained by exposure to the defined study treatment than by other causes, or the defined study treatment was the most likely cause of the AE

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to Ovid or its designee via CRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

8.3.1.3. Serious Adverse Events

Serious adverse event collection begins after the patient has signed informed consent. If a patient experiences an SAE after signing informed consent, but prior to receiving study drug, the event will be reported, but will be classified as a pre-treatment SAE unless the Investigator feels the event may have been caused by a protocol procedure.

Planned surgeries and/or hospitalizations should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Study site personnel must alert Ovid or its designee of any SAE within 24 hours of Investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

An SAE is any AE from this study that results in 1 or more of the following outcomes:

- Results in death
- Requires or prolongs hospitalization
- Is life threatening (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly or birth defect
- Other medically important serious event

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse events occurring up to and including the patient's last study visit will be collected, regardless of the Investigator's opinion of causation.

If an Investigator becomes aware of SAEs occurring to a patient after the patient's participation in the study has ended (including any protocol-required post-treatment follow-up), the Investigator should report the SAEs to the sponsor, regardless of the Investigator's opinion of causation.

8.3.1.4. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the Investigator identifies as related to study drug or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidance or national regulatory requirements in participating countries require the reporting of SUSARs. Ovid has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidance.

8.3.1.5. Reporting Adverse Events

All non-serious AEs must be recorded in the eCRF upon awareness.

Any AE that meets SAE criteria (Section 8.3.1.3) must immediately (i.e., within 1 business day) be sent to the Sponsor upon learning of any SAE that occurs (whether or not attributable to the study drug). It is the Investigator's responsibility to ensure that SAE reporting procedures are followed appropriately. All SAE reports and any revisions to an SAE report must be sent to the following fax number or email. All supporting source information concerning the SAE (e.g., hospital records) should also be provided by fax or email.

Country-specific fax numbers will be provided in a separate document.

Email: PPD

If there is a question concerning an SAE, the site needs guidance regarding reporting of an SAE, the site is returning a call from the Sponsor's safety specialist, or the site urgently needs to report an SAE or make the Sponsor aware of an SAE, the safety hotline should be used (country-specific hotline numbers provided in a separate document).

If an SAE is reported via the hotline, the site should first submit the SAE paper form and then enter the SAE in the eCRF. Any AE that meets SAE criteria must be entered into the EDC system immediately (i.e., within 1 business day) after site personnel first learns about the event in addition to faxing/emailing the SAE Report form. Once the qualifying SAE data are entered into EDC, the Sponsor will be notified by an email alert, which will contain high-level safety information.

All SAEs must be reported starting from the time that informed consent for study participation is provided. If the Investigator becomes aware of an SAE within 30 days after the patient's last dose of study drug or within 30 days after the last study visit, the SAE must be reported. Serious AEs must be followed until the event resolves, the event or sequelae stabilize, or it is unlikely that additional information can be obtained after demonstration of due diligence with follow-up efforts (i.e., the patient or health care practitioner is unable to provide additional information, or the patient is lost to follow up). Serious AEs that occur more than 30 days after the last dose of study drug need not be reported unless the Investigator considers them related to study drug.

8.3.1.6. Sponsor Reporting Requirements

The Sponsor or its legal representative is responsible for notifying the relevant regulatory authorities of SAEs meeting the reporting criteria. This protocol will use Appendix A of the current IB as the Reference Safety Document. The expectedness and reporting criteria of an SAE will be determined by the Sponsor from the Reference Safety Information.

8.3.1.7. Investigator Reporting Requirements

The Investigator must fulfill all local regulatory obligations required for the study Investigators. It is the Principal Investigator's responsibility to notify the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of all SAEs that occur at his or her site. Investigators will also be notified of all SUSAR events that occur during the clinical study. Each site is responsible for notifying its IRB/IEC of these additional SAEs.

Investigators will receive blinded information unless unblinded information is judged necessary for safety reasons.

8.3.2. Exposure During Pregnancy and/or Lactation

TAK-935 should not be administered to pregnant and lactating females because the potential for adverse reactions to TAK-935 in pregnant females, fetuses, and nursing infants is unknown.

Pregnancy data will be collected during this study for all patients. Exposure during pregnancy (also referred to as exposure in-utero [EIU]) can be the result of either maternal exposure or transmission of drug product via semen following paternal exposure.

For all Ovid products, both in development or post-approval, exposure during pregnancy must be recorded and the patient followed until the outcome of the pregnancy is known (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), even if the patient discontinues study drug or discontinues from the study.

If a patient within this study or a patient's partner becomes pregnant while treated or exposed to study drug, the Investigator must submit a pregnancy form to Ovid via the same method as SAE reporting. Pharmacovigilance will supply the Investigator with a copy of a "Pregnancy Reporting and Outcome Form/Breast Feeding." When the outcome of the pregnancy becomes known, the form should be completed and returned to Ovid or Ovid Pharmacovigilance delegate. If additional follow-up is required, the Investigator will be requested to provide the information.

Exposure of an infant to an Ovid product during breastfeeding must also be reported and any AEs experienced by the infant must be reported to Ovid Pharmacovigilance or designee via Email or fax (Section 8.3.1.5).

Pregnancy is not regarded as an AE unless there is a suspicion that study drug may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet criteria for an SAE (such as ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly). Elective abortions without complications should not be reported as AEs.

8.3.3. Safety Monitoring

The Sponsor's Medical Monitor and/or Pharmacovigilance physician will monitor safety data throughout the course of the study.

8.3.3.1. Reporting of Abnormal Liver Function Tests

If a patient is noted to have ALT or AST elevated >3 × ULN on 2 consecutive occasions, as specified in Section 8.1.11, the abnormality should be recorded as an AE.

If a patient is noted to have ALT or AST >3 × ULN and total bilirubin >2 × ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 8.3.1.5. The Investigator must contact the Medical Monitor for discussion of the relevant patient details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 8.1.11 must also be performed.

8.4. Appropriateness of Measurements

All efficacy and safety assessments included in this study are generally regarded as reliable and accurate with respect to the efficacy and safety assessments in individuals and populations with Dravet syndrome and LGS.

9. DATA QUALITY ASSURANCE

To ensure accurate, complete, and reliable data, the Sponsor or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate
- Sponsor start-up training to instruct the Investigators and study coordinators. This training will give instruction on the protocol, the completion of the eCRFs, and study procedures
- Make periodic visits to the study site
- Be available for consultation and stay in contact with the study site personnel by Email, telephone, and/or fax
- Review and evaluate CRF data and use standard computer edits to detect errors in data collection
- Conduct a quality review of the database

In addition, the Sponsor or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by the Sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the Investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the Investigator will provide the sponsor, applicable regulatory agencies, and applicable IRBs/IECs with direct access to original source documents.

9.1. Data Collection and Storage

All clinical raw data will be recorded promptly, accurately, and legibly, either directly into the source document or indelibly on paper (e.g., ECG readings). When recorded electronically, case report forms will be electronically generated. All raw data will be preserved to maintain data integrity. The Investigator or designee will assume the responsibility of ensuring the completeness, accuracy, and timeliness of the clinical data.

The electronic data capture system is fully validated and Code of Federal Regulations Title 21 Part 11 compliant. The electronic data capture system will maintain a complete audit trail of all data changes. At each scheduled monitoring visit, the Investigator or designee will cooperate with the Sponsor's representative(s) for the frequent review of study documents to ensure the accuracy and completeness of the data capture system.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the respective study sites by means of electronic or manual queries.

The Investigator or designee will prepare and maintain adequate and accurate study documents (medical records, ECGs, AE and concomitant medication reporting, raw data collection forms) designed to record all observations and other pertinent data for each patient receiving study drug or placebo.

The Investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors, and the IRB/IEC to have direct access to all documents pertaining to the study.

10. STATISTICAL METHODS AND PLANNED ANALYSES

10.1. General Considerations

All statistical analyses will be performed using SAS® Version 9.3 or higher. All clinical study data will be presented in patient data listings. Data summaries will be presented for all endpoints and will include descriptive statistics (number of patients [n], mean, standard deviation [SD], first quartile [Q1], median, third quartile [Q3], minimum and maximum) for continuous variables, and frequency and percentage for categorical and ordinal variables. If there are missing values, the number of missing will be presented, but without a percentage. For all analyses, 'Baseline' refers to the prospective 4-week Baseline Period.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan (SAP) which will be finalized and approved prior to database lock. Additional exploratory analyses of the data may be conducted as deemed appropriate.

