Title: MULTICENTER, OPEN-LABEL, PILOT STUDY OF TAK-935 (OV935) IN PATIENTS WITH 15Q DUPLICATION SYNDROME OR CDKL5 DEFICIENCY DISORDER (ARCADE STUDY)

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OVID THERAPEUTICS INC.

STATISTICAL ANALYSIS PLAN

A MULTICENTER, OPEN-LABEL, PILOT STUDY OF TAK-935 (OV935) IN PATIENTS WITH 15Q DUPLICATION SYNDROME OR CDKL5 DEFICIENCY DISORDER (ARCADE STUDY)

TAK-935-18-002 (OV935)

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LIST OF ABBREVIATIONS

Abbreviation	Full Term
ABC-C	Aberrant Behavior Checklist-Community
AE	adverse event
AED	antiepileptic drug
BID	twice a day
BLQ	below the limit of quantitation
BMI	body mass index
Care GI-C	Caregiver Global Impression of Change
CDD	CDKL5 deficiency disorder
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
COVID-19	Coronavirus Disease 2019
CRF	case report form
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
Dup15q	15q duplication syndrome
ECG	electrocardiogram
EOT	end of treatment
ET	early termination
HLGT	high level group term
HLT	high level term
ICF	informed consent form
iDMC	independent Data Monitoring Committee
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities

mITT	modified intent-to-treat
OLE	open-label extension
PK	pharmacokinetics
PT	preferred term
Q1	1st quartile
Q3	3rd quartile
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	treatment emergent adverse event
VABS	Vineland Adaptive Behavior Scales
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

TAK-935-18-002 (OV935) (ARCADE) is a multicenter, open-label, Phase 2 pilot study of TAK-935 (OV935) in patients aged ≥2 and ≤55 years with 15q duplication syndrome (Dup15q) or CDKL5 deficiency disorder (CDD) demonstrating ≥3 motor seizures excluding myoclonic seizures per month during the 3 months immediately prior to Screening.

The statistical analysis plan (SAP) contains a detailed description of the data presentations and statistical analyses that will be included in the clinical study report (CSR) for Protocol TAK-935-18-002. The statistical methods and analyses described here are based on those presented in the study protocol (Amendment 2 dated November 21, 2019). The two patients who completed the study under the original protocol (May 22, 2018) will be analyzed where the data allows. Special handling of the time intervals for efficacy analysis for these patients is described in Section 4.2.

An interim (ad hoc) analysis was performed in March 2020. The March 2020 analysis followed the Ad Hoc Analysis Plan Version 3.0.

This study is ongoing during the Coronavirus Disease 2019 (COVID-19) pandemic, and as a result, there are expected to be protocol deviations related to COVID-19, including virtual visits instead of clinic visits and use of local labs. Data will be collected as closely as possible to the Schedule of Assessments (Table 1), and analysis will be performed using the observed data.

2 STUDY SUMMARY

2.1 Study Objectives

The primary objective of this open-label study is to investigate the effect of TAK-935 on the frequency of motor seizures for patients with Dup15q or CDD during the Maintenance Period.

The secondary objectives are:

- To investigate the effect of TAK-935 on the frequency of motor seizures for patients with Dup15q or CDD during the Treatment Period (Dose Optimization and Maintenance).
- To investigate the proportion of patients considered as treatment responders for patients with Dup15q or CDD throughout the Maintenance Period; treatment responders are defined as those with:
    - Reduction of 25% or more in motor seizures from baseline

  - Reduction of 50% or more in motor seizures from baseline
  - Reduction of 75% or more in motor seizures from baseline
  - Reduction of 100% in motor seizures from baseline
- To investigate the effect of TAK-935 on the frequency of motor seizures lasting >5 minutes for patients with CDD throughout the Treatment Period
- To investigate the effect of TAK-935 on the percent/frequency of motor seizure free days in patients with Dup15q or CDD during the Maintenance Period
- To assess Clinical Global Impression of Severity (CGI-S) provided by the Investigator
- To assess the Clinical Global Impression of Change (CGI-C) provided by the Investigator
- To assess the Caregiver Global Impression of Change (Care GI-C) responses of the parent/family-reported impression of efficacy and tolerability of study drug
- To investigate the relationship between 24HC level and motor seizure frequency

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The safety objectives are:

- To evaluate safety and tolerability of TAK-935
- To investigate the effect of TAK-935 on behavior and adaptive function using the Vineland Adaptive Behavior scales (VABS) and Aberrant Behavior Checklist Community questionnaire (ABC-C)
- To evaluate the percent of days free of absence seizures in patients who report absence seizures at baseline, to determine if there is worsening of this seizure type during treatment with TAK-935

2.2 Study Design

TAK-935-18-002 (OV935) is a multicenter, open-label, 2-cohort, Phase 2 study in patients aged ≥2 and ≤55 years with Dup15q or CDD demonstrating ≥3 motor seizures [i.e., hemiclonic, focal with motor signs, focal to bilateral tonic clonic convulsion, generalized tonic clonic convulsion, tonic, atonic, bilateral clonic, infantile spasms (if countable), epileptic spasms (if countable), convulsive status, cluster seizures with a code containing A, C, D, E, H, I, J, J, K, L, or N] per month during the 3 months immediately prior to Screening (based on the Investigator's assessment). Myoclonic seizures are not part of the count of motor seizures.

The maximum study evaluation period is 30 weeks, comprised of the periods:

- 4- to 6-week Screening/Baseline Period
- 20-week Treatment Period
    - 8-week Dose Optimization Period
    - 12-week Maintenance Period
- For patients who do not enroll in the long-term, open-label extension (TAK-935-18-001 ENDYMION OLE) study under a separate protocol:
    - 2-week Taper Period
    - 2-week Safety Follow-Up Period

At the end of the prospective Screening/Baseline Period, patients will return to the clinic (Visit 2 [Day 1]). Seizure diaries will be reviewed by the Medical Monitor and if a patient did not meet the eligibility criteria, including minimum number of seizures required for the study (≥3 motor seizures), the patient will be discontinued from the study and considered a screen failure.

The total daily dose of TAK-935 is calculated based on body weight at Visit 1 and will be given twice a day (BID) orally or via G-tube/PEG tube/J-tube with or without food (patients enrolled in clinical sites in China are not to receive study drug via G-tube/PEG tube/J-tube). Patients will receive the initial dose of study drug, Dose 1, for the first 7 days starting at Visit 2 (Day 1). The study drug dose will be increased to Dose 2 and Dose 3 at Day 8 (± 2 days) and Day 15 (± 2 days), respectively. The maximum dose for any patient will be 600 mg/day (300 mg BID). The dose may be changed during the Dose Optimization Period with approval from the Medical Monitor. The final dose level will be maintained until the end of the Maintenance Period. Patients who cannot tolerate Dose 1 will be withdrawn from the study (and will complete the early termination [ET] and safety follow-up visits).

Following completion of the study, patients will have the option to enroll in a long-term, OLE study (TAK-935-18-001 ENDYMION) or to enter a 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 end of the study for an individual patient is defined as the last protocol-specified contact with that patient.

