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

NCT Number: NCT03694275

Protocol Approve Date: 21 November 2019

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- Named persons or organizations associated with the study.
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PROTOCOL TAK-935-18-002 (OV935)

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

Sponsor:	Ovid Therapeutics Inc. 1460 Broadway New York, NY 10036 Telephone: +1 (646) 661-7661
Sponsor Contact:	PPD
Medical Monitor:	
Date of Amendment 2:	21 November 2019
Date of Amendment 1:	01 February 2019
Date of Original Protocol:	22 May 2018

SPONSOR SIGNATURE PAGE

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

PROTOCOL NUMBER: TAK-935-18-002 (OV935), Amendment 2

PPD

Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for TAK-935. I have read the Study TAK-935-18-002 (OV935) protocol (Amendment 2; 22 November 2019) and agree to conduct the study in accordance with this protocol, all applicable government regulations, the principles of the ICH E6 Guidelines for GCP, and the principles of the World Medical Association Declaration of Helsinki. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT 2 SUMMARY OF CHANGES

Rationale for Amendment 2:

This document describes the changes to Protocol TAK-935-18-002 (OV935) implemented by Amendment No. 2. The primary reason for this amendment is to provide clarification related to the secondary endpoints of Clinical Global Impression (CGI) and Caregiver Global Impression of Change (Care-GI-C).

Additionally, the age for participation was increased to 55 years because both 15Q duplication syndrome (Dup15q) and the CDKL5 deficiency disorder (CDD) occur in childhood and continue into adulthood; thus, current clinical sites have indicated potential older patients in their clinical practice for this study.

Key Changes Implemented by Amendment 2:

- Modified inclusion/exclusion criteria to increase the age for participation in the trial to 55 years old Expand the inclusion criteria to allow patients with a diagnosis of interstitial Dup15q.
- Correct an inadvertent error in the way the secondary endpoints CGI-S, CGI-C, and Care-GI-C were defined, from "percent change" to "change"
- Add that Jejunostomy tube (J-tube) may be considered based on approval from Medical Monitor and Sponsor
- Allow ad hoc analyses throughout the trial
- Add an additional subgroup in the treatment responder analysis (≥75% reduction in motor seizure frequency)
- Make corrections in schedule of assessment table including:
  - Separate out CGI-S from CGI-C
  - Remove collection seizure diary checks on Day 8, Day 22, Day 57, Day 113
- CCI [redacted]
- Revised contraception and pregnancy language
- Removed the optional blood sample for research analysis

Administrative and minor grammatical, editorial, and formatting changes are included for clarification purposes only. A detailed description of and rationale for changes implemented by Amendment 2 are provided in Appendix 6.

1. SYNOPSIS

Name of Sponsor/Company:
Ovid Therapeutics Inc.

Name of Study drug:
TAK-935

Title of Study:
A multicenter, open-label, pilot study of TAK-935 (OV935) in patients with 15q duplication syndrome or CDKL5 deficiency disorder (ARCADE STUDY)

Study Number: TAK-935-18-002 (OV935)	**Phase:** 2

Study Design:

This is a multicenter, open-label, 2-cohort study in patients aged ≥2 and ≤55 years with 15q duplication syndrome (Dup15q) or CDKL5 deficiency disorder (CDD) demonstrating ≥3 motor seizures (i.e., drop seizures, tonic-clonic, tonic, bilateral clonic, atonic, myoclonic-atonic, myoclonic-tonic-clonic, focal seizures with bilateral hyperkinetic motor features. Note - Isolated myoclonic seizures will not be part of the motor seizure count) per month during the 3 months immediately prior to Screening (based on the Investigator's assessment).

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

Study Periods:

This study consists of 2 periods:

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

At the Screening Visit (Visit 1), informed consent and assent (if applicable) will be obtained from the patients and patients' custodial parent or guardian. Patients will then undergo screening procedures to assess study eligibility in accordance with the study entry criteria. At this Screening visit and at subsequent visits, 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.

