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

SAP Approve Date: 15 June 2020

Certain information within this Statistical Analysis Plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable (PPD) information or company confidential information (CCI).

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.

Please note that the statistical output shells have been removed for brevity, since they are not a requirement of the statistical analysis plan.

Ovid Therapeutics, Inc.

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)

15 June 2020

Statistical Analysis Plan

Version Final *1.0*

Ovid Therapeutics, Inc.
1460 Broadway
New York, NY10036

Approved by

TABLE OF CONTENTS

List of Abbreviations and Definition of Terms

Term	Definition
24HC	24S-hydroxycholesterol
ABC-C	Aberrant Behavior Checklist-Community
AE	Adverse Event
AED	antiepileptic drugs
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BID	twice daily
CGI-S/C	Clinician's Clinical Global Impression of Severity and Change
Care GI-C	Caregiver Global Impression of Change
CI	confidence interval
CNS	central nervous system
CSR	Clinical Study Report
C-SSRS	Columbia–Suicide Severity Rating Scale
CYP	cytochrome P-450
DEE	developmental and epileptic encephalopathy
DS	Dravet syndrome
ECG	electrocardiogram
EE	epileptic encephalopathy
EEG	electroencephalogram
GGT	Gamma-glutamyl transferase
HDL	High-density lipoproteins
HLGT	High Level Group Term
HLT	High Level Term
ICH	International Conference on Harmonization
iDMC	independent Data Monitoring Committee
IEC	Independent Ethics Committee

Term	Definition
ILAE	International League Against Epilepsy
IRB	Institutional Review Board
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LDL	Low-density lipoproteins
LGS	Lennox-Gastaut syndrome
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MMRM	Mixed Model for Repeated Measure
PA1	Protocol Amendment 1
PA2	Protocol Amendment 2
PD	pharmacodynamic(s)
PEG	percutaneous endoscopic gastrostomy
PK	Pharmacokinetic(s)
PT	Preferred Term
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
VABS	Vineland Adaptive Behavior Scale
VNS	Vagal Nerve Stimulator
WBC	White Blood Cells
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

Epileptic encephalopathies (EE) refer to 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. 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. The revised classification now refers to Developmental Epileptic Encephalopathies (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). 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.

CCI

[redacted]

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.

This Statistical Analysis Plan (SAP) describes the data-handling and statistical procedures to be used for the statistical analysis and reporting of efficacy and safety data collected under the Ovid Protocol TAK-935-2002 (OV935) Amendment 2 (February 11, 2019). The methods of analysis in this SAP expand on statistical considerations identified in the protocol; where considerations are substantially different, they will be identified as such in this document.

This SAP has been developed and finalized prior to locking the clinical database for the primary analysis. Any additional analyses required to supplement the analyses specified in this SAP will be considered exploratory and will be identified in the Clinical Study Report (CSR).

The SAP was written in accordance with the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled "Guidance for Industry: Statistical Principals for Clinical Trials" and the most recent ICH-E3 Guideline entitled "Guidance for Industry: Structure and Content of Clinical Study Reports."

2. OBJECTIVES

2.1. 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.

2.2. 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:
  - 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:
  - 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 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 24HC levels and seizure frequency

2.3. Exploratory Objectives

CCI

[redacted]

2.4. Safety Objectives

- To evaluate safety and tolerability of TAK-935 as adjunctive therapy as compared to placebo
- 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
- 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)

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

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 and ≥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 patients with evaluable primary endpoint. 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.

For patients consented to protocol amendment 1 (PA1) and terminated prior to protocol amendment 2 (PA2), the study consists of 2 main periods:

- 4- to 6-week Screening/Baseline Period
- 14-week Treatment Period
  - 2-week Titration Period
  - 12-week Maintenance Period

The 4-week minimum baseline period will be used to collect seizure diary data. All the data collected prior to first dose date will be used to calculate baseline seizure data.

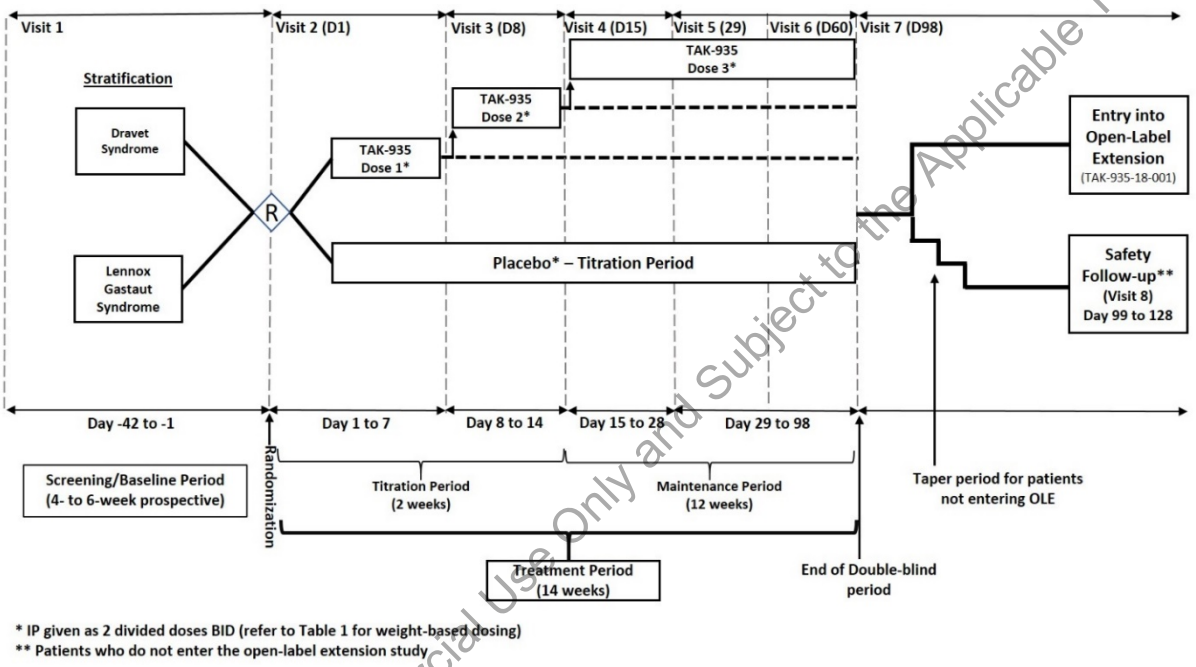
The Treatment Period consists of Titration Period and Maintenance Period. Figure 1 illustrates the study design.