For the purpose of this SAP, 'motor seizures' refers to motor seizures excluding myoclonic seizures.

2.2.1 Number of Patients

Approximately 30 total male and female patients with Dup15q or CDD (approximately 15 patients in each syndrome) will be enrolled.

2.2.2 Enrollment Procedures

All patients will receive TAK-935 throughout this open-label study. Assignment to analysis groups will be determined by the seizure syndrome: Dup15q or CDD. The study will begin with a phased enrollment based on age:

- Two patients aged ≥9 years will be enrolled for assessment of safety and pharmacokinetics (PK). The independent Data Monitoring Committee (iDMC) will review safety (adverse events [AEs] and clinical laboratory results) and available PK data for these 2 patients at the end of initial up-dosing or Day 21
- The iDMC may then recommend treatment for additional patients aged ≥9 years and the first 2 patients aged ≥2 to <9 years
- Safety and available PK data for the first 2 patients aged ≥2 to <9 years will be reviewed by the iDMC at the end of initial up-dosing or Day 21
- The iDMC may then recommend treatment for additional patients aged ≥2 to <9 years
- The Sponsor's Medical Monitor and/or Pharmacovigilance Physician will review safety data and available PK of the first 2 patients aged ≥9 years and the first 2 patients aged ≥2 to <9 years during each step of dose escalation.

2.2.3 Efficacy Assessments

2.2.3.1 Seizure Diary

The seizure diary is an observer-reported clinical outcome assessment measure that captures the total number and duration of seizures by type. Seizure type will be recorded as one of: hemiclonic, focal without motor signs, focal with motor signs, focal to bilaterial tonic clonic convulsion, myoclonic, generalized tonic clonic convulsion, absence or atypical absence, tonic, atonic, bilaterial clonic, infantile spasms (if countable; in patients under 3 years of age), epileptic spasms (if countable; in patients 3 years of age and older), non-convulsive status (greater than 30 min), convulsive status (greater than 30 min), or cluster seizures with a corresponding code. Myoclonic seizures are captured in the seizure diary although they are not part of the motor seizure count. Refer to Appendix 1 for the classification of seizure types.

Patients and/or patients' caregivers may record seizures throughout the day but must ensure that the daily diary assessment is completed each evening, even if no seizures occurred. The seizure events will be recorded starting at the Screening/Baseline Period up until the Follow-up Visit and collected at each clinic visit: Day 1, Day 15, Day 36, Day 85, Day 141 End of Treatment (EOT)/ET, and Follow-up Day 169 (for patients under the original protocol: Day 1, Day 8, Day 15, Day 29, Day 57, Day 85/ET, and Follow-up Day 86-Day 115).

2.2.3.2 Caregiver Global Impression of Change (Care GI-C)

The Care GI-C comprises a single question assessing the status of the patient's overall condition compared to pre-treatment baseline rated on a 7-point scale (1=Very much improved to 7=Very much worse) that will be given at Day 36, Day 85, and Day 141 EOT/ET (for patients under the original protocol: Day 29, Day 57, and Day 85/ET). 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. At Visit 2 (Day 1; 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.

2.2.3.3 Clinical Global Impression of Severity/Change (CGI-S/C)

The CGI-S is a clinician-reported rating of illness severity. The Principal Investigator or designee will complete the CGI-S at Day 1, Day 36, Day 85, and Day 141 EOT/ET (for patients under the original protocol: Day 29, Day 57, and Day 85/ET). Ratings are made on a 7-point scale from 1 (normal, not at all ill) through to 7 (amongst the most extremely ill). A score of 0 may be recorded on the case report form (CRF), indicating "not assessed"; this score will be treated as missing for the calculation of descriptive statistics.

The CGI-C is a clinician-reported rated of change compared to the pre-treatment baseline. The Prinicpal Investigator or designee will complete the CGI-C at Day 36, Day 85, and Day 141 EOT/ET (for patients under the original protocol: Day 29, Day 57, and Day 85/ET). The rating considers both therapeutic efficacy and treatment-related AEs. The ratings range from 0 (marked improvement and no side-effects) through 4 (unchanged or worse and side-effects outweigh the therapeutic effect). Each component of the CGI is rated separately; the instrument does not yield a global score.

2.2.3.4 Plasma 24HC Level

A plasma sample to assess pharmacodynamics (concentration of plasma 24HC) will be collected pre-dose on Day 1, Day 15, Day 36, Day 85, Day 141 EOT/ET, and Follow-up Day 169 (for patients under the original protocol: Day 1, Day 29, and Day 85/ET).

2.2.3.5 Pharmacokinetics of TAK-935

Five (5) PK blood draws will occur at the following time points on Day 1: within 1 hour prior to first dose, 30 minutes (± 10 minutes), 1, 2, and 4 hours (± 10 minutes) post-first dose. On Day 15, Day 36, Day 85, and Day 141 EOT/ET, two PK blood draws will be collected; one within 1 hour prior to the morning dosing and the other at 30 minutes (± 10 minutes) post-morning dose. For patients under the original protocol, PK blood draws are at pre-dose and post-dose on Day 1; then additional PK samples at pre-dose and post-dose at Day 8 and Day 15, and a single PK draw at either pre-dose or post-dose at Day 29 and Day 85/ET.

2.2.3.6 Plasma Concentrations of AEDs

A plasma sample for AED analysis will be collected on Day 1, Day 36, Day 85, and Day 141 EOT/ET (for patients under the original protocol: Day 1, Day 29, and Day 85/ET). The AEDs to be analyzed are listed in Appendix 4.

2.2.4 Safety Assessments

2.2.4.1 Adverse Events

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. All AEs occurring after the patient receives the first dose of study drug must be reported to the Sponsor or its designee via the CRF. Serious adverse

events (SAEs) must be reported as such, starting from the time that informed consent for study participation is provided.

Investigators will rate the severity of AEs (mild, moderate, or severe) using the criteria in Protocol Section 8.3.1.1 and will report the potential relatedness of each AE to protocol procedure and/or study drug using the criteria in Protocol Section 8.3.1.2.

For the purpose of this study, reporting of seizures should meet the AE/SAE reporting requirements. As seizures are a baseline condition among subjects in the study, 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. 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 the risk-benefit evaluation.

2.2.4.2 Serious Adverse Events

Serious adverse event collection begins after the patient has signed the ICF. If a patient experiences an SAE after signing the ICF, 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 procedure listed in the protocol.

2.2.4.3 Clinical Laboratory Evaluation

The central laboratory will perform laboratory tests for hematology, serum chemistry, and urinalysis. Local laboratory tests may be performed as needed. Samples are to be collected at Screening, Day 1, Day 15, Day 36, Day 85, and Day 141 EOT/ET (for patients under the original protocol: Screening, Day 1, Day 29, Day 85/ET). The clinical laboratory tests to be performed are listed in Appendix 4.