At the end of the 4-week Baseline Period, patients will return to the clinic (Visit 2). Seizure diaries will be reviewed by the Medical Monitor and if a patient does not meet the eligibility criteria, including minimum number of seizures required for the study (≥3 motor seizures, excluding myoclonic seizures), the patient will be discontinued from the study and considered a screen failure.

The patients who meet the entry criteria will be enrolled for 20 weeks (8-week Dose Optimization Period and 12-week Maintenance Period) of open-label treatment with TAK-935. After completion of the treatment period, the patients will have a taper period of maximum 14 days and a 2-week Follow-up Period or will be enrolled to an open-label extension study. The total study duration from Screening to the last visit in this study will be a maximum of 30 weeks.

Dosing and Titration Schedule

The total daily dose of TAK-935 for all patients is calculated based on body weight at Visit 1 and will be given twice a day (BID) with or without food. Patients will receive the initial dose of study drug, Dose 1, for the first

7 days starting at Visit 2. The study drug dose will be increased to Dose 2 and Dose 3 at Day 8 (± 2 days) and Day 15 (± 2 days). The maximum dose for any patient will be 600 mg/day (300 mg BID). The final dose level will be maintained until the end of the Maintenance Period; however, the dose may be changed during the Dose Optimization Period with approval from the Medical Monitor. Patients who cannot tolerate Dose 1 will be withdrawn from the study (and will complete the early termination and safety follow-up visits).

Dosing Schedule by Weight:

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

[a] Total dose administered twice daily.

The study will begin with a phased enrollment based on age and irrespective of the underlying syndrome:

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, clinical laboratory tests) 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. Details will be outlined in the iDMC charter.

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.

Following completion of the Maintenance Period, patients will have the option to enroll in a long-term, open-label extension study (OLE) (under a separate protocol [Study TAK-935-18-001 (OV935)]) or to enter a taper period (maximum 14 days). During the taper period, the TAK-935 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 TAK-935 dose is discontinued. After tapering, the patients will

complete a Safety Follow-up visit approximately 15 days after the last dose of TAK-935 and exit the study.

Pharmacokinetic Assessments:

Pharmacokinetic assessment will start at Visit 2 (Day 1). All enrolled patients in the study will receive the first dose of TAK-935 in the clinic. Five (5) PK blood draws will occur at these following timepoints on the first study day: pre-first dose, 30 minutes (± 10 minutes), 1, 2, and 4 hours (± 10 minutes) post-first dose. On other study visit days, two (2) PK blood draws will be collected: one within 1 hour prior to the morning dose (pre-dose) and the other at 30 minutes (± 10 minutes) post-morning dose.

Concomitant and Prohibited Medications:

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

All medications including vitamin supplements, over-the-counter medications, and herbal preparations including (medical) marijuana and cannabidiol products will be documented throughout the study. (Medical) Marijuana and cannabidiol products should not be altered during the study.

Use of strong inducers and inhibitors of cytochrome P450 (CYP) 3A4 (e.g., prescription medications, over-the-counter medications, dietary supplements, and certain foods such as grapefruit/grapefruit juice) within 30 days before enrollment through end of taper is prohibited, except for AEDs that are strong inducers or inhibitors only (e.g., carbamazepine, phenobarbital, phenytoin). Refer to Appendix 4 for a list of prohibited CYP3A4 inducers.

Use of perampanel during the study is prohibited.

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

Procedures:

Daily seizure diaries (collected at each visit) will be used to determine the monthly seizure frequency for the evaluation of efficacy.

Blood samples for clinical safety laboratory tests including hematology and chemistry, will be collected at Visit 1 (Screening), Visit 2 (Day 1), Visit 3 (Day 15), Visit 4 (Day 36), Visit 5 (Day 85), and Visit 6 (Day 141), the study completion/end of study visit. In addition, urinalysis will be performed at the specified visits. Blood samples to assess AED and plasma 24HC levels will also be collected.