10.2. Stratification by Seizure Type

At Visit 2, all eligible patients will be stratified by 2 categories: patients with Dravet syndrome with convulsive seizures, and patients with LGS with drop seizures to ensure balance of treatments within each stratum. Note that patients with both the minimum number of convulsive and drop seizures will be assigned to a stratum following the noted rules.

Patients with Dravet syndrome:

- 46 eligible patients diagnosed with Dravet syndrome with ≥3 convulsive seizures per 28 days during the prospective Baseline period will be randomized into the Dravet syndrome stratum

Patients with LGS:

- 80 eligible patients diagnosed with LGS with ≥4 drop seizures per 28 days during the prospective Baseline period will be randomized into the LGS stratum

If a patient does not meet any of these criteria, the patient will be considered a screen failure.

10.3. Determination of Sample Size

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[redacted]

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[redacted]

10.4. Analysis Sets

10.4.1. Modified Intent-to-Treat Analysis Set

All randomized patients who have received at least 1 dose of study drug and have been assessed for at least 1 day in the Treatment Period will be included in the modified intent-to-treat (mITT) analysis set. All mITT analyses will be based on each patient's randomized treatment assignment.

10.4.2. Efficacy Analysis Set

All mITT patients whose efficacy assessments are compliant with Protocol Amendment 2 will be included in the efficacy analysis set. Efficacy analyses for primary and secondary efficacy endpoints will be based on the efficacy analysis set. CCI [redacted] Efficacy analyses will be based on each patient's randomized treatment assignment.

10.4.3. Safety Analysis Set

All randomized patients who take at least 1 dose of study medication will be included in the Safety Analysis Set. Safety analyses will be based on the medication that was actually administered to each patient.

10.5. Demographics and Baseline Characteristics

Demographic characteristics include age, gender, race, ethnicity, and study center. Baseline characteristics include baseline body weight, height, and the randomization stratum. Summary statistics by treatment group and overall will include counts and percentages for discrete variables, and means, SD, Q1, medians, Q3, minimum and maximum for continuous variables.

10.6. Patient Disposition

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

Disposition data will be summarized and provided in patient listings.

10.7. Concomitant Medications and Non-Pharmacologic Therapies and Procedures

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). A by-patient listing of concomitant medications will include all medications taken during the study regardless of the timing for the start of the medication. All medications started prior to the administration of the study drug will be included in the data but will be identified as prior in the listing. Only the concomitant medication use will be summarized.

The number and percentage of patients who took at least 1 medication during the double-blind period as well as the number and percentage of patients who took each type of medication will be presented for each treatment group. Medications will be listed according to their WHO-DD anatomic therapeutic chemical (ATC) class level 4 and preferred drug name within ATC class level 4 by decreasing frequency of incidence for all active treatment groups combined.

10.8. Treatment Compliance

Treatment compliance will be summarized by treatment group over the entire treatment period. Compliance rates during the treatment period will be derived using the following formula:

100*(Total number of tablets/mini-tablets dispensed – Total number of tablets/mini-tablets returned) / (Expected number of tablets/mini-tablets)

Expected number of tablets/mini-tablets to be taken is based on the date of first study medication dose and the date of last study medication dose (ie, [date of last study medication dose – date of first study medication dose] +1). Compliance rates will be presented for the safety analysis set using summary statistics and percentage for the frequency distributions (0% to <20%, 20% to 40%, 40% to <60%, 60% to <80%, 80% to <100%, 100% to ≤120%) by treatment group and overall.

10.9. Efficacy Analyses

10.9.1. Primary Efficacy Analyses

For the patients randomized to the Dravet syndrome stratum (≥3 convulsive seizures per 28 days), convulsive seizure frequencies per 28 days for the 4-week prospective Baseline Period and the Maintenance Period will be calculated.

For the patients randomized to the LGS stratum (≥4 drop seizures per 28 days), drop seizure frequencies per 28 days for the 4-week prospective Baseline Period and the Maintenance Period will be calculated.

The seizure frequency per 28 days in a study period will be calculated as

(# of seizures) / (# of days seizures were assessed) × 28

For each patient, percent change from Baseline to the frequency during Maintenance Period (per 28 days) will be calculated for the seizure type corresponding to the assigned stratum of that patient (convulsive for the Dravet and drop for the LGS stratum). Percent change from Baseline will be compared between TAK-935 and placebo using a Mann-Whitney (Wilcoxon) test adjusting for Baseline seizure frequency and randomization stratum.

The null hypothesis of no treatment difference will be tested at a two-sided 0.05 level of significance. The Mann-Whitney estimator and the corresponding 95% confidence interval (CI) comparing TAK-935 with placebo will also be displayed.

10.9.2. Secondary Efficacy Analyses

For Dravet stratum, percent change in convulsive seizure frequency from Baseline to the frequency of convulsive seizures during the Maintenance Period will be compared between TAK-935 and placebo using a Mann-Whitney test adjusting for Baseline convulsive seizure frequency and randomization stratum. For the LGS stratum, percent change in drop seizure frequency from Baseline to the frequency of drop seizures during the Maintenance Period will be compared between TAK-935 and placebo using a Mann-Whitney test adjusting for Baseline drop seizure frequency. The Mann-Whitney estimator and the corresponding 95% CI comparing TAK-935 with placebo will also be displayed.

The primary efficacy analysis will be repeated for the 20-week Treatment Period.

For the Dravet syndrome strata, the proportion of treatment responders based on ≥25% worsening, <25% and >1% worsening, no change (Worsening of 1% to Reduction of 1%), ≥25% reduction, ≥50% reduction, ≥75% reduction, and 100% reduction from Baseline in convulsive seizure frequency for the Maintenance Period will be summarized for TAK-935 and placebo. The 95% CIs for the difference of proportions will be displayed for each responder category. For the LGS stratum, the proportion of treatment responders based on ≥25% worsening, <25% and >1% worsening, no change (Worsening of 1% to Reduction of 1%), ≥25% reduction, ≥50% reduction, ≥75% reduction, and 100% reduction from Baseline in drop seizure frequency for the Maintenance Period will be summarized for TAK-935 and placebo; 95% CIs for the difference of proportions will be displayed for each responder category.

Change in CGI-S/C responses of Investigator reported impression of efficacy and tolerability of study drug and change in Care GI-C responses of parent/family reported impression of efficacy and tolerability of study drug will be analyzed descriptively.

Correlation of seizure frequency reduction and plasma 24 HC level will be explored.

Techniques for handling missing information with respect to reporting of seizures in the treatment period (Dose Optimization and Maintenance) will be specified in detail in the statistical analysis plan (SAP).

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[redacted]

10.10. Safety Analyses

All safety analyses will be conducted based on the Safety Analysis Set.

Descriptive statistics will be used to summarize all safety endpoints by treatment group. Two-sided 95% CIs will be presented where meaningful. Data summaries will be displayed for incidence of AEs, clinical laboratory variables, vital signs, body weight and height, ECG parameters, percent myoclonic- and atypical absence-free days, as well as changes in behavioral and adaptive functioning measures using VABS and sub-scales of ABC-C, as appropriate.

All data will be listed by patient.

10.10.1. Physical Examination, Vital Signs, and Other Physical Findings

Physical examinations (general appearance; skin; head, ear, eye, nose, and throat; neck; lymph node; chest; heart; abdominal cavity; limb; central nervous system; and musculoskeletal) at Baseline will be summarized. Shifts from Baseline to post-baseline study visits in each body system/site will be summarized by treatment group.

Vital signs (temperature, heart rate, respiratory rate, and systolic and diastolic blood pressure), weight, and height will be summarized descriptively at Baseline and all post-baseline study visits by treatment group. Change from Baseline to all post-baseline study visits also will be summarized descriptively by treatment group.

Data listings will be provided.