2.2.4.4 Vital Signs, Height, and Weight

Vital signs should be measured at the same time of day across visits, if possible. Vital signs to be measured are oral body temperature, blood pressure (sitting, standing, and supine), heart rate [beats per minute] (sitting, standing, and supine), and respiratory rate. Height and weight will also be measured. Measurements will be taken at Screening, Day 1, Day 15, Day 36, Day 85, Day 141 EOT/ET, and Follow-up Day 169 (only vitals at Day 169). For patients under the original protocol, measurements were taken at Screening, Day 1, Day 8 (height and weight only), Day 15, Day 29, Day 57, and Day 85/ET. Weight at screening is used to determine the dosing schedule.

2.2.4.5 Electrocardiogram (ECG)

A 12-lead ECG will be recorded at Screening and at 30 minutes (± 10 minutes) after the morning dose at Day 1, Day 15, Day 36, Day 85, and Day 141 EOT/ET (for patients under the original protocol: Screening, Day 1, Day 29, and Day 85/ET). 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 one of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The following parameters will be recorded on the CRF from the patient's ECG trace: heart rate, RR interval, PR interval, QT interval, QRS interval, and corrected QT interval.

2.2.4.6 Physical Examination

The physical examination will be performed at Screening, Day 1, Day 15, Day 36, Day 85, Day 141 EOT/ET, and Follow-up Day 169 (for patients under the original protocol: Screening, Day 1, Day 15, Day 29, Day 57, and Day 85/ET), and will assess the following body systems: head, eyes, ears, nose, throat; cardiovascular; respiratory; gastrointestinal; dermatologic; extremities; musculoskeletal; lymph nodes; psychiatric status; and additional results for other systems may be specified. At Day 15, the physical examination can be limited to general appearance; head, ears, nose, and throat; cardiovascular; respiratory; and abdominal.

2.2.4.7 Neurological Examination

A separate neurological examination will be performed at Screening, Day 1, Day 15, Day 36, Day 85, Day 141 EOT/ET, and Follow-up Day 169 (for patients under the original protocol: Screening, Day 1, Day 15, Day 29, Day 57, and Day 85/ET) and collected in the CRF. This will include testing mental status, gait, cerebellar function, cranial nerves, motor function, reflex, and sensation. CCI

2.2.4.8 Clinical Assessment of Suicidal Ideation and Behavior

Suicidal ideation and behavior will be assessed in children aged ≥6 years using the Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening, Day 1, Day 85, Day 141 EOT/ET, and Follow-up Day 169 (for patients under the original protocol: Screening, Day 1, Day 29, and Day 85/ET). The C-SSRS is a 3-part scale that measures suicidal ideation, intensity of ideation, and suicidal behavior.

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. The investigator will use clinical judgment to determine presence of suicidal ideation or behavior.

2.2.4.9 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 and subdomain scores will be provided by Pearson's Qglobal and will be used for analysis. 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 presented 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 behavior 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).

2.2.4.10 Aberrant Behavior Checklist-Community (ABC-C)

The ABC-C measures psychiatric symptoms and behavioral disturbance exhibited by individuals across 5 subscales with 58 items: irritability, agitation, and crying (Irritability subscale: 15 items); lethargy, social withdrawal (Lethargy/Social Withdrawal subscale: 16 items); stereotypy (Stereotypic Behavior subscale: 7 items); hyperactivity/noncompliance (Hyperactivity subscale: 16 items); and inappropriate speech (Inappropriate Speech subscale: 4 items). Each item is rated on a scale of 0 to 3 ("not at all a problem" to "the problem is severe in degree").

The total score is calculated by summing the scores on all 58 items. Each subscale score is calculated by summing the items below:

The scale includes the following 5 subscales with the sub scores derivation:

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
Inappropriate speech	9, 22, 33, 46

*For missing data, the following upper limits will apply (number of missing items tolerated for each subscale before discarding the data for that subscale): (I) Irritability (15-item scale): 3 items; (II) Lethargy/Social Withdrawal (16-item scale): 3 items; (III) Stereotypic Behavior (7-item scale)" 2 items; (IV) Hyperactivity/Noncompliance (16-item scale): 3 items; (V) Inappropriate Speech (4-item scale): 1 item. If more items than the stated upper limit have been left blank, the subscale will not be computed. If the subscale has the required minimum number of items, the subscale scores will be prorated as follows: (a) Take the total number of items on the subscale and divide this by the number of completed items. This will result in a number larger than 1.00. (b) Multiply that number by the total score for that subscale. (c) This becomes the new total score for this subscale for the given subject.

The ABC-C questionnaire is completed by the caregiver at Screening and at Day 141 EOT/ET (Day 85/ET for patients who completed the study under the original protocol).

2.2.4.11 Absence Seizures

Patients and/or patients' caregivers will also observe and report absence seizures using the seizure daily diary (seizure type "absence or atypical absence").

2.2.4.12 New seizure types

New seizure types are defined as any seizure type that was not listed at screening or during baseline period but were observed and reported during treatment period. The number of patients with at least 1 new seizure type will be listed.

2.2.5 CCI

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2.2.6 Other Assessments

Demographics, medical history, and medication history will be collected at Screening. Ongoing comorbidities are considered concurrent medical conditions and will also be documented. Additionally, an optional severity assessment may be conducted in only the CDD patients at Screening and at the end of treatment to capture degrees of severity associated with motor function, cognition, and vision and autonomic dysfunction.

A serum/urine pregnancy test will be given at Screening, Day 1, and Day 141 EOT/ET (Screening, Day 1, and Day 85/ET for patients under the original protocol).

Concomitant medications (including AEDs) will be reported on an ongoing basis.

Table 1. Schedule of Assessments

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3 STATISTICAL METHODS

3.1 General Methods

3.1.1 Computing Environment

All statistical analyses will be performed using SAS® Version 9.4 or higher for Windows.

3.1.2 Presentation of Data Summaries

Unless otherwise specified, tables will be presented by analysis group (Dup15q or CDD) within analysis set. An "All Patients" column will be included as appropriate.

All clinical study data will be presented in patient data listings.

3.1.3 Reporting of Numerical Values

Descriptive statistics (number of patients [n], mean, standard deviation [SD], first quartile [Q1], median, third quartile [Q3], minimum, and maximum) will be calculated by analysis group for all continuous variables. Confidence intervals will be provided where appropriate.

Frequencies and percentages will be presented by analysis group for categorical and ordinal variables. If there are missing values, the number of missing will be presented, but without a percentage.

Means, quartiles, and confidence intervals will be reported to one decimal place more than the data reported on the CRF or by the laboratory/vendor. Standard deviations will be reported to two decimal places more than the data reported. Minimum and maximum will be reported to the same number of decimal places displayed on the CRF or by the laboratory/vendor.

3.1.4 Baseline Value and Change from Baseline

For seizure endpoints (frequency and duration) based on the seizure diary, baseline values will be calculated over the 4 to 6 week Screening/Baseline Period prior to first dose (starting at date of initial screening visit). The period from the initial screening visit until the day prior to the first dose will be considered baseline even in the case of an extended screening period. For measures taken at a single time point, the baseline value will be defined as the most recent non-missing value obtained immediately prior to administration of first dose. Change from baseline will be calculated by

subtracting the baseline value from the post-dose assessment for each patient (i.e., post-dose – baseline).