Five (5) PK blood draws will occur at the following timepoints on the first study day: pre-first dose, 30 minutes (± 10 minutes), 1, 2, and 4 hours (± 10 minutes) post-first dose. On other study visit days, 2 PK blood draws will be collected; one within 1 hour prior to the morning dose (pre-morning-dose) and the other at 30 minutes (± 10 minutes) post-morning dose.

The total blood volume collected during the study will be approximately 120 mL for each patient. The maximum blood volume collected during a 30-day period will be approximately 40 mL and maximum blood volume collected during a single visit will be approximately 25 mL. The total blood volume limits are consistent with physiological minimal risk as specified by the WHO guidelines.[1]

Primary Objective:

- To investigate the effect of TAK-935 on the frequency of motor seizures for patients with Dup15q or CDD during the Maintenance Period

Secondary Objectives:

- 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 seizure free days in patients with Dup15q or CDD during the Maintenance Period
- To assess the Clinical Global Impression of severity (CGI-S-C) provided), as assessed 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

Exploratory Objectives:

CCI [redacted]

Safety Objectives:

- 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, to determine if there is worsening of this seizure type during treatment with TAK-935

Study Population:

Patients aged ≥2 and ≤55 years with Dup15q or CDD

Number of Patients:	**Number of Sites:**
Approximately 30 male and female patients (approximately 15 patients per syndrome) will be enrolled	Estimated total: Approximately 10 sites
Study Drug:	**Route of Administration:**
Patients will be dosed with TAK-935 (Table 1)	Oral or via gastrostomy tube (G-tube)/percutaneous

	endoscopic gastrostomy (PEG) tube. Jejunostomy tube (J-tube) may be considered following approval by the Sponsor and Medical Monitor Note - Patients enrolled in clinical sites in China are not to receive study drug via G-tube/PEG tube/J-tube.
Duration of Treatment: 20 weeks plus a maximum taper period of 14 days	**Period of Evaluation:** ~30 weeks (includes up to 4- to 6-week Screening/Baseline period, 20-week Treatment Period [8-week Dose Optimization Period, and 12-week Maintenance Periods], 14-day taper, and 2-week safety follow-up period)

Main Criteria for Inclusion:

1. The patient has a documented diagnosis of Dup15q or CDD supported by:
   - Dup15q, diagnosed per standard of care and consistent with literature described phenotype
   - CDD
     - A pathogenic or likely pathogenic variant in CDKL5

       OR
     - A variant of uncertain significance (VUS) in the kinase domain of CDKL5 that has been confirmed to be de novo. Unless both parents have been tested and found to not harbor the VUS, a patient with a VUS cannot be enrolled. Participants with a VUS found outside of the kinase domain will not be enrolled.
     - A patient with mosaicism for a CDKL5 variants is eligible.
2. The patient or patient's custodial parent or guardian are willing and able to read, understand, and sign the informed consent form and assent, if applicable
3. Male and female patients aged ≥2 and ≤55 years at the time of informed consent
4. A history of, on average, ≥3 motor seizures (excluding isolated myoclonic seizures) per month during the 3 months immediately prior to Screening based on the Investigator's assessment, and the patient has ≥3 motor seizures (excluding isolated myoclonic seizures) during the 4-week prospective Baseline Period
5. Weight of ≥10 kg at the Screening visit (Visit 1)
6. Currently taking 1 to 6 AEDs at a stable dose for 4 weeks prior to the Screening visit (Visit 1); benzodiazepines used chronically (on daily frequency) to treat seizures are considered AEDs. Antiepileptic drug treatment, (medical) marijuana, cannabidiol products, VNS settings, and ketogenic diet should not be altered during the study.
7. The use of cannabidiol products must be stable for 4 weeks prior to screening
8. If using a VNS, must have VNS placed at least 3 months prior to the Screening visit with stable settings for >1 month; VNS parameters must remain constant throughout the study (VNS will not be counted as an AED)
9. If on a ketogenic diet, must have started the ketogenic diet at least 3 months prior to the Screening visit (Visit 1), diet should be stable for 4 weeks before the Screening visit (Visit 1); and should continue through the duration of the study (ketogenic diet will not be counted as an AED)
10. Failed to become and remain seizure-free with trials of at least 2 AEDs
11. The patient or patient's legal representative (parents or legal guardian) is willing to keep the AED, (medical) marijuana, cannabidiol products, VNS, and ketogenic diet regimen(s) stable throughout the