10.10.2. Clinical Laboratory Tests

Changes from Baseline to study timepoints in clinical chemistry, hematology, and urinalysis results will be summarized descriptively. Each laboratory parameter will be classified as low, normal, or high relative to the parameter's reference range. Laboratory abnormalities for each treatment will also be summarized with shift tables. Listings of patients with abnormal results will be provided.

10.10.3. Adverse Events

The following definitions will be used for AEs:

- Treatment-emergent adverse event (TEAE): Any AE that starts or increases in severity during or after the first dose of study drug
- Treatment-emergent SAE: A TEAE that is serious

The incidence of TEAEs, discontinuations due to TEAEs, drug-related, serious, and severe TEAEs will be summarized. All AEs will be coded using MedDRA and will be summarized by SOC and PT and treatment group. Detailed listings of AEs, SAEs, IARs, related AEs, and discontinuations due to AEs will be provided.

10.11. Pharmacokinetic/Pharmacodynamic Analyses

CCI [redacted]

10.12. Other Statistical Issues

10.12.1. Significance Levels

A primary endpoint is defined and will be tested at 0.05 level of significance. CCI [redacted]

10.12.2. Missing or Invalid Data

Techniques for handling missing information with respect to reporting of seizures in the treatment period (Dose Optimization and Maintenance) will be specified in detail in the statistical analysis plan (SAP).

10.13. Interim Analyses

Plasma concentrations of TAK-935 in first 12 patients within each category of aged ≥9 years and aged <9 years will be used to estimate PK parameters using the current population PK model. If needed, the dose will be adjusted. The frequency of PK sample collection may be changed based on results of interim analysis.

Overall and by-stratum futility and interim analyses may be performed. Enrollment may be stopped for 1 of the strata if the treatment effect is not sufficiently strong. If one stratum is discontinued, then the remaining patients may be re-allocated to continuing stratum. Thresholds for stopping enrollment will be pre-specified in the interim analysis plan.

11. INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

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 the patient and/or patient's legal representative (i.e., parent or legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, US Food and Drug Administration, Health Authorities, Ethics Committees, and/or IRBs.

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.

11.1. Informed Consent

The Investigator is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study.

The ICF will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The Investigator is responsible for ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of study drug.

A legal representative must give informed consent for a child to participate in this study. In addition to informed consent given by the legal representative, the child may be required to give documented assent, if capable.

11.2. Data Monitoring Committee

The specific responsibilities of the iDMC are described in the DMC Charter, which is maintained as a separate document.

11.3. Ethical Review

The Sponsor or its representatives must approve all ICFs before they are used at investigative sites(s). All ICFs must be compliant with the ICH guideline on GCP.

Documentation of IRB/IEC approval of the protocol and the ICF must be provided to the Sponsor before the study may begin at the investigative site(s). The IRB/IEC(s) will review the protocol as required.

The study site's IRB/IEC(s) should also be provided with the following:

- The current IB and updates during the study
- ICF
- Relevant curricula vitae

11.4. Regulatory Considerations

This study will be conducted in accordance with:

- Consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- The ICH GCP Guideline (E6)
- Applicable laws and regulations

The Investigator or designee will promptly submit the protocol to applicable IRB/IEC(s). Some of the obligations of the Sponsor may be assigned to a Third-Party Organization.

An identification code assigned to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and/or other study-related data.

11.4.1. Confidentiality

The Sponsor affirms that subject's rights to protection against invasion of privacy are in compliance with ICH and other local regulations (whichever is most stringent). Information about patients and their records will be kept confidential by the Sponsor and its representatives. Study related records identifying patients will be kept confidential and, to the extent permitted by applicable laws and/or regulations will not be made publicly available.

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject 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 the patient and/or patient's custodial parent or guardian, except as necessary for monitoring and auditing by the sponsor, its designee, FDA, Health Authorities, Ethics Committees, and/or IRBs.

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.

If any of the results of the study are published, patient's identity will remain confidential.

The Sponsor requires the Investigator to permit sponsor representatives and, when necessary, representatives from FDA and other regulatory authorities, monitor, auditor, IRB to have access to study related medical records in accordance with local privacy laws.

11.4.2. Investigator Information

Physicians with a specialty in neurology and/or epilepsy disorders will participate as investigators in this clinical study.

11.4.3. Protocol Signatures

The Sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each Principal Investigator will sign the protocol signature page and send a copy of the signed page to a Sponsor representative.

11.4.4. Final Report Signature

The clinical study report Coordinating Investigator will sign the final clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The Sponsor's responsible medical officer and statistician will approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

11.5. Publication Policy

The full terms regarding publication of the results of this study are outlined in the Clinical Study Agreement, Statement of Agreement, or the Master Clinical Study Agreement. Publication is permitted only after multi-center results are available and all disclosure requirements for clinical study registries have been met. Any data to be submitted for publication, including abstract submissions or presentations, are required to be submitted to Ovid for review at least 30 days prior to submission.

12. LIST OF REFERENCES

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

Table 3 Schedule of Assessments

	Screening/ Baseline Period	Double-blind Treatment Period									Follow-up Period
		Rand/ Dosing Day									
Visit (V) or Phone Call (P) Number[k]	**V1**	**V2**	**P1**	**V3**	**P2**	**V4**	**P3**	**V5**	**P4**	**V6**	**V7**
Study Day	**Days -42 to -1**	**Day 1**[a]	**Day 8**[a,l]**/ phone call**	**Day 15**[a]	**Day 22**[l]**/ phone call**	**Day 36**	**Day 57**[l]**/ phone call**	**Day 85**	**Day 113**[l]**/ phone call**	**Day 141/ ET**[a,b,d]	**Day 169/ Follow-up**[c]
Visit Window (days)		**±2**	**±2**	**±2**	**+2**	**±7**	**+2**	**±7**	**+2**	**±7**	**-7**
Informed consent and assent (if applicable)	X										
Inclusion/exclusion criteria	X	X									
Randomization		X									
Demographics, medical history, medication history	X										
Height, weight	X	X		X		X		X		X	
Concurrent medical conditions	X									X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
CGI-S/C & Care GI-C[j]		X				X		X		X	
C-SSRS	X	X						X		X	
Vineland Adaptive Behavioral Scale (VABS)	X									X	
Aberrant behavior checklist (ABC-C)	X									X	
Quality of Life in Childhood Epilepsy		X						X			
Sleep Disruption Numerical Rating Scale		X						X			
Exit survey[j]										X	
Serum/urine pregnancy test[e]	X	X								X	
Vital signs	X	X		X		X		X		X	X
Physical examination	X	X		X[f]				X[f]		X	X
Neurological examination, [redacted]	X	X		X		X		X		X	X
12-lead ECG[n]	X	X				X				X	

	Screening/ Baseline Period	Double-blind Treatment Period									Follow-up Period
		Rand/ Dosing Day									
Visit (V) or Phone Call (P) Number[k]	**V1**	**V2**	**P1**	**V3**	**P2**	**V4**	**P3**	**V5**	**P4**	**V6**	**V7**
Study Day	**Days -42 to -1**	**Day 1**[a]	**Day 8**[a,l]**/ phone call**	**Day 15**[a]	**Day 22**[l]**/ phone call**	**Day 36**	**Day 57**[l]**/ phone call**	**Day 85**	**Day 113**[l]**/ phone call**	**Day 141/ ET**[a,b,d]	**Day 169/ Follow-up**[c]
Visit Window (days)		**±2**	**±2**	**±2**	**+2**	**±7**	**+2**	**±7**	**+2**	**±7**	**-7**
Clinical laboratory tests (Chemistry, hematology, and urine analysis)	X	X		X		X		X		X	
Distribute seizure diary and provide instructions on use	X	X		X		X		X		X	
Collect seizure diary data		X		X		X		X		X	X
Plasma sample for TAK-935 PK[g]		X		X		X		X		X	
Plasma sample for AED analysis		X				X				X	
Plasma sample for PD (plasma 24HC)[h]		X		X		X		X		X	X
CCI											
IWRS to obtain patient ID/medication ID/patient status	X	X		X		X		X		X	X
Dispense study drug		X		X		X		X		X[m]	
In-clinic administration of morning dose of study drug		X		X		X		X		X	
Study drug return/ accountability/compliance				X		X		X		X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X