3.1.5 Study Day

Study day will be defined in relation to date of the first dose of study treatment. For pre-dose records, study day will be calculated as (date of record – date of first dose). For records on or after the first dose of study treatment, study day will be calculated as (date of record – date of first dose + 1).

3.1.6 Handling of Missing/Incomplete Values

To the extent possible, attempts will be made to minimize the amount of missing data through measures planned in the study conduct. . Missing data will be kept as missing, no imputation will be done for missing data. All analyses will be conducted using observed values.

3.1.7 Handling of Repeated Assessments

If multiple results are available for a post-dose assessment at the same scheduled time point, then the earliest result recorded for that time point will be used in all descriptive summaries. All results will be displayed in patient data listings.

3.1.8 Handling of Missing/Incomplete Date/Time

Adverse Events

All analyses of AEs will be based on the principle of treatment emergence. An AE is considered to be treatment emergent if it has a start date/time or increases in severity on or after the date/time of first dose of study treatment; if the AE is missing a start time, it is considered to be treatment emergent if it has a start date on or after the date of first dose of study treatment. Furthermore, for the presentation of AE incidences, non-serious treatment emergent adverse events (TEAEs) starting on or before 7 days after the last dose date or last visit date and SAEs starting on or before 30 days after the last dose date or last visit date will be included. If an AE start date is incomplete or missing, imputation and the AE end date will be used to determine treatment emergence and occurrence within the 7- or 30-day window. First, partial AE start/end dates will be imputed as follows:

- Missing end day: Impute as the last day of the month.
- Missing end day and month: Impute as Dec 31.
- Missing start day: If the partial date contains the same month and year as the treatment start date, impute as the treatment start date; otherwise, impute as the first day of the month.

- Missing start day and month: If the partial date contains the same year as the treatment start date, impute as the treatment start date; otherwise, impute as January 1.

After the imputation of partial dates, use the following criteria:

- First, for treatment emergence:
  - If the start date is on or after the date of first dose, then the AE is considered treatment emergent.
  - If the start date is before the date of first dose, then the AE is not considered treatment emergent unless it worsens.
  - If the start date is missing and the end date is on or after the date of first dose or the AE is ongoing, then the AE is considered treatment emergent.
  - If the start date is missing and the end date is before the date of first dose, then the AE is not considered treatment emergent.
  - If both the start and end dates are missing, then the AE is considered treatment emergent.
- If treatment emergent, for occurrence within the 15-day or 30-day window:
  - The start date can be used to determine whether the AE is within the 15-day (for non-serious AEs) or 30-day (for SAEs) window.
  - If the start date is completely missing, the non-serious AE will be considered within the 15-day window, or for an SAE, it will be considered within the 30-day window.

Prior and Concomitant Medications

A concomitant medication is any drug taken on or after the first dose of study drug. A prior medication is any drug started before the first dose of study drug. Medications that are ongoing on the date of the first administration of study drug will be considered both prior and concomitant. For the purpose of computation, a medication or procedure is considered to be concomitant if it has an end date/time on or after the first dose or if it is indicated as ongoing on the CRF. Similarly, a medication is considered to be prior if it has either a start date/time or end date/time before the first dose. If time is not available, then only date will be used (e.g. end date on or after the date of first dose). In order to determine concomitance, partial end dates will be imputed as follows:

- Missing end day: Impute as the last day of the month.
- Missing end day and month: Impute as Dec 31.

After the imputation of partial dates, the following criteria will be used:

- If the end date is on or after the first dose, the medication will be considered concomitant.
- If the end date is prior to the first dose, the medication will not be considered concomitant.
- If the end date is missing, then the medication will be considered concomitant.

In order to determine whether a medication is prior, partial start dates will be imputed as follows:

- Missing start day: Impute as the first day of the month.
- Missing start day and month: Impute as Jan 1.

After the imputation of partial dates, the following criteria will be used:

- If the start date or end date is before the first dose, the medication will be considered prior.
- If the start date is on or after the first dose, the medication will not be considered prior.
- If the start date is missing, then the medication will be considered prior.

3.2 Analysis Sets

3.2.1 Modified Intent-to-Treat Analysis Set

The Modified Intent-to-Treat (mITT) Analysis Set will include all patients who have received at least 1 dose of study drug and have been assessed for at least 1 day in the Treatment Period. All efficacy analyses will be based on the mITT Analysis Set.

3.2.2 Safety Analysis Set

The Safety Analysis Set will include all patients who have received at least 1 dose of study drug. Safety analyses will be based on the Safety Analysis Set.

3.3 Analysis Variables

3.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the percent change from baseline in motor seizure frequency per 28 days during the Maintenance Period.

3.3.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints in this study are:

- Percent change from Baseline in motor seizure frequency per 28 days at each 4-week interval within the Treatment Period, and over the entire 20-week Treatment Period
- Percent change from Baseline in all seizure frequency per 28 days at each 4-week interval within the Treatment Period, the 12-week Maintenance Period, and over the entire 20-week Treatment Period
- Percent change from Baseline in frequency of each seizure type per 28 days at each 4-week interval within the Treatment Period, the 12-week Maintenance Period, and over the entire 20-week Treatment Period
- Proportion of patients considered treatment responders at each 4-week interval within the Treatment Period, the 12-week Maintenance Period, and over the entire 20-week Treatment Period, where treatment responders are defined as those with:
    - Reduction of 25% or more in motor seizures from baseline
    - Reduction of 50% or more in motor seizures from baseline
    - Reduction of 75% or more in motor seizures from baseline
    - Reduction of 100% in motor seizures from baseline
- Proportion of motor seizures longer than 5 minutes during Baseline period, at each 4-week interval within the Treatment Period, the 12-week Maintenance Period, and over the entire 20-week Treatment Period
- Proportion of motor seizure-free days during Baseline period, at each 4-week interval within the Treatment Period, the 12-week Maintenance Period, and over the entire 20-week Treatment Period
- Proportion of all seizure-free days during Baseline period, at each 4-week interval within the Treatment Period, the 12-week Maintenance Period, and over the entire 20-week Treatment Period
- Change from baseline in CGI-S responses
- Ratings by clinician using the CGI-C
- Ratings of caregiver-provided Care GI-C
- To characterize plasma 24HC levels and change in motor seizure frequency in patients treated with TAK-935 as an adjunctive therapy

3.3.3 Exploratory Efficacy Endpoints

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3.3.4 Safety Endpoints

The safety endpoints in this study are:

- Percentage of patients with at least 1 treatment emergent adverse event
- Change in behavioral and adaptive functional measures using the VABS
- Change in behavior measures using total scores and subscale scores of ABC-C
- Percentage of patients with at least 1 markedly abnormal value for clinical laboratory evaluations, vital signs, body weight and height, and ECG parameters after TAK-935 treatment
- Change from Baseline in clinical laboratory evaluations, vital signs, body weight, height, C-SSRS, and ECG parameter values after TAK-935 treatment
- Percent of absence seizure free days in patients who report absence seizures during baseline
- Number of patients with new seizure types during the treatment period

3.4 Patient Disposition and Evaluability

3.4.1 Patient Disposition

Patient disposition will be presented by analysis group and overall for all enrolled patients. The number of patients screened, failed screening, and eligible will be presented. The number and percentage of patients in each analysis set (mITT and Safety Analysis Sets), completing and not completing the study, as well as reasons for patient discontinuations will be summarized.