study

12. The patient is able to carry out all appropriate assessments and take study drug in the opinion of the Investigator and parent/caregiver
13. Sexually active female patients of childbearing potential (defined as first menarche) must agree to use a highly effective method of contraception during the study and for 30 days after the last dose of study drug. Sexually active male patients (post-pubertal unless permanently sterilized by bilateral orchidectomy) must agree to use male contraception (condom) during the study and for a minimum of 30 days following the last dose of study drug. Male patients must also not donate sperm during the Screening and Treatment Periods and for at least 30 days after the last dose of study drug.

Main Criteria for Exclusion:

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

1. The patient has been admitted to a medical facility and intubated for treatment of status epilepticus 2 or more times in the 3 months immediately prior to the screening visit
2. Patients with a history of confirmed cataract (untreated with surgery)
3. Unstable, clinically significant neurologic (other than the disease being studied), psychiatric, cardiovascular, ophthalmologic, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, immunologic, hematopoietic, or endocrine disease or other abnormality, which may impact the ability to participate in the study or that may potentially confound the study results. It is the responsibility of the Investigator to assess the clinical significance; however, consultation with the Medical Monitor may be warranted
4. Any history of alcohol, opioid, or other drug use disorder, as per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), within the 2 years immediately prior to the Screening Visit (Visit 1)
5. Suicide attempt within the last year, at significant risk of suicide (either in the opinion of the Investigator or defined as 'yes' to suicidal ideation question 4 or 5 on the Columbia-Suicide Severity Rating Scale [C-SSRS] at Screening), or appearing suicidal per Investigator judgment
6. Abnormal and clinically significant electrocardiogram (ECG) abnormality at Screening; QT interval with Fridericia's correction method (QTcF) >450 ms (males) or >470 ms (females) or above upper limit of normal for age, confirmed with one repeat testing, at the Screening visit
7. Abnormal clinical laboratory test results at the Screening visit that suggest a clinically significant underlying disease that would compromise the well-being of the patient (if the patient has alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST] >2.5 × the upper limit of normal [ULN], the Medical Monitor should be consulted)
8. Currently receiving a study drug or participated in a clinical study involving another investigational product in the previous month (or 5 half-lives of this investigational product, whichever is longer)
9. Received TAK-935 in a previous clinical study or as a therapeutic agent
10. Immediate family members, or in a dependent relationship with a study site employee who is involved in the conduct of this study (e.g., child, sibling)
11. Known hypersensitivity to any component of the TAK-935 formulation
12. Currently pregnant or breastfeeding or is planning to become pregnant within 30 days of the last dose of study drug

Endpoints:

Primary Efficacy Endpoint

- Percent change from Baseline in motor seizure frequency per 28 days in the patients with CDD during the Maintenance Period

  OR

- Percent change from Baseline in motor seizure frequency per 28 days in the patients with Dup15q during the Maintenance Period

Secondary Efficacy Endpoints

- Percent change from Baseline in motor seizure frequency per 28 days in the patients with CDD during the Treatment Period
- Percent change from Baseline in motor seizure frequency per 28 days in the patients with Dup15q during the Treatment Period
- Proportion of patients considered treatment responders for patients with CDD throughout the Maintenance Period; treatment responders are defined as those with:
  - Reduction of 25% or more in median motor seizures from baseline
  - Reduction of 50% or more in median motor seizures from baseline
  - Reduction of 75% or more in median motor seizures from baseline
  - Reduction of 100% in median motor seizures from baseline
- Proportion of patients considered treatment responders for patients with Dup15q throughout the Maintenance Period; treatment responders are defined as those with:
  - Reduction of 25% or more in median motor seizures from baseline
  - Reduction of 50% or more in median motor seizures from baseline
  - Reduction of 75% or more in median motor seizures from baseline
  - Reduction of 100% in median motor seizures from baseline
- Percent change from Baseline in frequency of motor seizures longer than 5 minutes in patients with CDD
- Percent change from Baseline in motor seizure-free days frequency in patients with Dup15q or CDD during the Maintenance Period
- Change from baseline in CGI-S
- Assessment of ratings as assessed by the clinician using the CGI-C
- Assessment of ratings as assessed by the caregiver using the Care GI-C
- To characterize plasma 24HC levels and change in motor seizure frequency in patients treated with TAK-935 as an adjunctive therapy