For patients enrolled in, or reconsented from protocol amendment 1 to, protocol amendment 2, the 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 2 illustrates the study design.

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

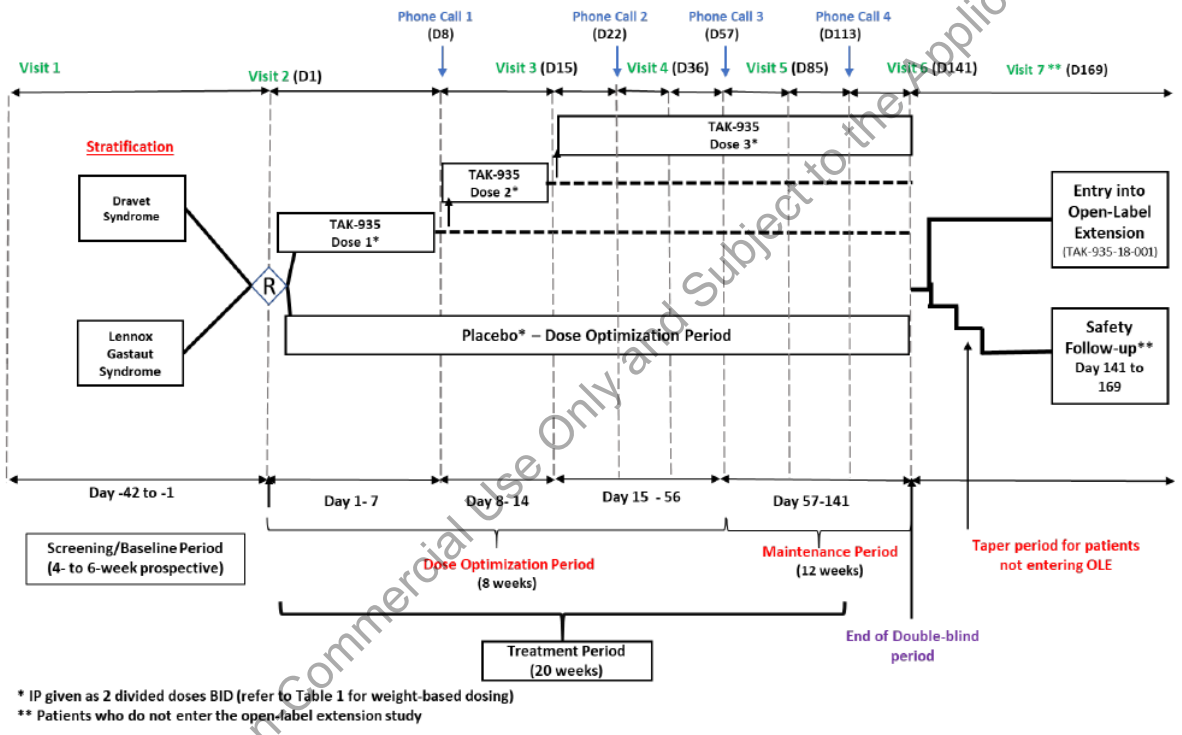


Dravet Syndrome patients who have had, on average, ≥3 convulsive or LGS patients who have had on average ≥4 drop seizures per month during the 3 months immediately prior to Screening (based on historical information) and ≥ 3convulsive or ≥ 4 drop seizures, respectively, during a minimum of 4 weeks during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

For subjects who completed PA1 only the titration and maintenance periods are defined by the PA1 visit schedule (Day 1 to 14 for the Titration Period and Day 15 to Day 98 for the Maintenance Period). For subjects who are randomized under PA2, Dose Optimisation (Day 1 to 56) and Maintenance periods (Day 57 to 141) are defined as per the PA2 visit schedule. For subject who randomized in PA1 and subsequently reconsents to PA2, the Titration period will be from Day 1 to 14, Dose Optimization will be from Day 15 to 56 and Maintenance will be from Day 57 to 141. Subjects in PA1 will be treated as being in the maintenance phase from Week 3 (Day 15) and subjects who reconsent to PA2 or who randomized in PA2 will be treated as being in the maintenance phase from Week 9 (Day 57).

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 2: Study Design for Clinical Protocol OV/TAK-935-2002 (Protocol Amendment 2)



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.

3.2. Study Endpoints

3.2.1 Primary Efficacy Endpoints

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.

3.2.2 Secondary Efficacy Endpoint

- Percent change from Baseline in seizure frequency per 28 days (based only on convulsive seizures for patients in the Dravet syndrome stratum and drop seizures for 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 in 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 in 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 are defined as those with:
  - 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:
  - 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 responses of Investigator reported impression of efficacy and tolerability of study drug
- Summary of CGI-C responses reported impression of efficacy and tolerability of study drug
- Summary of 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

3.2.3 Exploratory Endpoints

CCI

[redacted]

CCI

[redacted]

3.2.4 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

3.2.5 Safety Endpoints

- Incidence of treatment-emergent adverse events (TEAEs)
- Incidence of abnormal values for clinical laboratory evaluations, vital signs, body weight and height, and electrocardiogram (ECG) parameters after TAK935 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
- 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

3.3. Treatments

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 5 (Day 29) for patients consented on protocol amendment 1 and early terminated prior to protocol amendment 2 and Visit 4 (Day 36) for patients randomized/reconsented to protocol amendment 2.