Disposition data (extent of study participation) and inclusion/exclusion criteria not met will be provided in patient listings.

A separate patient listing of disposition data will be provided for patients affected by COVID 19.

3.4.2 Protocol Deviations

All protocol deviations will be shown in a patient listing, with a flag for whether the deviation was related to COVID-19.

3.5 Demographics and Characteristics at Screening

3.5.1 Demographics and Characteristics at Screening

Patient demographics and characteristics at screening will be summarized by analysis group and overall for all analysis sets. If any of the analysis sets are equivalent to each other, the demographics summary will only be presented for one of the equivalent sets. Descriptive statistics will be provided for age (as reported on the CRF), height at screening, weight at screening, and body mass index (BMI) at screening. Frequencies and percentages will be tabulated for sex, race, and ethnicity.

Demographic information and characteristics at screening will be listed by patient.

3.5.2 Medical History

Medical history will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of the data cut and presented by analysis group and overall for the Safety and mITT Analysis Sets, summarized by MedDRA system organ class (SOC) and preferred term (PT).

All medical history and concurrent medical conditions will be listed by patient.

3.6 Prior and Concomitant Medications

A concomitant medication is any drug taken after the first dose of study drug. Medications that are ongoing on the date of the first administration of study drug will be considered both prior and concomitant. Rules for determining whether medications with missing or incomplete dates/times are concomitant and/or prior are provided in Section 3.1.8.

Prior and concomitant medication use will be coded using the latest version of the World Health Organization Drug Dictionary (WHO-DD) at the time of the data cut. All concomitant medications will be summarized by Anatomic Therapeutic Class (ATC) Level 2, ATC Level 4 and Preferred Term (PT). Prior and concomitant AEDs will be summarized by PT and presented by analysis group and overall in the Safety

and mITT Analysis Sets. Medications will be sorted by decreasing frequency of incidence for both analysis groups combined.

All prior and concomitant medications will be presented in a listing, with AEDs and prior medications flagged. A separate listing of AEDs started during the Treatment Period [i.e. after the first dose of study drug, but before the tapering period (for any patients who do not roll over to the OLE)] will be presented.

3.7 Treatment Compliance and Exposure

3.7.1 Compliance to Study Treatment

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

$$100 \times \frac{\text{(Total number of tablets/mini-tablets dispensed - Total number of tablets/mini-tablets returned)}}{\text{(Expected number of tablets/mini-tablets)}}$$

Total dose administered will primarily be based on the drug accountability (Total dose dispensed – total dose returned). If the "bottle returned" information on the drug accountability eCRF page is missing, the dose administered will be based on the dosing eCRF page for that period. All non-missing doses are considered full dose for calculating the "dose administered". Expected numbers of tablets/mini-tablets is based on the date of first study medication dose, date of last study medication dose, and date and amount of each study drug titration approved by the Investigator. According to Protocol Table 1, a patient will take either only mini-tablets (20 mg) or only regular tablets (100 mg) throughout the study. This calculation assumes that all study drug not returned was taken by the patient.

Patient dosing is based on Protocol Table 1, but the daily dose may be adjusted per Investigator's discretion with approval of the Medical Monitor during the Dose Optimization Period; dose changes during the Maintenance Period must be discussed and approved by the Sponsor. Each time a new dose level (mg) and corresponding date of dose change is recorded, this will be considered the patient's planned daily dose until the date of the next reported dose change or end of treatment.

Compliance rates will be presented for the Safety and mITT Analysis Sets 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 analysis group and overall. Compliance >120% is not expected, but if it occurs, the category ">120%" will be included in the summary.

3.7.2 Exposure to Study Treatment

Treatment duration (weeks on treatment) will be described for the Safety and mITT Analysis Sets using summary statistics and frequency distributions (0 to <8 weeks, 8 to <12 weeks, 12 to <20 weeks, ≥20 weeks) by analysis group and overall. Treatment duration in weeks will be calculated as follows: [(Last dose date – First dose date + 1)/7].

Study drug dosing, exposure and compliance, and accountability will be listed by patient.

3.8 Efficacy Analysis

Unless otherwise specified, all efficacy analyses will be based on the mITT Analysis Set and will be presented by analysis group and overall.

3.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the percent change from baseline in motor seizure frequency per 28 days during the 12-week Maintenance Period, calculated according to Section 4.1. The start and end of the 12-week Maintenance Period are defined in Section 4.2.

The motor seizure types include hemiclonic, focal with motor signs, focal to bilateral tonic clonic convulsion, generalized tonic clonic convulsion, tonic, atonic, bilateral clonic, infantile spasms (if countable), epileptic spasms (if countable), convulsive status (greater than 30 min), and cluster seizures with a code containing A, C, D, E, H, I, J, J, K, L, or N.

Observed values, change from baseline, and percent change from baseline for motor seizure frequency per 28 days will be summarized separately for the patients with CDD and for the patients with Dup15q in the mITT Analysis Set. The mean of the change from baseline and of percent change from baseline will be presented along with its corresponding 90% confidence interval, separately for each analysis group and overall. Seizure frequency for each patient will be calculated using all available observed data within the 12-week Maintenance Period.

Histograms will be produced for the primary endpoint for each analysis group and will be repeated for all motor seizure types.

Compliance for seizure diary assessments will be summarized overall by subject group (<=80%, >80% to <100% and 100%) for the Treatment Period.

This primary analysis for the primary endpoint will be repeated for the all patients who completed the study.

3.8.2 Secondary Efficacy Endpoints

Unless otherwise specified, all secondary efficacy analyses will be based on the mITT Analysis Set and will be presented by analysis group and overall.

3.8.2.1 All and Motor Seizure Frequency During the Treatment Period

The observed values, change from baseline, and percent change from baseline for all and motor seizure frequency per 28 days will be summarized for each 4-week interval within the Treatment Period, the 12-week Maintenance Period, and over the entire 20-week Treatment Period. The start and end of each interval are defined in Section 4.2, and seizure frequency is calculated according to Section 4.1.

The time course of the mean ± SD of seizure frequency at baseline and over each 4-week interval in the Treatment Period will be displayed in a line graph by analysis group. This will be repeated for percent change from baseline in motor seizure frequency.

A line plot will be presented for each patient showing the patient's motor seizure frequency and all seizure frequency (two lines per patient) at baseline and over each 4-week interval in the Treatment Period. CCI [redacted] This figure will be repeated to show the percent change from baseline in motor seizure frequency and all seizure frequency for each patient over each 4-week interval in the Treatment Period.

The observed values, change from baseline, and percent change from baseline for frequency of each type of seizure per 28 days at each 4-week interval within the Treatment Period, the 12-week Maintenance Period, and over the entire 20-week Treatment Period.

Motor seizure frequencies will be listed by patient for each of the nine intervals. This will be repeated for each seizure type. Additionally, all seizure diary data will be listed.