Abbreviations: AED=antiepileptic drug; Care GI-C=Caregiver Global Impression of Change; CGI-S/=Clinician's Clinical Global Impression of Severity and Change; C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; ET=Early Termination; ID=identification; IWRS=interactive web response system; P=phone call; PD=pharmacodynamics; Rand=randomization; V=visit.

a Two days after each dose escalation or taper, patients will be contacted by phone to monitor study drug compliance, concomitant medication use, and AEs. Patients will be contacted by phone within first two days following escalation to the maximum dose to assess safety and tolerability of the study drug.

b Patients who do not continue into the open-label extension (OLE) study will undergo the dose taper procedures and will then proceed to the Follow-up Period. Patients who continue in OLE may do a combined visit, i.e., the last visit of this trial may be combined with the first visit of the OLE

c The timing of the Follow-up Period and Follow-up Visit will depend on the dose taper procedures followed. Patients who are on Dose 1 (the lowest administered dose) of TAK-935 during the Maintenance Period will not undergo dose taper. Visit may be eliminated for patients enrolled in OLE.

d Patients who withdraw early from the study should complete all Final Visit procedures at the ET Visit.
e For sexually active female patients of childbearing potential, a serum pregnancy (hCG) test will be performed at the Screening visit. If urine cannot be collected at Visit 2, the reason should be documented in the source document, the results of the serum pregnancy test obtained at Visit 1 must be confirmed to be negative by the Investigator prior to randomization, and the results of a serum pregnancy test at Visit 2 must be confirmed to be negative before the patient can receive the first dose of study drug. Additional pregnancy tests (serum or urine) may be performed throughout the study at the Investigator's discretion.
f Physical examination can be limited to general appearance; head, eyes, ears, nose, and throat [HEENT]; cardiovascular; respiratory, and abdominal at Day 15 and Day 85.
g For the first 12 randomized patients aged ≥9 years and 12 randomized patients aged <9 years, PK blood samples for measurement of TAK-935 and M-I concentrations in plasma will be collected within 1 hour before the morning dose (pre-morning dose) and 30 min (±10 min) and 1, 2, and 4 hours (± 10 min) after the morning dose at Visit 2 (Day 1); within 1 hour before the morning dose (pre-morning dose) and 30 min (±10 min) post-dose at Visits 3, 4, 5, and 6. In the remaining randomized patients, PK blood draws will occur within 1 hour before the morning dose (pre-dose) and 30 min (±10 min) post-morning dose at Visits 2, 3, 4, 5, and 6 (Days 1, 15, 36, 85, and 141, respectively) during the study. An intravenous line (IV) line may be inserted for collection of all blood samples during the visit.
h PD blood samples for measurement of 24HC levels in plasma will be collected at pre-morning dose on Visits 2, 4, 5, and 6 (Days 1, 36, 85, 141, and 169, respectively).
i CCI [redacted]
j The ET/Exit survey will be conducted at Visit 6.
k Based on local country regulations and Sponsor approval, some study visits may be conducted at home.
l The study visits on Days 8, 22, 57, and 113 (phone calls 1 through 4) will be conducted via telephone.
m At Visit 6 (Day 141), dispensing study drug is applicable only for patients not entering the Open-label Extension study.
n A 12-lead ECG will be recorded at Screening (Visit 1) and at 30 min (±10 min) after the morning dose at Visits 2, 4, and 6.

APPENDIX 2. STUDY TAK-935-2002 (OV935): CLINICAL LABORATORY TESTS

Hematology	Serum Chemistry	Urinalysis (a)	Study Specific
RBC	ALT	pH	Plasma
WBC with differential (% and absolute)	Albumin	Specific gravity	24HC
Hemoglobin	Alpha-1-acid glycoprotein	Protein	
Hematocrit	Alkaline phosphatase	Glucose	
Platelets	AST	Blood	Plasma (Concomitant AEDs)
PT/INR	Total bilirubin	Nitrite	Carbamazepine
aPTT	Total protein		Clobazam
	Creatinine		*N*-desmethylclobazam
	Blood urea nitrogen	Microscopic Analysis: (b)	Valproic acid
	Creatine kinase	RBC/high power field	Phenytoin
	GGT	WBC/high power field	Topiramate
	Potassium	Epithelial cells, casts etc.	Lamotrigine
	Sodium		Rufinamide
	Glucose		Zonizamide
	Chloride		Phenobarbital
	Bicarbonate		Levetiracetam
	Calcium		Lacosamide
	Total cholesterol		10-hydroxycabazepine (metabolite of oxcarbazepine)
	HDL cholesterol		
	LDL cholesterol		Trileptal
	Triglycerides		Epidiolex

Diagnostic Screening	
Serum	Urine (a)
hCG (for pregnancy) (c)	hCG (for pregnancy) (c)

Abbreviations: AED=antiepileptic drug; aPTT= activated partial thromboplastin time, GGT=γ-glutamyl transferase, HDL=high-density lipoprotein, LDL=low-density lipoprotein, PT=prothrombin time, RBC=red blood cell; WBC=white blood cell.

(a) If urine cannot be collected at the time of the Screening Visit or other Visits due to the patient's cooperation or because the patient is wearing a diaper, it is acceptable for the patient to continue in the study and the reason should be documented in the source document.

(b) Only if dipstick results are positive.

(c) Only for sexually active female patients of childbearing potential. If urine cannot be collected at Visit 2, the reason should be documented in the source document, the results of the serum pregnancy test obtained at Visit 1 must be confirmed to be negative by the Investigator prior to randomization, and results of a serum pregnancy test at Visit 2 must be confirmed to be negative before the patient can receive the first dose of study drug. An additional serum hCG pregnancy test will be performed at the Final Visit.

APPENDIX 3. STUDY TAK-935-2002 (OV935): SAMPLING SUMMARY

This table summarizes the maximum number of samples and volumes for all sampling and tests during the study. Fewer samples may be taken, but this will not require a protocol amendment.

Protocol TAK-935-2002: Sampling Summary for Patients Weighing ≥10 kg

Purpose	Sample Type	Maximum Amount per Sample[b]	Maximum Number Samples	Maximum Volume in 30-day Period	Maximum Total Amount
Standard laboratory tests[a]	Blood	5.7 mL	6	11.4	34.2 mL
Pharmacokinetic samples	Blood	1 mL	13	7	13 mL
AED Drug concentration	Blood	4 mL	3	4	12 mL
Plasma Biomarker (24HC)samples (PD)	Blood	2 mL	6	4	12 mL
Optional blood sample for research	Blood	2 mL	1	2	2 mL
Total	Blood	14.7 mL	41 mL	28.4 mL	73.2 mL

a Additional samples may be drawn if needed for safety purposes.
b Maximum volume per sample is 14.7 mL.
Howie SR. Blood sample volumes in child health research: review of safe limits. Bulletin of the World Health Organization. 2011;89(1):46-53. doi:10.2471/BLT.10.080010.

Blood Collection: Priority Order

- Coagulation
- Chemistry
- Pregnancy test
- Serum sample for AED analysis
- Hematology
- Plasma sample for TAK-935 PK
- Plasma sample for PD (plasma 24HC)

Optional blood sample for research analysis: Blood volume limitations will sometimes preclude the collection of all samples in a particular study visit. In case this happens, for blood sample analysis, safety labs should be prioritized over labs for efficacy and exploratory analyses.

APPENDIX 4. STRONG CYP3A4 INDUCERS AND INHIBITORS

Use of perampanel from screening through follow-up is prohibited.

The strong inducers and inhibitors of CYP 3A4 listed below also are prohibited:

Strong CYP3A4 INDUCERS	**Strong CYP3A4 INHIBITORS**
Bosentan	Clarithromycin
Efavirenz	Telithromycin
Etravirine	Nefazodone
Modafinil	Itraconazole
Nafcillin	Ketoconazole
Nevirapine	Following antivirals: atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir.
Rifampin	
Rifabutin	
St. John's Wort	

APPENDIX 5. OVERVIEW OF MAJOR CHANGES IMPLEMENTED BY AMENDMENTS

AMENDMENT 2

1. Clarified that iDMC will review the AE profiles of the first 12 patients aged ≥9 years completing 4 weeks of treatment

Description of Change: The iDMC will review the AE profiles of the first 12 patients (previously first 20) aged ≥9 years completing 4 weeks of treatment prior to recommending treatment for patients aged <9 years

Rationale for Change: iDMC has reviewed the data of patients aged ≥9 years from another study (TAK-935-18-002) who were treated with TAK-935, and iDMC have approved to initiate treatment of patients aged 2-9 years old in the study. As TAK-935 is deemed safe in patients aged ≥9 years in TAK-935-18-002, it will be appropriate to decrease the number of patients aged ≥9 years needed before initiation treatment of 2-9 years old patients.