Patients randomized in protocol amendment 1 will receive the initial dose of study drug, Dose 1, for the first 7 days after randomization at Visit 2. In the two subsequent visits (Visit 3 and Visit 4) the study drug dose will be increased to Dose 2 and Dose 3, respectively. The maximum dose for any patient will be 600 mg/day. The final dose level will be maintained until the end of the Maintenance Period; however, the dose may be decreased 1 time 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. If Dose 1 is not tolerated, the patient will be withdrawn from the study.

Patients randomized in protocol amendment 2 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, respectively. 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 the 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.

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

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
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.

3.4. Dose Adjustment/Modification

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 Titration Period for patients consented to protocol amendment 1 and Dose Optimization Period for patients consented to protocol amendment 2; dose changes during the Maintenance Period must be discussed and approved by the Sponsor.

4. GENERAL 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. Unless otherwise stated the baseline observation will be defined as the last non-missing observation on or before the date of first dose of study medication. Baseline seizure frequency normalized to 28 days will use all the seizure diary data prior to first dose date (4 – 6 weeks).

If there are multiple records within a pre-specified visit window the non-missing visit closest to the scheduled visit day will be included in the summary tables. The assessment record(s) from the unscheduled visit(s) will be used only if there is no assessment record available from any scheduled visit.

The following reporting conventions apply generally to tables, listings and figures:

- All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal

places than the measured value. Minimum and maximum will be formatted to the same decimal as the measured value;

- All percentages will be rounded to one decimal place. The number and percentage of responses will be presented in the form xx (xx.x), where the percentage is in the parentheses. In the case the numerator is equal to the denominator, the percentage should be presented as (100) instead of (100.0). For TEAEs, the number, percentage, and event incidence will be presented in the form of xx (xx.x) [E], where E is the number of events;
- All listings will be sorted for presentation in order of randomized treatment group, study center, subject, and date of procedure or event;
- All analysis and summary tables will have the analysis population sample size for each treatment group in the column heading (i.e., number of subjects);
- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as "<0.0001" and p-values that round to 1.0000 will be presented as ">0.9999";
- The day of first dose of study drug, TAK-935, will be defined as Day 1. For day calculation, if date is before first dose date then day=date - first dose date, if date is after first dose date then day=date - first dose date + 1;
- Listings of all data will identify the age group (adolescent/adult) of each subject.

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.

4.1. Visits and Day Ranges

Since it is not always possible for all study participants to come in for their clinic visits on the exact day specified in the protocol schedule, the subject's visit will be defined by the following relative day ranges. Study days below will be used for Unscheduled visits.

For patients consented under protocol v1.0 and terminated prior to protocol v2.0.

Visit	Target	Study Days
V2 Day 1	Day 1	Day 1
V3 Day 8	Day 8	Days 2 to 12
V4 Day 15	Day 15	Days 13 to 21
V5 Day 29	Day 29	Days 22 to 52
V6 Day 60	Day 60	Days 53 to 90
V7 Day 98	Day 98	Day 91 to 120
V8 Day 128	Day 128	Day 121 onwards

For patients randomized or reconsented to protocol v2.0.

Visit	Target	Study Days
V2 Day 1	Day 1	Day 1
P1 Day 8	Day 8	Days 2 to 12
V3 Day 15	Day 15	Days 13 to 21
P2 Day 22	Day 22	Days 22 to 28
V4 Day 36	Day 36	Days 29 to 54
P3 Day 57	Day 57	Days 55 to 77
V5 Day 85	Day 85	Days 78 to 110
P4 Day 113	Day 113	Days 111 to 133
V6 Day 141	Day 141	Days 134 to 161
V7 Day 169	Day 169	Day 162 onwards

All visits prior to reconsent date will follow protocol Version 1.0 visit structure and all visits after the reconsent date will follow protocol Version 2.0 visit structure. All patients reconsented to protocol Version 2.0 from protocol Version 1.0, the maintenance period starts at Week 9.

4.2. Sample Size

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

Randomization will be stratified by 2 categories:

• Dravet syndrome stratum

• 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.

If 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 study and will have power of 80%. Table 2 shows the within-stratum sample size calculations:

Table 2: Within-Stratum Size Calculations

	Dravet Syndrome Stratum	**Drop Seizure 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

A minimum of 46 patients (23 per treatment group) will be randomized to the Dravet syndrome stratum. A minimum of 80 patients (40 per treatment group) will be enrolled in the LGS stratum.

4.3. Randomization, Stratification and Blinding

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.

4.4. Analysis Set

4.4.1 All Randomized Analysis Set

The all randomized analysis set includes all patients who are randomized into the study. This includes all patients who are randomized into study based on protocol amendment 1 or protocol amendment 2.

4.4.2 Modified Intent-to-Treat Analysis Set

All Randomized Analysis Set who have received at least one dose of study drug and have been assessed for at least one 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.

4.4.3 Efficacy Analysis Set

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

This analysis set includes all patients who are randomized or reconsented into protocol amendment 2 with 20 weeks of treatment period.

4.4.4 Per-protocol Analysis Set

All mITT patients who did not deviate from the protocol in any major way. Per-protocol analyses will be based on each patient's treatment actually administered.

4.4.5 Safety Analysis Set

All Randomized Analysis Set who take at least one 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.

5. PATIENT DISPOSITION

5.1. Study Enrollment

Study enrollment will be summarized by site and stratum, by site and protocol group. These summaries will be presented for All Randomized Analysis Set.