3.8.2.2 Response to Treatment Based on Seizure Frequency

Response to treatment will be summarized by the number and percentage of patients with ≥25% reduction, ≥50% reduction, ≥75% reduction, and 100% reduction from baseline in motor seizure frequency at each 4-week interval within the Treatment Period, the 12-week Maintenance Period, and over the entire 20-week Treatment Period. For exploratory purposes, this tabulation will be repeated for the categories in percent seizure reductions: </=0, >0 to <25, >/=25 to <50, >/=50 to <75, >/=75 to 100.

3.8.2.3 Duration of Motor Seizures

A summary of motor seizures longer than 5 minutes will be presented, calculated according to the formula in Section 4.1. The proportion of patient with motor seizures longer than 5 minutes during the Baseline period, at each 4-week interval within the 12-week Maintenance Period, and the 20-week Treatment Period will be presented as defined in Section 4.2.

The frequency of motor seizures longer than 5 minutes will be included in the seizure frequency listing described in Section 3.8.2.1.

3.8.2.4 All and Motor Seizure Freedom

The number of motor seizure-free days during the 20-week Treatment Period will be summarized only for patients who have completed the study. The proportion of motor seizure-free days during Baseline period, at each 4-week interval within the 12-week Maintenance Period, and over the entire 20-week Treatment Period will also be summarized for these patients and is calculated for each patient as:

$$\frac{\text{Number of days with 0 motor seizures during the Treatment Period}}{\text{Number of days patient was in the Treatment Period (observed)}}$$

A separate summary will be presented for only patients who have completed the study and will include the number and percentage of these patients who were motor seizure-free during the Baseline period, at each 4-week interval within the 12-week Maintenance Period, and over the entire 20-week Treatment Period.

Additionally, each patient's longest motor seizure-free duration will be calculated as the longest number of consecutive days that the patient had a motor seizure count of 0 recorded in the seizure diary during the 12-week Maintenance Period and over the 20-week Treatment Period using observed data. These patient-specific longest motor seizure-free durations will be listed, along with the number and proportion of motor seizure-free days for each patient during the 12-week Maintenance Period and over the 20-week Treatment Period, whether each patient was motor seizure-free over the last 28 days of the Treatment Period, and the number of days each patient was in the Treatment Period.

All seizure-free days will be analyzed similarly to motor seizure-free days.

3.8.2.5 CGI-S/C and Care GI-C

For CGI-S assessments, the observed values and change from baseline in CGI-S score will be summarized with descriptive statistics by visit.

Additionally, the number of subjects and percentage of each category in CGI-S will be summarized by visit. A shift in CGI-S categories will also be summarized from Baseline to the end of Maintenance Period.

For CGI-C, and Care GI-C, the number of subjects and percentage for each category in the readings will be listed by visit during the Maintenance Period. A shift from baseline in the category of the ratings will be summarized at the end of Maintenance Period. The proportion of subjects who achieved positive improvement will be summarized by visit.

CGI-S, CGI-C and Care GI-C Scores will be listed by subject.

3.8.2.6 Plasma 24HC Level

Observed and change from baseline in plasma 24HC levels will be summarized by visit by subject group. BLQ values will be treated as missing for the calculation of summary statistics. The level of plasma 24HC at each visit will be listed by patient. BLQ will be listed as not detectable.

Additionally, the relationship between motor seizure frequency and the level of plasma 24HC will be explored. The motor seizure frequency line plots for each patient, described in Section 3.8.2.1, will be annotated with the 24HC levels. A corresponding listing will present the 24HC levels side-by-side with the observed and change from baseline in motor seizure frequencies at each 4-week interval in the 20-week Treatment Period. The 24HC collection visits will be paired with the 4-week seizure frequency intervals as follows:

24HC Collection Visit	Seizure Frequency Interval
Baseline	Baseline Period
Day 15	Day 1 – Day 28
Day 29/Day 36	Day 29 – Day 56
-	Day 57 – Day 84
Day 85	Day 85 – Day 112
Day 141 EOT/ET	Day 113 – Day 141

3.8.3 Exploratory Endpoints

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3.8.3.1 Plasma Concentration of TAK-935

The plasma concentration of TAK-935 will be summarized descriptively by visit and planned time point. A line plot of the mean ± SD of the TAK-935 plasma concentration will be displayed by planned time point and analysis group.

Additionally, spaghetti plots of TAK-935 plasma concentration over time will be shown separately for each analysis group. For both plots, all time points will be shown on one plot, with wider spacing along the x-axis between days. For the calculation of descriptive statistics for tables and figures, BLQ concentration values will be set to undetectable.

Plasma concentrations at each planned time point will also be listed by patient. For BLQ concentrations, the undetectable values will also be listed.

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3.9 Safety Analysis

All safety assessments will be based on the Safety Analysis Set and presented by analysis group and overall, unless otherwise indicated.

3.9.1 Adverse Events

All AEs will be coded using the latest version of MedDRA at the time of the data cut and will be classified by MedDRA SOC, high level group term (HLGT), high level term (HLT), and PT.

Analyses of AEs will be based on the principle of treatment emergence. A TEAE is any AE that starts or increases in severity during or after the first dose of study drug.

For presentations of AE incidences, non-serious TEAEs starting on or before 15 days after the last dose date or last visit date and SAEs starting on or before 30 days after the last dose date or last visit date will be included, unless otherwise specified below. Refer to Section 3.1.8 for the handling of incomplete or missing date/time in determining treatment emergence and occurrence within the 15- or 30-day window.

The SOCs, HLGTs, and HLTs will be sorted alphabetically, and within SOC, HLGT, or HLT, the PT will be presented by decreasing total frequency in all patients and then alphabetically. If a patient has more than one occurrence of the same PT, then the PT will be counted only once for that patient. Similarly, if a patient has more than

one PT within the same SOC, HLGT, or HLT, the patient will be counted only once in that SOC, HLGT, or HLT.

All serious and non-serious AEs will be presented in a data listing, with flags for treatment emergence and occurrence after the 15- or 30-day window.

3.9.1.1 Summary of TEAEs

The numbers and percentages of patients who experienced any TEAE, treatment-related TEAE, severe TEAE, severe treatment-related TEAE, serious TEAE, TEAE leading to permanent withdrawal of study drug, and TEAE leading to discontinuation from study will be presented. Treatment-related TEAEs will be defined as events with a study drug causality of "Possibly Related" or "Related".

3.9.1.2 Incidence of TEAEs

The number and percentage of patients who experienced any TEAE as well as the number and percentage of patients who experienced any TEAE within each specific SOC and PT will be presented. Three similar summary tables will also be presented: (1) TEAEs by PT; (2) TEAEs by SOC, HGLT and PT; (3) TEAEs by SOC, HLT and PT. The SOC/PT and PT summaries will be presented once where occurrence within the 15- or 30-day window is required for a TEAE to be included, and again where occurrence within the 15- or 30- day window is not required. The last two summaries that use HGLT and HLT will be presented once, with TEAEs required to be within the 15- or 30- day window in order to be included.