Sections Impacted:

- Synopsis
- Section 5.1

2. Renamed the Titration Period to the Dose Optimization Period and increased the period duration from 2 weeks to 8 weeks

Description of Change: Changed the period during which patients will titrate to the optimal dose from 2 weeks to 8 weeks in order to allow for 6 weeks of dose optimization. This revision resulted in a change in the Treatment Period from 14 weeks to 20 weeks. Updated Figure 1 to reflect the name change and the extension of the Dose Optimization Period. Updated the Schedule of Assessments to reflect the increase in the number of days on study. Updated the total duration of the study to approximately 30 weeks.

Rationale for Change: To allow for an additional 6 weeks to adjust patient dosing to optimal levels after the maximum dose had been reached, based on Investigator judgment and with approval of the Medical Monitor.

Sections Impacted:

- Synopsis
- Section 5.1
- Figure 1
- Section 7.2
- Section 10.9.2
- Section 10.12.2
- Appendix 1 (Table 3)

3 Added additional phone calls to monitor dose optimization and safety

Description of Change: Phone calls were added due to the increase in the duration of the Dose Optimization Period (formerly Titration Period) to 6 weeks. Updated the Schedule of Assessments to reflect the increase in the number of days on study. Phone calls will be made at Days 8, 22, 57, and 113. Clinic visits will occur at Screening (Visit 1), Day 1 (Visit 2), Day 15 (Visit 3), Day 36 (Visit 4), Day 85 (Visit 5), Day 141 (Visit 6), and Day 169 (Visit 7; follow-up).

Rationale for Change: To allow for an additional 6 weeks to adjust patient dosing to optimal and to monitor safety and compliance.

Sections Impacted:

- Synopsis
- Section 5.1 (Figure 1)
- Section 7.2
- Appendix 1 (Table 3)

4. Removed hepatitis B and C serology panel

Description of Change: Removed clinical laboratory tests for hepatitis B and C, including an additional blood sample for HCV qPCR for patients who are positive for hepatitis C Ab. Removed from exclusion criterion #7 that patients who are positive for hepatitis C Ab are eligible if they have a negative hepatitis C viral load by qPCR.

Rationale for Change: There is no need to actively screen for hepatitis B and C.

Sections Impacted:

- Synopsis
- Section 6.2
- Appendix 2

5. Changed the follow-up visit from a phone call to a clinic visit

Description of Change: The Follow-up Period previously consisted of a phone call with the option to have follow-up assessment performed at the clinic. This Follow-up Visit is now a clinic visit with final assessments for concomitant medications, vital signs, physical examination, neurological examination, collection of seizure diary, plasma sample for 24HC, IWRS for patient status, study drug accountability, and AEs.

Rationale for Change: Because this amendment added an assessment of 24HC at the Follow-up Visit, it is necessary for patients to visit the clinic to have samples obtained for 24HC. Additionally, the patient can return any unused study drug to the site.

Sections Impacted:

- Synopsis
- Section 7.2
- Appendix 1 (Table 3)

6. Revised the PK collection timepoints and added sampling windows

Description of Change: The PK collection text was revised as follows:

Pharmacokinetic (PK) sample collection will start at Visit 2 (Day 1), and it is designed to investigate the PK in all patients. The first ~~16~~ 12 randomized patients aged ≥9 years and the first ~~16~~ 12 randomized patients aged <9 years will receive the first dose of TAK-935 or placebo in the clinic; PK blood draws will occur within 1 hour before the morning dose (pre-morning-dose) and 30 min (±10 min) and 1, 2, and 4 ~~3, and 5~~ hours (±10 min) after the ~~first~~ morning dose. After Visit 2 (Day 1), additional PK samples will be collected within 1 hour before the morning dose (pre-morning-dose) and 30 min (±10 min) post-morning-dose ~~(1 to 5 hours after the dose)~~ at Visits 3, 4, 5, and 6 ~~7 4, 5, 6, and 7~~ during the study.

The remaining randomized patients in the study will receive the first dose of TAK-935 or placebo in the clinic, with PK blood draws occurring within 1 hour before the morning dose (pre-dose) and 30 min (±10 min) ~~one draw~~ post-dose ~~(1 to 5 hours after the dose)~~ at Visits 2, 3, 4, 5, and 6 ~~4, 5, 6, and 7~~ during the study.

Rationale for Change: No window was previously provided in the protocol; adding a window grants flexibility to the sites in collection of this sample. The phrase "within 1 hour before dose" was not previously consistent throughout the protocol. Adjusted the visit days to reflect new schedule of phone calls and visits. The PK sampling times were changed to better capture the PK profile and when C_{max} is reached.

Sections Impacted:

- Synopsis
- Section 8.1.22.1
- Section 10.13
- Appendix 1 (Table 3)

7. Added concomitant medications that should not be altered during study or that require approval

Description of Change: Medical marijuana and cannabidiol products were added to the list of concomitant medications that should not be altered during the study. Added that use of traditional Chinese medicines should be approved by the Medical Monitor at screening.

Rationale for Change: Medical marijuana and cannabidiols are used as antiepileptic drugs and, therefore, like other AEDs, they should not be altered during the study. Traditional Chinese medicine may include a number of chemical components that may potentially have a drug-drug interaction with TAK-935 and, therefore, must be approved by the Medical Monitor.

Sections Impacted:

- Synopsis
- Section 7.6

8. Added perampanel as prohibited concomitant medication

Description of Change: Use of perampanel from screening through follow-up is prohibited.

Rationale for Change: The new data from the TAK-935-2001 (OV935) study in adult patients with epileptic encephalopathy indicated that there is a potential drug-drug interaction between TAK-935 and perampanel, which may compromise the efficacy of TAK-935.

Sections Impacted:

- Synopsis
- Section 7.6
- Appendix 4

9. Updated the approximate total blood volume collected

Description of Change: The approximately total blood volume collected from each patient over the course of the study was revised from 69 to 73.2 mL.

Rationale for Change: Revised based on changes in the Schedule of Assessments (Table 3) and central laboratory requirements.

Sections Impacted:

- Synopsis
- Section 8.1.11

10. Revised the primary objective

Description of Change: The primary objective was revised as follows:

To investigate the effect on the frequency of all seizures (convulsive and drop) in patients treated with TAK-935 as an adjunctive therapy compared to placebo ~~at the end of the Treatment Period (Titration plus~~ in the Maintenance Period ~~periods)~~

Rationale for Change: The preliminary data from the TAK-935-2001 (OV935) study in adult patients with epileptic encephalopathy indicate that full effects of TAK-935 are observed after 8 weeks of treatment. Accordingly, to observe the full efficacy effects, the primary endpoint was changed to the last 12 weeks of treatment, which is the Maintenance Period.

Sections Impacted:

- Synopsis
- Section 4.1.1

11. Revised the secondary objectives

Description of Change: The secondary objective for comparing patients treated with TAK-935 as an adjunctive therapy to placebo for the frequency of all seizures (convulsive and drop) was revised from throughout the Maintenance Period to throughout the Treatment Period.

The secondary objective for comparing patients treated with TAK-935 as an adjunctive therapy to placebo for the frequency of convulsive seizure in patients with Dravet Syndrome, the frequency of drop seizure in patients with LGS, the frequency of patients considered treatment responders in patients with LGS, and the frequency of patients considered treatment responders with Dravet Syndrome was revised from through the Treatment Period to the Maintenance Period.