5.2. Inclusion and Exclusion Criteria

All inclusion/exclusion information on enrolled subjects will be included in a by-patient listing. The listing will include whether all criteria were satisfied. For subjects who did not satisfy the criteria, the criterion number will be listed with the deviation, along with whether an exception was obtained.

5.3. Disposition

The number of patients enrolled in the study by investigator and treatment group as well as overall/total columns will be tabulated. Tables showing study participant accounting will be provided. Tables will indicate number of patients who were randomized into the study, the number of patients who completed the study, number of patients who completed the treatment, and the number of patients who discontinued treatment for any of the following reasons:

- Liver function test abnormalities
- QTcF interval > 500 ms
- Greater than 100% increase in 28-day seizure frequency
- Not tolerating dose 1
- Enrollment in other clinical study
- Depression and/or suicidal ideation
- Physician decision
- Withdrawal by patient
- Withdrawal by parent/guardian
- Sponsor decision
- Adverse event
- Lack of Efficacy
- Lost to follow-up
- Non-compliance with study drug

- Protocol deviation
- Death
- Other

Also, the number of patients who discontinued study for any of the following reasons will be summarized:

- Liver function test abnormalities
- QTcF interval > 500 ms
- Greater than 100% increase in 28-day seizure frequency
- Not tolerating dose 1
- Enrollment in other clinical study
- Depression and/or suicidal ideation
- Physician decision
- Withdrawal by patient
- Withdrawal by parent/guardian
- Sponsor decision
- Adverse event
- Lost to follow-up
- Non-compliance with study drug
- Protocol deviation
- Death
- Other

Disposition data will be provided in patient listings. Also, disposition tables will be summarized for subjects who did not reconsent to PA2 or completed/early terminated to PA1, PA1 subjects reconsented to PA2, and subjects randomized under PA2 and by stratum.

All analyses on disposition will be based on All Randomized Analysis Set.

A separate summary of disposition will also be presented for patients whose participation of this trial was affected by COVID 19 in anyway (visit schedule, discontinuation, etc.).

5.4. Protocol Deviations

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) and agreed to by the investigator. Major protocol deviations will be classified by categories and will be summarized in a table by treatment group and total column and will be displayed in a listing. All protocol deviations will be presented in a by-patient listing.

A separate listing of all protocol deviations due to COVID19 and a listing of visits affected by COVID19 will be presented.

All analyses on protocol deviations will be based on All Randomized Analysis Set.

6. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

6.1. Demographics

Demographic characteristics include age, gender, race, ethnicity, and study center. 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.

The following variables will be summarized by treatment group and by randomization stratum:

1) Continuous variable: age (years)
2) Categorical/discrete baseline and demographic variables: gender (female or male), ethnicity (Hispanic or Latino, Not Hispanic or Latino), race (American Indian or Alaska Native, Asian, Black or African-American, Native Hawaiian or Other Pacific Islander, White or Caucasian, or Other)

6.2. Baseline Characteristics

Baseline characteristics include baseline body weight (kg), height (cm), BMI, disease characteristics, number of AEDs (categorized as 1, 2, 3, 4 etc.) at baseline, reproductive system, neurologic examination, ophthalmic examination. 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.

All analyses on Demographics and baseline characteristics will be performed on the following populations,

- All Randomized Analysis Set
- Efficacy Analysis Set.

- mITT
- The subgroup of all patients from Chinese sites

7. MEDICAL HISTORY

All medical history will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA, version 21.0 or later) and will be summarized by Stratum and by SOC and PT.

Patient medical history including specific details will be presented in a listing.

Analyses on medical history will be performed on mITT, Efficacy Analysis Set and the subgroup of all patients from Chinese sites.

8. Prior and Concomitant Medications and Procedures

8.1. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD), June 2017. 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 ended prior to the administration of the study drug will be included in the data but will be identified as prior in the listing. Only 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 2 and level 4 and preferred drug name within ATC class level 4 by decreasing frequency of incidence for all active treatment groups combined.

Summary of Concomitant medication will be performed on the mITT, Efficacy Analysis Set and the subgroup of all patients from Chinese sites.

Anti-epileptic drugs (AED) and rescue medications will also be summarized. List of AEDs is in Appendix 2 of the protocol. The total number of AEDs and rescue medications will be presented as well as the number and percentage of patients with at least 1 AED and rescue medication. AED listing will also be presented.

The summary of AED and seizure rescue medication will be based on the All, Randomized Set, mITT Analysis Set and Efficacy Analysis Set.

8.2. Prior and Concomitant Procedures

All prior and concomitant procedures or clinically significant non-drug therapies will be presented in a listing.

9. STUDY TREATMENTS

Analyses on study treatment will be based on Safety Analysis Set.

9.1. Extent of Exposure

Total dose given, average daily dose, duration of exposure (days), total missed doses, and total doses not fully administered will be summarized for all patients by stratum, treatment, and overall for the safety analysis set using mean, median, standard deviation, 1st quartile, 3rd quartile and range. Total dose is the sum of the actual dose (All non-missed doses are considered full dose) and the duration of exposure will be computed as the last dose date – first dose date +1. Dose type (tablets/mini-tablets) will also be summarized.

9.2. Treatment Compliance

Treatment compliance will be summarized by treatment group, stratum and overall over the treatment period. Compliance rates will be derived using the following formula:

100*(Total dose administered) / (total planned dose)

Total planned dose will be derived as (date of last study medication dose – date of first maintenance dose + 1)*(planned dosage during the treatment period). Total dose administered will primarily be based on the drug accountability (Total dose dispensed – total dose returned). 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. Also, number and percentage of patients who are compliant (compliance ≥ 80%) and non-compliant will be summarized.

10. EFFICACY ANALYSES

10.1. Analyses of the Primary Endpoint

10.1.1 Primary Analysis

The analysis performed on Efficacy Analysis Set is considered the primary analysis.