3.9.1.3 Treatment-Related TEAEs

TEAEs with a study drug causality of "Possibly Related" or "Related" occurring within the 15- or 30-day window will be classified as treatment-related and presented by SOC and PT. TEAEs with missing relationship will be classified as treatment-related in the summarization.

All treatment-related TEAEs will be listed by patient.

3.9.1.4 TEAEs by Maximum Severity

The incidence of TEAEs occurring within the 15- or 30-day window will be presented by maximum severity for each SOC and PT. If a patient experiences more than one occurrence of the same PT, the patient will be counted only once under the maximum severity at which it was experienced. Missing severity will remain classified as missing, and will be considered to be the maximum severity only if the patient never had the same TEAE with a non-missing severity; if missing severity is

considered to be the maximum, the TEAE will be counted in only the "Total" column of the table.

3.9.1.5 Severe TEAEs

The incidence of TEAEs classified as severe occurring within the 15- or 30-day window will be presented by SOC and PT.

3.9.1.6 Severe Treatment-Related TEAEs

The incidence of severe treatment-related TEAEs occurring within the 15- or 30-day window will be presented by SOC and PT.

3.9.1.7 Serious TEAEs

The incidence of SAEs starting on or before 30 days after the last dose date or last visit date will be summarized by SOC and PT. All SAEs will be listed by patient.

3.9.1.8 TEAEs Leading to Discontinuation from Study

The incidence of TEAEs leading to discontinuation from study will be summarized by SOC and PT. TEAEs leading to discontinuation from study will be listed by patient.

3.9.1.9 TEAEs of Special Interest

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3.9.2 Clinical Laboratory Evaluation

A list of hematology, coagulation, chemistry, and urinalysis parameters collected during the study is provided in Appendix 4.

Observed values and change from baseline to each visit for continuous chemistry, hematology, coagulation, and urinalysis results will be summarized descriptively. For each continuous laboratory parameter, results will be categorized as low, normal, or high based on the laboratory normal ranges. Frequencies and percentages will be presented for the shifts from baseline to each post-baseline visit (i.e., low to normal, low to high, high to low, etc.) for each parameter.

All laboratory results will be listed by patient, with out of normal range values flagged. A separate listing of abnormal results will be provided, as well as a listing of serum and urine pregnancy test results.

3.9.3 Vital Signs, Height, and Weight

Observed values and change from baseline in oral body temperature, heart rate (sitting, standing, and supine), respiratory rate, systolic and diastolic blood pressure (sitting, standing, and supine), height, and weight will be summarized descriptively by visit.

All vital sign measurements, height, and weight, will be listed by patient.

3.9.4 ECG

Observed values and change from baseline in heart rate, RR interval, PR interval, QT interval, QRS interval, and corrected QT interval will be summarized by study visit.

All ECG results will be listed by patient, with a flag for clinical significance.

3.9.5 Physical Examination

For each body system (head, eyes, ears, nose, throat; cardiovascular; respiratory; gastrointestinal; dermatologic; extremities; musculoskeletal; lymph nodes; psychiatric status), shifts from baseline to final visit (no change, normal to abnormal, or abnormal to normal) will be presented.

All physical examination results will be listed by patient.

3.9.6 Neurological Examination

For each component of the neurological examination (mental status, gait, cerebellar function, cranial nerves, motor function, reflex, and sensation), shifts from baseline to final visit (no change, normal to abnormal, or abnormal to normal) will be presented.

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3.9.7 Clinical Assessment of Suicidal Ideation and Behavior

A patient will be considered to have suicidal ideation if the response to either C-SSRS Suicidal Ideation question 1 or 2 (Wish to be Dead, Non-Specific Active Suicidal Thoughts) is "Yes". A patient will be considered to have suicidal behavior if the response to any of the six C-SSRS Suicidal Behavior questions (Actual Attempt, Interrupted Attempt, Aborted Attempt, Preparatory Acts or Behavior, Suicidal Behavior, Completed Suicide) is "Yes".

The number and percentage of patients aged ≥6 years considered to have suicidal ideation, and the number and percentage of patients considered to have suicidal behavior based on the C-SSRS will be summarized by visit. The results of all C-SSRS assessments will be listed by patient.

3.9.8 Vineland Adaptive Behavior Scale (VABS)

VABS raw domain scores for behavior, communication, daily living, socialization, and problem behavior will be reported along with the relevant raw subdomain scores. Observed and change from baseline in the VABS raw domain and subdomain scores will be summarized descriptively. All VABS results will be listed by patient.

3.9.9 Aberrant Behavior Checklist-Community

ABC-C total score and subscale scores will be calculated according to Appendix 3. Observed and change from baseline in the ABC-C total score and subscale scores will be summarized descriptively. All ABC-C questionnaire results will be listed by patient.

3.9.10 Absence Seizure-Free Days

The percentage of absence seizure-free days will be calculated over the 4 to 6 week prospective Screening/Baseline Period, during the 12-week Maintenance Period, and during the 20-week Treatment Period. Observed values and change from baseline will be summarized for patients who reported absence seizures at baseline using descriptive statistics.

The percentage of absence seizure-free days at each specified interval will be calculated as:

$$\frac{\text{Number of days with 0 absence seizures during the Treatment Period}}{\text{Number of days patient was in the Treatment Period (observed)}}$$

The percentage of absence seizure-free days at baseline, during the 12-week Maintenance Period, and during the 20-week Treatment Period will be listed by patient.

3.9.11 New seizure types

For each subject, any new seizure type is defined as a seizure type that was not listed at screening or during baseline period but was observed and reported during treatment period. Subjects with at least one new seizure will be summarized by seizure type and overall. All subjects with at least 1 new seizure type will be listed.

3.9.12 Exit Survey

The frequency and percentage for each response option ("Most Improved", "Much Improved", "Slightly Improved", "No Change", "Slightly Worsened", "Much Worsened", "Most Worsened") will be summarized for each of the six exit survey questions. All exit survey results will be listed by patient.

3.10 Other Analyses

3.10.1 Severity Assessment for CDD

The results of the optional severity assessment for CDD will be listed by patient.

3.11 Modifications to the Statistical Section of the Protocol

All efficacy analyses will be based on the Modified Intent-to-Treat Analysis Set, in order to include the two patients who completed the study under the original protocol, dated May 22, 2018. The Efficacy Analysis Set was originally defined in Protocol Amendment 1 to be used for primary and secondary efficacy analyses. The following endpoints were updated or added to the SAP in comparison to Protocol Amendment 2:

- **Additional secondary endpoints**
  - Percent change from Baseline in all seizure frequency per 28 days at each 4-week interval with the Treatment Period, the 12-week Maintenance Period and over the entire 20-week Treatment Period
  - Percent change from Baseline in the frequency of each seizure type per 28 days at each 4-week interval within the Treatment Period, the 12-week Maintenance Period, and over the entire 20-week Treatment Period
  - Proportion of all seizure-free days during Baseline Period, at each 4-week interval within the 12-week Maintenance Period, and over the entire 20-week Treatment Period.