The PK secondary objective was revised as follows:

> To characterize the relationship between ~~the PK and~~ plasma 24HC levels and seizure frequency

The following secondary objective was deleted:

> ~~To investigate changes in plasma concentrations of concomitant AEDs and their pharmacologically active metabolites in patients treated with TAK-935 as an adjunctive therapy~~

Rationale for Change: Secondary objectives were revised to be consistent with the primary objective and to evaluate the changes in seizure frequency that may potentially occur earlier, i.e., during the entire treatment period. The relationship between the plasma 24HC levels and seizure frequency was deemed to be more clinically meaningful.

Sections Impacted:

- Synopsis
- Section 4.1.2

CCI

[redacted]

13. Updated language regarding patient's legal representative

Description of Change: Changed "patient's custodial parent or guardian" to "patient's legal representative (i.e., parent or legal guardian)."

Rationale for Change: For consistency throughout the document.

Sections Impacted:

- Synopsis
- Section 6.1
- Section 6.3.1
- Section 7.2
- Section 11

14. Clarified definition of benzodiazepines as AEDs

Description of Change: Added text to inclusion criterion #5 to state that benzodiazepines used chronically (on daily frequency) to treat seizures are considered AEDs.

Rationale for Change: For clarification and based on feedback from the clinical sites.

Sections Impacted:

- Synopsis
- Section 6.1

15. Clarified diagnosis of Dravet syndrome and Lennox-Gastaut syndrome for inclusion

Description of Change: Revised the text of inclusion criterion #11 to update the symptoms that support the diagnosis of Dravet syndrome and LGS for inclusion in this study.

Rationale for Change: Based on guidelines from the Epilepsy Consortium; clarification is provided to enhance diagnosis of Dravet Syndrome and LGS.

Sections Impacted:

- Synopsis
- Section 6.1

16. Clarified that convulsive status epilepticus requiring hospitalization is an exclusion criterion for this study

Description of Change: Revised exclusion criterion #1 to state that patients that have been admitted to a medical facility and intubated for treatment of status epilepticus 2 or more times in the 3 months immediately prior to the screening visit will be excluded from the study.

Rationale for Change: Status epilepticus can be a long seizure over 5 minutes and several patients, especially with Dravet Syndrome, can have prolonged seizures (>5 minutes) that are not severe enough to exclude them from the study. Therefore, patients whose status epilepticus required hospitalization and intubation will be excluded.

Sections Impacted:

- Synopsis
- Section 6.2

CCI

18. Added malignancy (including progressive tumors) as an exclusionary condition

Description of Change: Added to exclusion criterion #4 that malignancy (including progressive tumors) would be an exclusionary unstable clinically significant condition

Rationale for Change: Based on unpredictable effects on efficacy and that progressive tumors have poor prognosis.

Sections Impacted:

- Synopsis
- Section 6.2

19. Clarified the duration for avoidance of pregnancy and donation of ova and sperm for female and male patients, respectively

Description of Change: Added text to clarify that avoidance of pregnancy and donation of ova and sperm should be up to 90 days (previously 30 days) after the last dose of study drug.

Rationale for Change: The original text was not consistent with other sections of the protocol.

Sections Impacted:

- Section 10.1.12

19. Revised the primary endpoint

Description of Change: Changed the primary endpoint from percent change from Baseline in seizure frequency during the Treatment Period to percent change from Baseline in seizure frequency during the Maintenance Period.

Rationale for Change: The preliminary data from the TAK-935-2001 (OV935) study in adult patients with epileptic encephalopathy may indicate that full effects of TAK-935 are observed after 8 weeks of treatment. Accordingly, because treatment duration is extended to 20 weeks and to observe the full effects, the primary endpoint was changed to the last 12 weeks of treatment, which is the Maintenance Period.

Sections Impacted:

- Synopsis
- Section 4.2.1
- Section 10.9.1

20. Revised the secondary endpoints

Description of Change: The secondary endpoint for percent change from Baseline in seizure frequency per 28 days (convulsive and drop) was revised from during the Maintenance Period to during the Treatment Period.

The secondary endpoints for percent change from Baseline frequency of convulsive seizure in patients with Dravet Syndrome and the frequency of drop seizure in patients with LGS was revised from during the Treatment Period to during the Maintenance Period, and the proportion of patients with LGS considered treatment responders in patients and patients with Dravet Syndrome considered treatment responders was revised from during the Treatment Period to during the Maintenance Period.

The PK secondary endpoint was revised as follows:

~~Correlation of TAK-935 concentration and plasma 24HC levels with seizure frequency~~

To characterize plasma 24HC levels and change in seizure frequency in patients treated with TAK-935 as an adjunctive therapy

Rationale for Change: Because the primary objective was changed to the Maintenance Period, the secondary objective was changed to the Treatment period to evaluate the changes in seizure frequency that may potentially occur earlier, ie, during the entire treatment period.

Consistent with the primary objective/endpoint and given the importance of the responder analysis, the frequency of patients considered as treatment responders was changed to the Maintenance Period (last 12 weeks of treatment).

The PK secondary objective of the correlation of 24HC levels with seizure frequency is more clinically meaningful.

Sections Impacted:

- Synopsis
- Section 4.2.2
- Section 10.9.2

CCI

[redacted]

22. Revised the pharmacokinetic endpoints

Description of Change: The PK endpoints were revised as follows:

To determine the plasma concentrations of the TAK-935 and the TAK-935 metabolite (M-I) at multiple time points

Estimate exposure parameters from sparse PK samples using population modelling

Determine any potential relationship with estimated TAK-935 exposure parameters with changes in seizure frequency

~~Population pharmacokinetic parameter estimates (eg apparent clearance CL/F, apparent volume of distribution VD/F, Cmax, AUC, Cavg within dosing interval) at steady-state for TAK-935~~

~~Correlation of TAK-935 concentrations on the serum levels of concomitant AEDs and their pharmacologically active metabolites~~

~~Outcome from an exposure-response model utilizing reduction in seizure rate for convulsive and drop seizures and TAK-935 concentrations~~

Rationale for Change: Estimate of exposure parameters using population modeling provides more clarification. Relationship between exposure and seizure frequency is more clinically meaningful.

Sections Impacted:

- Synopsis
- Section 4.2.4
- Section 10.11

23. Revised and added analysis sets

Description of Change: Deleted the statement that efficacy analysis would be based on the modified intent-to-treat (mITT) analysis set. Added a definition for the new efficacy analysis set, defined as all mITT patients whose efficacy assessments are compliant with protocol amendment 2.

Rationale for Change: To provide further clarification on efficacy analysis data set.

Sections Impacted:

- Synopsis
- Section 10.4

24. Clarified and revised PK analyses

Description of Change: The plasma concentration-time and PD (24HC) data obtained in this study will be used to estimate TAK-935 exposure parameters, analyze target engagement in terms of 24HC reduction, and evaluate potential relationships between TAK-935 exposure or 24HC responses and clinical and safety endpoints. Details will be included in a separate data analysis plan, and results will be reported separately.

Rationale for Change: To provide clarification on those parameters that are considered clinically meaningful.

Sections Impacted:

- Synopsis
- Section 8.1.22.3
- Section 10.11

25. Updated study rationale

Description of Change: Revised the summary statements for clinical study TAK-935-2001 (OV935) (Phase 2a study) to state that the study has been completed.

Rationale for Change: Updated text to reflect the current status of the study

Sections Impacted:

- Section 3.2

26. Add new section to define end of the study

Description of Change: Added the following text:

The end of the study for an individual patient is defined as the last protocol-specified contact with that patient. The overall end of the study is defined as the last protocol-specified contact with the last patient ongoing in the study.

Rationale for Change: To ensure sites had a clear understanding of what defined the end of the study and to ensure consistency with antecedent studies.

Sections Impacted:

- Section 5.1.1

27. Simplified the background information provided for selection and timing of doses

Description of Change: Deleted Section 5.2.1 (Nonclinical Efficacy and Safety) and Section 5.2.2 (Clinical Safety)

Rationale for Change: To remove information that is already provided in the IB.

Sections Impacted:

- Section 5.2.1
- Section 5.2.2

28. Added 2 new forms of approved contraceptive methods

Description of Change: Added vasectomized partner and sexual abstinence as approved contraceptive methods.

Rationale for Change: Based on feedback from the clinical sites and IRBs.