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

where:

# of seizures=Total number of Seizures (either convulsive or drop depending on the strata) reported from Start date to the End Date

days seizures were assessed = Number of days during the period seizures were assessed.

Baseline Period:

From up to 6 weeks prior to the day before first dose.

Maintenance Period:

For PA1 patients, between Day 15 and Day 84 (inclusive), and for PA2 and PA1 reconsented to PA2, between Day 57 and Day 140 (inclusive).

Treatment Period:

For PA1 patients, between Day 1 and Day 84 (inclusive), and for PA2 and PA1 reconsented to PA2, between Day 1 and Day 140 (inclusive).

For each patient, percent change from Baseline to Maintenance Period of seizure frequencies (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 rank test adjusting for Baseline seizure frequency and randomization stratum.

Percentage change from baseline will be defined as:

((Frequency of seizures per 28 days during maintenance period – Frequency of seizures per 28 days at baseline)/ Frequency of seizures per 28 days at baseline) * 100

The null hypothesis of no treatment difference will be tested at a two-sided 0.05 level of significance.

The Hodges-Lehmann confidence interval based on unadjusted rank statistic will also be presented.

For convenience from here on in this document, all references to the "number of seizures" in percent change calculations will imply "number of seizures per 28 days" even without the explicit expression.

10.1.2 Supportive Analysis

The analysis performed in 10.1.1 will also be repeated for mITT and Per-protocol analysis set as supportive analysis.

The model for the mITT and Per-protocol population will include treatment, baseline, randomization stratum, and treatment cohort (14 weeks vs 20 weeks) so that it could produce an estimate of the treatment difference for the combined cohorts under the assumption that the treatment differences within the separate cohorts are similar. That assumption would be addressed by additionally including treatment*cohort in the model so that its assessment can confirm similarity of the treatment differences for the separate cohorts through a sufficiently large p-value such as $p > 0.15$.

10.1.3 Sensitivity Analysis

Sensitivity analysis will be conducted using multiple imputation method to impute seizure dairy data during maintenance period. The imputation model (proc mi) will include the following variables, seizure count from seizure dairy (convulsive or drop), age, gender, treatment group, randomization stratum, and study day for the impact of missing data.

The analysis model in 10.1.1 will be applied for multiple imputation analysis (PROC MIANALYZE).

The compliance of seizure dairy completion for each patient will be summarized descriptively. The compliance is defined as Number of days dairy are available/Number of days dairy are expected. A listing of seizure diary compliance will also be presented.

10.2. Analyses of the Secondary Efficacy Endpoints

All analyses on the secondary endpoints will be performed for both Efficacy Analysis Set and mITT Analysis Set.

- 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

The percent change from baseline will be calculated as

((Frequency of seizures per 28 days during treatment period – Frequency of seizures per 28 days at baseline)/ Frequency of seizures per 28 days at baseline) * 100

The same calculation for the number of seizures and the same statistical approach as described in 10.1.1 and 10.1.2 will be used for the analysis of percent change in seizure frequency from baseline to 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

For the Dravet stratum, the percent change in convulsive seizure frequency from Baseline to the frequency of convulsive seizures during the Maintenance Period will be calculated as

((Number of convulsive seizures during treatment period – Number of convulsive seizures at baseline)/ Number of convulsive seizures at baseline) * 100

The same statistical approach as described in 10.1.1 and 10.1.2 will also be applied to this endpoint.

- 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

For the LGS stratum, the percent change in convulsive seizure frequency from Baseline to the frequency of convulsive seizures during the Maintenance Period will be calculated as

((Number of drop seizures during treatment period – Number of drop seizures at baseline)/ Number of drop seizures at baseline) * 100

The same statistical approach as described in 10.1.1 and 10.1.2 will also be applied to this endpoint.

- Proportion of patients in the LGS stratum considered treatment responders throughout the Maintenance Period; treatment responders defined as those with:
  - 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

For each response category, the proportion of responders will be summarized by treatment groups and the 95% confidence intervals will be calculated.

A bar chart representing proportion of subjects in each of the following percent change categories will also be presented, ≤0; >0 to ≤25; >25 to ≤50; >50 to ≤75; >75 to ≤100.

- Proportion of patients in the Dravet syndrome stratum considered treatment responders throughout the Maintenance Period; treatment responders are defined as those with:
  - 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

For each response category, the proportion of responders will be summarized by treatment groups and the 95% confidence intervals will be calculated.

A bar chart representing proportion of subjects in each of the following percent change categories will also be presented, ≤0; >0 to ≤25; >25 to ≤50; >50 to ≤75; >75 to ≤100.

- Change in CGI-S responses of Investigator reported impression of efficacy

Observed and change from baseline in CGI-S scores will be summarized with descriptive statistics (N, mean, standard deviation, median, minimum, maximum) treatment groups and by visit. Additionally, the number and percentage of patients with each score level will also be summarized by treatment group and by visit.

Shift tables representing best and worst changes will be presented.

The change from baseline scores will be compared between the 2 treatment groups. The comparison will be based on mixed model repeated measures (MMRM) to account for the repeated assessments at multiple visits. The model will include treatment, visit and randomization stratum as factors along with treatment*visit interaction and baseline score as a covariate.

- Summary of CGI-C responses (0, 1, 2, 3 and 4) reported impression of efficacy and tolerability of study drug

The number and percentage of patients with each CGI-C score level will be summarized by treatment groups and by visit.

The number and percentage of patients with the combine score levels of improvement (0, 1) and no improvement or worse (2, 3, 4) will also be summarized by treatment groups, stratum and by visit. The treatment groups will be compared using a generalized linear mixed model to account for the repeated measures. The model will be based on the binomial distribution (logit link function) with treatment group, stratum and visit as factors along with treatment*visit interaction.