- **Updated secondary efficacy endpoint**

Original

Percent change from Baseline in motor seizure-free days frequency in patients with Dup15q or CDD during Maintenance Period

Update

Proportion of motor seizure-free days during the baseline period, at each 4-week interval within the 12-week Maintenance Period, and over the entire 20-week Treatment Period

- **Additional exploratory efficacy endpoint**

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4 DATA HANDLING

4.1 Computation of Seizure Frequency

Seizure frequency per 28 days may be calculated over nine different intervals: the 4 to 6 week prospective Screening/Baseline Period, each of the two 4-week intervals in the 8-week Dose Optimization period, each of the three 4-week intervals in the 12-week Maintenance Period, the 8-week Dose Optimization Period, the 12-week Maintenance Period, and the entire 20-week Treatment Period. The start and end of each interval are defined by study day and/or visit date according to Section 4.2.

Only days with no missing seizure count will be included in the calculation of seizure frequency. Seizure frequency per 28 days will be calculated at each specified interval as:

$$\frac{\text{(number of seizures in that interval)}}{\text{(days with no missing seizure count in that interval)}} \times 28$$

4.2 Seizure Frequency Intervals

Seizure frequency may be calculated over the following intervals, defined by visit/phone call date and/or study day:

Interval Name	First Day in Interval	Last Day in Interval
Study Periods		
Baseline	date of initial Screening visit	study day -1
20-week Treatment Period	date of first dose (study day 1)	Day 141 EOT/ET visit date [Patients under original protocol: Day 85/ET (+/- 7 days)]
8-week Dose Optimization Period	date of first dose (study day 1)	date of Day 57 phone call – 1 day (+/- 7 days) [For patients under original protocol, Day 57 is a clinic visit. For patients who discontinue from the study prior to Day 57, use date of study discontinuation.]

Interval Name	First Day in Interval	Last Day in Interval
12-week Maintenance Period	date of Day 57 phone call [For patients under original protocol, this is an in-person visit]	Day 141 EOT/ET visit date (+/- 7 days)[Patients under original protocol: Day 85/ET]
4-Week Intervals		
Day 1 – Day 28	date of first dose (study day 1)	study day 28 (+/- 2 days)
Day 29 – Day 56	study day 29	date of Day 57 phone call – 1 day(+/- 7 days) [For patients under original protocol, Day 57 is a clinic visit. For patients who discontinue from the study prior to Day 57, use date of study discontinuation.]
Day 57 – Day 84	date of Day 57 phone call [For patients under original protocol, Day 57 is a clinic visit.]	study day 84 (+/- 7days)
*Day 85 – Day 112	study day 85	study day 112 (+/- 7 days)
*Day 113 – Day 141	study day 113	Day 141 EOT/ET visit date(+/- 7 days)

*The two patients who completed the study under the original protocol do not have sufficient data to calculate seizure frequency for these intervals.

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5 INDEX OF TABLES, LISTINGS, AND FIGURES

The table of contents of the tables, listings and figures can be separate documents.

6 INTERIM (AD HOC) ANALYSES

An interim (ad hoc) analysis was performed in March 2020. The March 2020 analysis followed the Ad Hoc Analysis Plan Version 3.0. The purpose of this analysis was exploratory and not for decisions on study conduct.

7 APPENDICES

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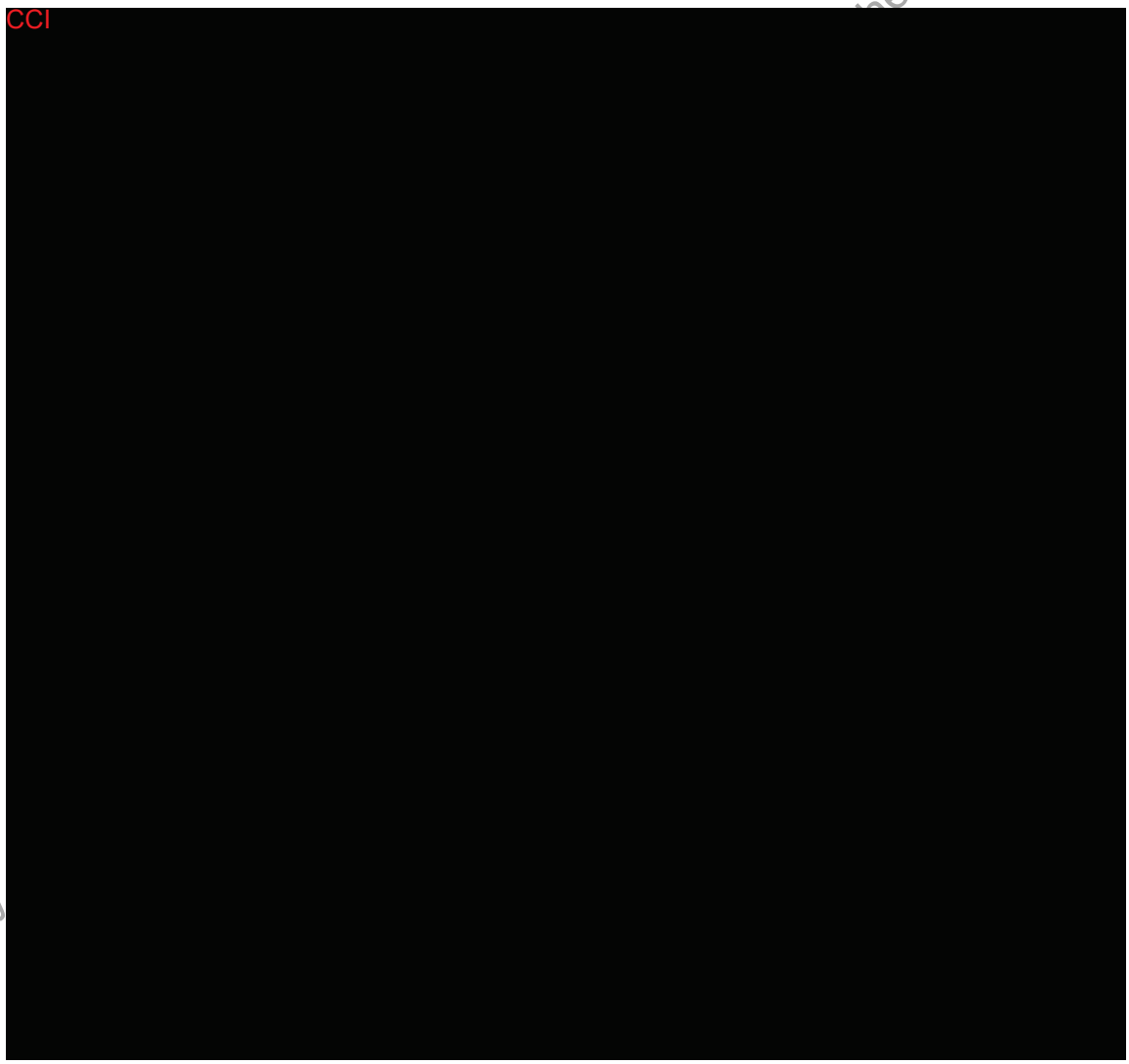

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8 REFERENCES

Berglund, P. & Heeringa, S. (2014). *Multiple Imputation of Missing Data Using SAS®*. SAS Press.