Sections Impacted:

- Section 6.1

29. Added depression and/or suicidal ideation as a reason for study drug discontinuation

Description of Change: Added that depression and/or suicidal ideation could be a reason for study drug discontinuation as assessed using the C-SSRS and with ultimate determination of the presence of suicidal ideation or behavior depending on the clinical judgment of the investigator.

Rationale for Change: To be compliant with patient safety guidelines and for consistency within the protocol.

Sections Impacted:

- Section 6.3.1
- Section 8.1.14

30. Added storage temperatures for ex-US sites

Description of Change: Added the following language:

For US sites, TAK-935 tablets/mini-tablets must be stored at 20°C to 25°C (USP controlled room temperature), with excursions permitted from 15°C to 30°C. For sites in all other countries, TAK-935 tablets must be stored at 1°C to 25°C.

Rationale for Change: The previous version of the protocol did not include storage temperatures for ex-US sites, which are different from the recommended storage temperatures in the United States.

Sections Impacted:

- Section 7.1.1

31. Added that study drug may be shipped via courier service if patient is unable to come for clinic visit to obtain resupply

Description of Change: If a patient is unable to come for a clinic visit to obtain study drug, the study drug may be shipped via a courier service.

Rationale for Change: To ensure patients do not run out of study drug in the event that they are unable to return to the clinic.

Sections Impacted:

- Section 7.1

32. Clarified the handling of missed doses

Description of Change: Added the following text:

If a patient misses a dose, the missed dose should be skipped, and the patient should continue with his/her normal dosing schedule. Skipped doses should be reported as missed doses.

Rationale for Change: Based on inquiries from clinical sites, clarification was required for proper instructions to study patients on how to handle missing doses. Skipped doses should be reported as missed doses.

Sections Impacted:

- Section 7.2

33. Clarified how unblinding events will be recorded and reported

Description of Change: Emergency unblinding for AEs may be performed through an IWRS.

Rationale for Change: Removed reference to emergency codes being generated by a computer drug-labeling system, as IWRS will serve this role.

Sections Impacted:

- Section 7.5

34. Changed demographic collection from "date of birth" to "year of birth"

Description of Change: Updated the text clarifying that only year of birth will be collected for demographics data collection.

Rationale for Change: To be compliant with current patient privacy standards.

Sections Impacted:

- Section 8.1.2

35. Revised requirement for heart rate and blood pressure collection

Description of Change: Removed text that stated that heart rate and blood pressure will also be measured after 5 minutes supine and after 1 to 3 minutes standing, if possible.

Rationale for Change: Based on feedback from the clinical sites and to provide further clarification.

Sections Impacted:

- Section 8.1.6

36. Added a formula for assessment of seizure frequency

Description of Change: Added the following formula for assessment of seizure frequency:

(# of seizures) / (# of days seizures were assessed) × 28

Rationale for Change: The formula for seizure frequency was not previously noted in the protocol.

Sections Impacted:

- Section 8.1.7

37. Clarified the use of the dosing card

Description of Change: Added the text as follows to clarify the use of the dosing card: A dosing card will be provided to the patient and/or caregiver at each clinic visit to record actual time of the last 2 dose administrations prior to PK sample collection, to record exact time of the last meal relative to dosing prior to PK or PD sample collection, and to record any changes in dosing regimen that may occur between visits and during the de-escalation period of the study; these will be recorded in the patient's source documents and transcribed into electronic case report forms (eCRFs)~~, including changes in dosing regimen (de-escalation) that may occur between visits and during the de-escalation period of the study~~.

Rationale for Change: The description of the dosing card was incomplete.

Sections Impacted:

- Section 8.1.8

38. Clarified that only sexually active female patients of childbearing potential will have pregnancy tests performed

Description of Change: Added the phrase "sexually active" where needed to clarify that only sexually active female patients of childbearing potential will have pregnancy tests performed.

Rationale for Change: As this patient population includes patients of severely impaired faculties, this change was made to reduce the clinical test burden on patients.

Sections Impacted:

- Section 8.1.11
- Section 8.1.12
- Appendix 1 (Table 3)
- Appendix 2

39. Clarified the duration for avoidance of pregnancy and donation of ova/sperm for female and male patients

Description of Change: Added text to clarify that avoidance of pregnancy and donation of ova/sperm should be 90 days after the last dose of study drug.

Rationale for Change: The original text was not consistent with other sections of the protocol.

Sections Impacted:

- Section 8.1.12

40. Clarified pregnancy testing at Day 1

Description of Change: Added the following language: If urine cannot be collected at Visit 2, the reason should be documented in the source document, the results of the serum pregnancy test obtained at Visit 1 must be confirmed to be negative by the Investigator prior to randomization, and the results of a serum pregnancy test at Visit 2 must be confirmed to be negative before the patient can receive the first dose of study drug.

Rationale for Change: Much of this language was already present in Appendix 2 (now footnote c). Language was added to the other sections to ensure consistency, and all 3 sections were updated to ensure that pregnancy test results are obtained before female patients of childbearing potential receive study drug.

Sections Impacted:

- Section 8.1.12
- Appendix 1 (Table 3)
- Appendix 2

41. Adding window for ECGs

Description of Change: For ECGs performed after the screening ECG (ie, after the start of dosing), the ECG will be recorded 30 min (±10 min) after the morning dose.

Rationale for Change: This sampling time point coincides with the C_{max} and T_{max} of TAK-935.

Sections Impacted:

- Section 8.1.13
- Appendix 1 (Table 3)

42. Clarified language for the C-SSRS administration

Description of Change: Removed text that indicated that a parent proxy could complete the C-SSRS. Clarified that trained study staff will administer the C-SSRS and that determination of the presence of suicidal ideation or behavior depends on the clinical judgment of the investigator.

Rationale for Change: Revised for consistency with the instructional language on the C-SSRS.

Sections Impacted:

- Section 8.1.14

43. Clarified that the Exit survey is a separate questionnaire from the Care GI-C

Description of Change: Removed reference to the Care GI-C in description of the Exit survey

Rationale for Change: Wording for exit survey previously was misinterpreted in the clinic.

Sections Impacted:

- Section 8.1.21
- Appendix 1 (Table 3)

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[redacted]

45. Added statement about AEs or SAEs associated with overdose

Description of Change: Added the following text:

Adverse events (including SAEs) associated with overdose should be reported according to the procedure outlined in Section 8.3.1.5. In the event of drug overdose, the patient should be treated symptomatically.

Rationale for Change: Based on safety guidelines, clarification on overdose is provided.

Sections Impacted:

- Section 8.3.1

46. Clarified reporting seizures as AEs/SAEs

Description of Change: Instruction text for reporting seizures as AEs was revised from the following:

~~For the purpose of this study, seizures will not be considered immediately reportable as an(S)AEs unless: 1) there is a clear increase in frequency of seizures compared to the patient's baseline, 2) there is an emergence of a new seizure type, or 3) the patient experiences status epilepticus, and any other time the investigator feels the seizure should be captured as an (S)AE in which case the investigator should document her/his reasoning.~~

To:

Seizures in this patient population will be measured using the seizure diary and seizure frequency as a primary study endpoint (see Section 8.1.7). For the purpose of this study, reporting of seizures should meet the AE/SAE reporting requirements. As seizures are considered a baseline condition, seizures should be reported as an AE/SAE if: 1) there is a clear increase in the frequency of seizures compared to the patient's baseline, 2) there is an emergence of a new seizure type, or 3) the patient experiences status epilepticus, and any other time the Investigator feels the seizure should be captured as an AE/SAE, in which case the Investigator should document his/her reasoning..

Rationale for Change: To provide clarification for the clinical sites on when seizures can be considered as AEs or SAEs.

Sections Impacted:

- Section 8.3.1

47. Removed text that stated that expected SAEs were provided in the Investigator's Brochure

Description of Change: Deleted the following text:

~~Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the study may be found in Appendix A of the current Investigator's Brochure.~~

Rationale for Change: The current version of the Investigator's Brochure does not include Appendix A, and the SAE information indicating as being included in The Investigator's Brochure is not provided.