- Summary of Care GI-C responses (1, 2, and 3 vs 4, 5, 6, and 7) of parent/family reported impression of efficacy and tolerability of study drug

The number and percentage of patients in each Care GI-C score level will be summarized by treatment groups, stratum and by visit.

The number and percentage of patients with the combine score levels of improvement (1, 2, 3) and no improvement or worse (4, 5, 6, 7) will also be summarized by treatment groups, stratum and by visit. The treatment groups will be compared using a generalized linear mixed model to account for the repeated measures. The model will be based on the binomial distribution (logit link function) with treatment group, stratum and visit as factors along with treatment*visit interaction.

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

Observed and change from baseline in plasma 24HC levels will be summarized by treatment groups and by visit. The level of plasma 24HC at each visit will be listed by patient. Concentration values below the limit of quantitation (BLQ) will be listed as not detectable in the listing and treated as missing values in the summary.

The relationship between the plasma 24HC level and the seizure count will be explored by summarizing the seizure count per 28 day by 24HC collection time points.

10.3. Exploratory Analysis

CCI

[redacted]

CCI

[redacted]

10.3.1 Proportion of Patients with reduction in frequency of seizures requiring rescue medication

The analysis performed on this endpoint will depend on the availability of rescue medication data.

10.3.2 Seizure Frequency Reduction

The reduction in seizure frequency in each period is calculated as follows:

Baseline seizure frequency per 28 days minus Treatment Period seizure frequency per 28 days as calculated in 10.1.1.

The reduction in seizure frequency will be compared between TAK-935 and placebo using the same statistical model as in 10.1.1 and 10.1.2.

Proportion of patients with reduction in seizure frequency will be compared between TAK-935 and Placebo using exact test to test for the difference of the treatments.

10.3.3 Proportion of Seizure-free Days

The proportion of seizure-free days during the Treatment period will be calculated as:

(Days with number of seizures=0 during the Treatment period)/(Days with recorded/non-missing data in seizure diary during the Treatment period).

The proportion of seizure-free during the Maintenance period will be calculated as:

(Days with number of seizures=0 during the Maintenance period)/(Days with recorded/non-missing data in seizure diary during the Maintenance period).

Proportion of seizure-free days will be compared between TAK-935 and Placebo using ANCOVA model with treatment group, stratum as factors and baseline values as a covariate. For analyses on mITT population, the treatment cohort and treatment*cohort effect will be included.

10.3.4 Seizure Frequency Reduction Time Effect

The seizure frequency reduction in the treatment Period will be divided to 4-week intervals starting from Day 1. Seizure frequency (per 28 days) reductions from baseline to each period will be summarized by treatment groups and overall.

This endpoint will be analyzed for both Efficacy Analysis Set and mITT Analysis Set.

10.3.5 Seizure Frequency at Weeks 4, 8, 12, 16, and 20

The seizure frequency at weeks 4 (weeks 1-4), 8 (weeks 5-8), 12 (weeks 9-12), 16 (weeks 13-16) and 20 (weeks 17-20) will be analyzed using the same statistical approach as in 10.3.4.

This analysis will be performed on the Efficacy Analysis Set and mITT Analysis set.

10.3.6 Longest Seizure-free Days

The longest of consecutive seizure-free days during the Treatment period will be calculated as the maximum number of consecutive days with number of seizures=0 during the Treatment period. The longest seizure-free days during the Treatment Period will be summarized descriptively by treatment groups and compared between TAK-935 and placebo using a Mann-Whitney test.

10.3.7 Use of Rescue Medication

The analyses on rescue medication will be performed based on data availability.

10.3.8 New Seizure Type

New seizure type development post baseline
The number and percentage of patients who develop new seizure types post baseline will be summarized by treatment group.

CCI

10.3.10 Quality of Life in Childhood Epilepsy (QoLCE)

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. Based on the data availability, patient listing will be provided.

10.4. Pharmacokinetic Analysis

The details of PK analysis will be described in a separate document.

11. SAFETY ANALYSES

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

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.

11.1. Adverse Events

11.1.1 Incidence of 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.

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.

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 and within 15 days of last study medication.
- Treatment-emergent SAE: A serious AE that starts or increases in severity during or after the first dose of study drug and within 30 days of last study medication.

The incidence of TEAEs, non-serious TEAEs with incidence > 5%, discontinuations due to TEAEs, drug-related, serious, and severe TEAEs will be summarized. All AEs will be coded using MedDRA Version 21.0 and will be summarized by SOC and PT and treatment group. Detailed listings of AEs, SAEs, related AEs, and discontinuations due to AEs will be provided.

11.1.2 Study Medication-related TEAEs

A TEAE is considered a study medication-related if the relationship is judged as either possibly related or related. If the relationship of a TEAE is missing, the TEAE is reported as related. The number and percentage of patients experiencing TEAEs which are related to the study medication will be summarized.

11.1.3 Severity of TEAEs

A summary of TEAEs by severity will be presented in a table. The severity that will be presented represents the most extreme severity captured on the CRF page. The possible severities are 'Mild,' 'Moderate,' and 'Severe'. In the TEAE severity table, if a patient reported multiple occurrences of the same TEAE, only the most severe TEAE is presented. TEAEs that are missing severity will be presented in tables as 'Severe' but will be presented in the data listing with a missing severity.

11.1.4 Serious TEAEs

A serious treatment-emergent adverse event is any untoward medical occurrence that, at any dose, results in death, life-threatening, requires hospitalization or prolongation of existing hospitalization, hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE, results in disability/incapacity, and congenital anomaly/birth defect.

Serious TEAEs will be categorized and presented by SOC and PT in the same manner to that described in Section 9.1.1.

11.1.5 TEAEs Leading to Treatment Discontinuation/Study Termination

The number and percentage of patients with TEAEs leading to treatment and study discontinuation will be categorized and presented by SOC and PT in the same manner to that described in Section 9.1.1.