Exploratory Efficacy Endpoints

CCI [redacted]

Safety Endpoints

- Percentage of patients with at least 1 treatment-emergent adverse event (TEAE)
- 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.

Safety:

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

The study will begin with a phased enrollment based on age and irrespective of the underlying syndrome:

- Two patients aged ≥9 years will be enrolled for assessment of safety and PK. The iDMC will review safety (adverse events, 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.
- The Sponsor's Medical Monitor and/or Pharmacovigilance physician will review safety data and available PK of first 2 patients aged ≥9 years and first 2 patients aged ≥2 to <9 years during each step of dose escalation.

Statistical Considerations:

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

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

Modified Intent-to-Treat (mITT) Analysis Set

All patients who have received at least 1 dose of study drug and have been assessed for efficacy (i.e., has at least one efficacy outcome measure) for at least 1 day in the Treatment Period will be included in the modified intent-to-treat (mITT) analysis set.

Efficacy Analysis Population

All mITT subjects whose assessments are compliant with Protocol Amendment 2 will be included in the efficacy analysis population. Efficacy analyses for primary and secondary efficacy endpoints will be based on the efficacy analysis population and the mITT set, and those for exploratory efficacy endpoints will be based on the mITT set.

Safety Analysis Set

All patients who take at least 1 dose of study medication will be included in the Safety Analysis Set.

Analysis Groups

All analyses will be performed on 2 analysis groups: theDup15q group and the CDD group.

Efficacy Analyses

Motor seizure (with exclusion of isolated myoclonic seizures) frequency per 28 days will be calculated at each specified interval as [(number of seizures in that interval) / (days with no missing seizure count in that interval)] × 28.

For all patients, motor seizure frequencies per 28 days for the 4-week prospective Screening/Baseline Period, each 4-week interval in the Maintenance Period, the Maintenance Period and the 20-week Treatment Period will be calculated.

Observed values, change from Baseline, and percent change from Baseline for the motor seizure frequency (per 28 days) will be summarized descriptively by analysis group for the following intervals: the three 4-week intervals in the Maintenance period, the Maintenance Period and the entire 20 weeks of Treatment Period. For

each analysis group, the median of primary endpoint will be presented along with its corresponding 90% confidence interval. Histograms will be produced for the primary endpoint for each analysis group. The analysis will be repeated for all motor seizure types.

The time course of seizure frequencies (per 28 days) in consecutive 4-week intervals in the Maintenance Period will be displayed in a line graph by analysis group.

The proportion of treatment responders based on ≥25% worsening, <25% and >1% worsening, no change (Worsening of 1% to Reduction of 1%), ≥25% reduction, ≥50% reduction, ≥75% reduction, and 100% reduction from Baseline in motor seizure frequency during the Maintenance Period will be summarized at each 4-week interval, the 12 weeks of maintenance period, and the entire 20 weeks of the Treatment Period by analysis group.

Observed values and change from Baseline in Clinical Global Impression of Severity (CGI-S) will be analyzed descriptively at each study visit. Ratings of Clinical Global Impression - Change (CGI-C) and Caregiver Global Impression of Change (Care GI-C) responses will be assessed.

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

Safety Analyses

All safety assessments will be summarized using descriptive statistics. All safety analyses will be based on observed data only, and no missing values will be imputed. Reported AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by preferred term and system organ class categories. Serious adverse events (SAEs) and AEs leading to study discontinuation will also be summarized.