Sections Impacted:

- Section 8.3.1.3

48. Clarified SAE reporting process

Description of Change: Clarified that AEs must be recorded in the eCRF upon awareness. Any AE that meets the criteria of an SAE must be reported to sponsor immediately using fax or email. Email address was updated to CCI. If sites use the safety hotline telephone number to report an SAE, the site should first submit the SAE paper form and then enter the SAE in the eCRF.

Removed AE reporting FAX numbers from the protocol and added a sentence stating that "country-specific FAX numbers will be provided in a separate document." Also removed AE reporting safety hotline telephone number from the protocol, and added a sentence stating "country-specific hotline numbers will be provided in a separate document."

Rationale for Change: To clarify that sites should submit the SAE paper form before entering the SAE in the eCRF and to state that country-specific FAX and safety hotline numbers will be provided to sites in a separate document.

Sections Impacted:

- Section 8.3.1.5

49. Added text stating that TAK-935 should not be administered to pregnant or lactating females

Description of Change: Added the following text:

<u>TAK-935 should not be administered to pregnant and lactating females because the potential for adverse reactions to TAK-935 in pregnant females, fetuses, and nursing infants is unknown</u>.

Rationale for Change: Based on guidelines and feedback from the clinical sites.

Sections Impacted:

- Section 8.3.2

50. Added text on site responsibilities for record keeping

Description of Change: Added general text on how data records are to be kept or released during and after the study.

Rationale for Change: Based on GCP Guidelines.

Sections Impacted:

- Section 11

51. Updated the schedule of assessments

Description of Change: All applicable revisions made in the body of the protocol were implemented in the schedule of events, including the following:

Add additional phone calls

Clearly identify clinic visits and phone calls

Revise study day number to account for added weeks in Dose Optimization Period

Update time point and window for PK sampling and 12-lead ECGs

Dispensing study drug was added to Day 141/ET (Visit 6) for patients not entering the OLE; study drug return/accountability/compliance was removed from Day 1

Changed follow-up from a phone call to clinic visit and added assessments to be performed at this visit

Rationale for Change: Because the duration of treatment was changed to 20 weeks, additional study visits were incorporated. Other changes were implemented for clarification.

Sections Impacted:

- Appendix 1 (Table 3)

52. Updated Appendix 2

Description of Change: Removed Perampanel and added Trileptal and Epidiolex to the list of concomitant AEDs and added alpha-1-acid glycoprotein to the list of serum chemistry analytes.

Rationale for Change: To ensure the table shown in Appendix 2 accurately reflects the tests that will be performed by the central laboratory. Perampanel was removed because it is now a prohibited medication.

Sections Impacted:

- Appendix 2

53. Updated the Appendix 3 study sampling summary

Description of Change: Updated the maximum amounts per sample and the maximum number of samples.

Rationale for Change: To be consistent with the current laboratory manual for the study.

Sections Impacted:

- Appendix 3

54. Replaced table in Appendix 3

Description of Change: Removed the previous table and inserted a new table for blood volume collection of pediatric patients.

Rationale for Change: The previous table did not accurately reflect the blood volumes for the primarily pediatric populations in this study**.**

Sections Impacted:

- Appendix 3

AMENDMENT 1

1. Removal of 'Non-Dravet patients with convulsive seizures"

Description of Change: Third stratum of the study is removed, and there will be only two strata Dravet syndrome and Lennox Gastaut syndrome.

Rationale for Change: Third stratum of the study was removed based on feedback received from the FDA to stratify patients according to their individual DEE syndromes and reduce the number of syndromes in the study.

Sections Impacted:

Synopsis: Section 6.2.1

Section 6.2.2

Section 7.1

Section 9.3

Section 12.2

Section 12.3

Section 12.9.1

Section 12.9.2

Section 12.13

2. To change name of 'Drop seizure' stratum to 'LGS stratum'

Description of Change: Name of Drop seizure stratum will be changed to LGS stratum

Rationale for Change: Based on feedback from the FDA the study is limited to two syndromes only, LGS and Dravet syndrome. Drop seizure stratum will only be limited to LGS patients and the name is changed accordingly.

Sections Impacted:

Synopsis

Section 6.2.1

Section 6.2.2

Section 7.1

Section 9.3

Section 12.2

Section 12.3

Section 12.9.1

Section 12.9.2

Section 12.13

3. To increase duration of maintenance period from 10 weeks to 12 weeks

Description of Change: Maintenance period of the study is increase from 10 weeks to 12 weeks.

Rationale for Change: A 12-week efficacy assessment is an FDA requirement to properly evaluate maintenance of treatment effect. With the availability of 9-month chronic toxicity data, it is now justified to extend the maintenance duration to 12 weeks.

Sections Impacted:

Synopsis

Section 7.1

Section 12.9.1

Section 12.9.2

Appendix 1 (Schedule of Assessments)

4. To allow administration of TAK-935 via gastrostomy tube (G-tube)/percutaneous endoscopic gastrostomy (PEG) tube

Description of Change: To clarify administration of TAK-935 in patients with G- or PEG-tube.

Rationale for Change:

Approximately 30% of pts with DEE can't swallow oral medications or eat food orally, so these patients are fed and administered medication via gastric tube. With the availability of a CMC study report showing that administration of TAK-935 is viable through G- or PEG-tube, this option is justified.

Sections Impacted:

Section 9.2

5. Change in sample size the sample size

Description of Change:

The total sample size was changed from 152 to 112.

Rationale for Change:

Due to the reduction in the number of strata from 3 to 2 (above Changes 1 and 2), the total sample size was recalculated (Dravet stratum: 46 and LGS stratum: 80).

Sections Impacted:

Synopsis

Section 12.3

6. Remove exclusion criterion for status epilepticus (exclusion criterion #1)

Description of Change: To remove exclusion of patients admitted to a medical facility and intubated for treatment of status epilepticus within 1 month of the Screening visit.

Rationale for Change: It was a repetitive and created confusion. Patients with frequent status epilepticus will be excluded per exclusion criterion #2

Section Impacted:

Synopsis

Section 8.2

7. Remove exclusion criterion for inability to swallow study drug safety (exclusion criterion #3)

Description of Change: Remove exclusion based on the inability to swallow study drug safety by mouth

Rationale for Change: To allow administration of TAK-935 or placebo via G-tube/PEG tube after finalization of CMC in vitro studies demonstrating nearly 100% drug delivery through a G-tube when crushed and suspended in water.

Sections Impacted:

Synopsis

Section 8.2

8. Remove exclusion criterion for positive drug screen at screening

Description of Change: Remove exclusion based on positive drug screen at Screening

Rationale for Change: Patients with history of drug use disorder would continue to be ineligible for the study, but screening for illicit drugs is removed. We were advised by clinical advisors and representative of patient foundations that majority of Dravet and LGS syndromes who have treatment resistant seizures will not be capable of buying and using illicit drugs. And this test would result in an unnecessary blood draw.

Sections Impacted:

Synopsis

Section 8.2

9. BMI assessment removed

Description of Change: Measurement of BMI at screening removed

Rationale for Change: Changes in percentile and absolute weight and height of pediatric patients will be used for assessment. BMI assessment was repetitive, and its utility is less useful in pediatric patients compared to adult patients.

Sections Impacted:

Synopsis

Section 6.2.5

Section 10.1.5

Section 12.5

Section 12.10

Section 12.10.1

Appendix 1 (Schedule of assessments)

10. Perampanel added as a concomitant AED medication

Description of Change: Perampanel was added as a concomitant AED medication for which plasma concentrations will be investigated

Rationale for Change: Level of perampanel was missed from the list of AEDs in the original protocol.

Section Impacted:

Appendix 2

11. Patients with Hepatitis B and C are excluded

Description of Change: Patients will be excluded based on a history of active hepatitis B or active hepatitis C infection.

Rationale for Change: Active Hepatitis B and C infection would not interfere with TAK-935 administration or metabolism or effectiveness, therefore, patients will not be tested for hepatitis infection. However, patients with known hepatitis infection will be excluded. Other exclusion criteria exclude patients with abnormal liver enzymes or unstable medical conditions that could be caused by Hepatitis infection. Patients with Dravet and LGS syndromes with active hepatitis B and C would be known to their treating physicians because these are frequently seen in the clinics for their treatment resistant seizures.

Sections Impacted:

Synopsis

Section 8.2

Appendix 3 (Sampling summary)