11.1.6 Death

The number and percentage of deaths will be tabulated by treatment. Adverse events leading to death will be categorized and presented by SOC and PT in the same manner to that described in Section 9.1.1.

CCI

[redacted]

11.2. Clinical Laboratory Evaluations

All laboratory results are from PPD central laboratory and only standard results in SI unit will be summarized in the outputs.

Descriptive statistics for laboratory values at each visit and change from Baseline values to each post-baseline visits in clinical chemistry, hematology, urinalysis, and microscopic results will be summarized.

Shift tables for laboratory parameters will be presented to show the change of normality from baseline to each post-baseline time point. For each continuous laboratory parameter, results will be classified as low, normal, or high relative to the parameter's reference range.

Listings of subjects with abnormal results will be provided.

11.2.1 Hematology

The parameters to be analyzed for hematology includes red blood cell count (RBC), hemoglobin, white blood cell count (WBC) and differential, hemoglobin, hematocrit, platelets, prothrombin time and international normalized ratio (PT/INR), and activated partial thromboplastin time (aPTT).

A summary of the descriptive statistics of the hematology parameters in SI units, together with changes from baseline, will be presented for each visit by treatment. In addition, shift tables will be produced, one with the results categorized using the normal ranges. This categorical data will be summarized in shift tables comparing the results at each scheduled post-baseline visit with those at the baseline visit.

11.2.2 Clinical Chemistry

The parameters to be analyzed for clinical chemistry are ALT, albumin, alpha-1acid glycoprotein, alkaline phosphatase, AST, total bilirubin, total protein, creatinine, blood urea nitrogen, creatinine kinase, GGT, potassium, sodium, glucose, chloride, bicarbonate, calcium, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides.

A summary of the descriptive statistics of the serum chemistry parameters in SI units, together with changes from baseline, will be presented for each visit by treatment. In addition, shift tables will be produced, one with the results categorized using the normal ranges. This categorical data will be summarized in shift tables comparing the results at each scheduled post-baseline visit with those at the baseline visit.

11.2.3 Urinalysis

The parameters to be analyzed for urinalysis includes pH, specific gravity, protein, glucose, blood, and nitrite. These parameters will be summarized by treatment in shift tables comparing the results at each scheduled post-baseline visit with those at the baseline visit.

11.2.4 Microscopic Results

Microscopic results will be presented in a listing.

11.3. Vital Signs

Vital signs (temperature in °C, heart rate [beats per minute], respiratory rate [breaths per minute], and systolic and diastolic blood pressure [mmHg]), weight (kg), and height (cm) will be summarized descriptively at Baseline and all post-baseline study time points by treatment group and overall. Change from baseline and post-baseline study time points will be summarized descriptively by treatment group and overall.

Data listings will be provided.

11.4. Physical Examination

Physical examinations (general appearance; skin; head, eyes, ears, nose, throat; respiratory; cardiovascular; gastrointestinal/abdominal; neurological; lymph node; musculoskeletal; extremities; other)) will be summarized descriptively at Baseline and all post-baseline study time points as well as shifts from baseline to post-baseline will be summarized by treatment group and overall.

Data listings will be provided.

11.5. Safety ECG (12-lead ECG)

Individual safety ECG values will be listed by treatment and visit and will be summarized using descriptive statistics. Intervals to be provided for each ECG are: heart rate, RR interval, PR. Post-baseline ECGs will be compared with the baseline ECG. Summary statistics will also be provided for change from baseline in ECG values.

Additionally, each ECG reading will be interpreted as 'abnormal' or 'within normal limits' or 'not evaluable', and the relevance of the abnormality will be summarized as 'clinically significant' or 'not clinically significant'. This categorical data will be summarized in shift tables comparing the results at each scheduled post-baseline visit with those at the baseline visit by dose cohort.

11.6. 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).

• Suicidal Ideation and Intensity of Ideation

The number and percentage of patients with suicidal ideation will be presented for each visit by treatment groups and overall. A patient is considered to have suicidal ideation if the answer to either C-SSRS Suicidal Ideation Question 1 or 2 (Wish to be dead, Non-specific Active Suicidal Thoughts) was "Yes".

• Suicidal Behavior

The number of percentage of patients with suicidal behavior will be presented for each visit by treatment groups and overall. A patient is considered to have suicidal behavior if the response to any of the six Suicidal Behavior questions (Actual attempt; Interrupted attempt; Aborted attempt; Preparatory acts or behavior; Suicidal behavior; Completed suicide) was "Yes".

A by patient listing of C-SSRS and investigator assessment of C-SSRS will also be presented.

11.7. Myoclonic and Atypical Absence Free Days Seizures

Descriptive statistics will be used to summarize the percent of myoclonic- and atypical-absence free days in patients receiving TAK-935 as compared to placebo during the treatment Period. The percent myoclonic- and atypical-absence free days is computed as:

(per patient number of seizure free day/total # of days seizure was assessed in the treatment period)*100

11.8. Neurological and Ophthalmic Examination

Neurological examination will include testing mental status, gait, cerebellar function, cranial nerves, motor function, reflex, and sensation.

As part of the neurological exam, vision testing is recommended to include fundoscopy and best corrected visual acuity using a pocket vision screening card, if possible.

Worst shift from baseline in neurological and ophthalmic examination will be summarized by treatment.

Listing of neurological and ophthalmic examination results will be presented.

11.9. Sleep Disruption Numerical Rating Scale

Sleep disruption numerical rating scale range from 0 (slept extremely well) to 10 (unable to sleep at all) and summary statistics will be provided for observed and change from baseline in sleep disruption numerical rating scale by treatment and visit.

11.10. Vineland Adaptive Behavior Scale

The Vineland Adaptive Behavior Scale, 3rd Edition, Comprehensive Parent Caregiver Form (VABS-3 Parent Caregiver Form), is a caregiver-report questionnaire that assesses adaptive functioning across the following 4 domains and 11 subdomains.

The following domain names and subdomain names are used in the data based in Pearson's Q global and will be used for reporting or clinical study report. They are consistent with VABS-3 Parent Caregiver form manual pages 25-26.

The Motor domain data was collected prior to the current protocol amendment and will be listed in the listing.

Domain	Subdomains
Communication	Receptive Expressive Written

Daily Living Skills	Personal Domestic Community
Socialization	Interpersonal Relationships Play and Leisure Coping Skills
Maladaptive Behaviors	Internalizing Externalizing

Each item is scored from 0 to 2. If a caregiver estimates a response, the item score is reported as a 97, 98, or 99 on the CRF to indicate that they are estimates, but for the calculation of domain and subdomain totals, 97 is mapped to 2, 98 is mapped to 1 and 99 is mapped to 0.

For the Communication, Daily Living, and Socialization and Maladaptive behaviors domains, each domain yields a normative-based standard score. Each subdomain within these three domains yields a v-scale score, age equivalent score, and total raw score. For the Problem Behavior domain, the Internalizing (Section A) and Externalizing (Section B) subdomains yield a v-scale score and total raw score. All raw score calculations respect the basal and ceiling rules of the scale. Scoring will be completed using the publisher's scoring software program, Pearson's Qglobal.

The VABS-3 will be administered at Screening and Day 141 EOT/ET (Day 85/ET for patients who completed the study under the original protocol).

Summary statistics will be provided for observed and change from baseline in VABS and in VABS as assessed by the investigator.

11.11. Behavior Checklist – Community Edition (ABC-C)

Behavior will be assessed by the use of the Aberrant Behavior Checklist-Community (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. 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). Sub scores are derived by getting the sum of the individual scores per domain and the total score is the sum of the scores for all domains. Changes from baseline in

behavior measures using total scores and subscale scores of Aberrant Behavior Checklist-Community Edition (ABC-C) as assessed by the caregiver and the investigator for patients ≥6 years of age will be summarized descriptively.

Total score is the sum of the scores of the 58 questions and scores for the subscales will be obtained as follows:

Subscales	Sum of Questions
Irritability	2, 4, 8, 10, 14, 19, 25, 29, 34, 36, 41, 47, 50, 52, 57
Lethargy/Social Withdrawal	3, 5, 12, 16, 20, 23, 26, 30, 32, 37, 40, 42, 43, 53, 55, 58
Stereotypic Behavior	6,11,17,27,35,45,49
Hyperactivity	1, 7, 13, 15, 18, 21, 24, 28, 31, 38, 39, 44, 48, 51, 54, 56
Behavior	Mean of 61-74 scores
General Health	Score of question 75
General Quality of Life	Score of question 76

The change from baseline of ABC-C total and subscale scores will be summarized.

11.12. Investigator's assessments of VABS and ABC-C

Investigator's assessment results for VABS and ABC-C will be included in listings.

11.13. Exit Survey

The results of the exit summary will be presented with a listing.

CCI

[redacted]

12. OTHER STATISTICAL ISSUES

12.1. Significance Levels

For the sample size calculation, 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 study and will have power of 80%.

The primary and secondary endpoints are defined and will be tested at 0.05 level of significance. All other testing is considered exploratory and significance level of 0.05 will be used.

12.2. Handling of Missing Data

For missing baseline, the last screened value close to baseline visit will be used.

For the primary efficacy endpoint, observed values will be used. Sensitivity analysis will be conducted using multiple imputation (Rubin, 1987) based on missing at random for missing data in primary and key secondary efficacy endpoints. The multiple imputation method will be implemented using PROC MI and PROC MIANALYZE in SAS. Imputations of each missing value will be derived from a parametric Bayesian model using a noninformative prior distribution that is proportional to the inverse of the standard deviation of the observed values. For each timepoint at which imputation is necessary and for each imputation at that timepoint, a random variance and mean will be generated from the prior distribution; these are then used as parameters of the posterior Gaussian distribution for random selection of a single value. Repeating this process 50 times provides a sufficient number of replications. Sensitivity analyses based on the imputed data will be specified in the efficacy analysis section.

13. REFERENCES

Howie S. Blood sample volumes in child health research: review of safe limits. Bulletin of the World Health Organization, 2011;89:46-53. doi: 10.2471/BLT.10.080010.

Northrup H, Krueger DA. Tuberous sclerosis complex diagnostic criteria update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol. 2013;49(4):243-54.

Paul SM, Doherty JJ, Robichaud AJ, Belfort GM, Chow BY, Hammond RS, et al. The major brain cholesterol metabolite 24(S)-hydroxycholesterol is a potent allosteric modulator of N-methyl-D-aspartate receptors. J Neurosci 2013;33(44):17290-300.

Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia 2010;51(4):676-85.

Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58(4):512-21.

Wagner T, Tsai M, et al. Clinical trial simulations using a pharmacokinetic/enzyme occupancy/pharmacodynamic model of TAK-935, a cholesterol 24S-hydroxylase inhibitor; poster presented at the American Epilepsy Society 71st Annual Meeting (Washington, D.C. 2017).

Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017.

Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2011;168(12):1266-77.

Aman MG, Singh NN, Stewart AW, Field CJ. The aberrant behavior checklist: a behavior rating scale for the assessment of treatment effects. Am J Ment Defic 1985;89(5):485-91.

de Bildt A, Kraijer D, Sytema S, Minderaa R. The Psychometric Properties of the Vineland Adaptive Behavior Scales in Children and Adolescents with Mental Retardation. J Autism Dev Disord. 2005;35(1):53-62.

Rubin DB. Multiple imputation for nonresponse in surveys. New York: John Wiley, 1987.