Observed values and change from baseline in laboratory parameters, vital signs, and ECG parameters will be summarized by study visit. The number and percentage of patients who have met potentially clinically significant criteria at any post baseline visit will be summarized for laboratory, vital signs, and ECG parameters. The number and percentage of patients with shifts in laboratory will be summarized. The number and percentage of patients with C-SSRS assessments of suicidal ideation and behavior will also be summarized.

Prior and concomitant medication use will be summarized by World Health Organization Anatomical Therapeutic Chemical (WHO-ATC) classification system.

Exploratory Analyses

CCI [redacted]

Sample Size Justification:

A formal sample size calculation was not performed for this study. Given the rare occurrence of these epileptic encephalopathy syndromes and based on prior clinical development programs for treatment of rare diseases, the current sample size is deemed appropriate to evaluate the efficacy and safety of TAK-935 in patients with Dup15q and CDD.

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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
24HC	24S-hydroxycholesterol
ABC-C	Aberrant Behavior Checklist community questionnaire
AE	adverse event
AED	antiepileptic drugs
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{24}	area under the plasma concentration-time curve from time 0 to 24 hours
$AUC_{24,ss}$	area under the plasma concentration-time curve from time 0 to 24 hours at steady state
AUC_{τ}	area under the plasma concentration-time curve during a dosing interval
BID	twice daily
Care GI-C	Caregiver Global Impression of Change
CDD	Cyclin-Dependent Kinase-Like 5 Deficiency Disorder
CDKL5	Cyclin-Dependent Kinase-Like 5
CGI	Clinical Global Impression
CGI-C	Clinical Global Impression - Change
CGI-S	Clinical Global Impression of Severity
CH24H	cholesterol 24-hydroxylase
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum observed plasma concentration
$C_{max,ss}$	maximum observed plasma concentration during a dosing interval, at steady state
CNS	central nervous system
C-SSRS	Columbia–Suicide Severity Rating Scale
CYP	cytochrome P-450
DEE	developmental and epileptic encephalopathy
DSM-V	Diagnostic and Statistical Manual of Mental Disorders – 5th edition
Dup15q	15q Duplication syndrome
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EEG	electroencephalogram

Term	Definition
EO	enzyme occupancy
GABA	γ-amino butyric acid
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
G-tube	gastrostomy tube
hCG	human chorionic gonadotropin
IAR	infusion-associated reaction
IB	Investigator Brochure
ICF	informed consent form
iDMC	independent Data Monitoring Committee
INR	international normalized ratio
IRB/IEC	institutional review board/independent ethics committee
IxRS/IWRS	Interactive Voice/Web Response System
J-tube	jejunostomy tube
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
NMDA	*N*-methyl-D-aspartate
OLE	open-label extension
OTC	over the counter
PD	pharmacodynamic(s)
PEG	Percutaneous endoscopic gastrostomy
PET	positron emission tomography
PK	pharmacokinetic(s)
PT	preferred term
PWACR	Prader-Willi/Angelman critical region
Q1	first quartile
Q3	third quartile
QD	once daily
QTcF	QT interval with Fridericia's correction method
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class

Term	Definition
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of C_{max}
ULN	upper limit of normal
VABS	Vineland Adaptive Behavior scales
VNS	vagal nerve stimulator
VUS	variant of uncertain significance
WHO-ATC	World Health Organization Anatomical Therapeutic Chemical classification system
WHO-DD	World Health Organization Drug Dictionary

3. INTRODUCTION

3.1. Background

CCI

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Additional information about the risks, known and expected benefits, of TAK-935 may be found in the current edition of the Investigator's Brochure (IB).

3.2. Study Rationale

3.2.1. 15q Duplication Syndrome (Dup15q)

Duplications of the proximal arm of chromosome 15q11.2-q13.1 result in the genetic condition Dup15q.Multiple genes including UBE3A from this region are implicated in the pathogenesis of autism spectrum disorders, epilepsy, and schizophrenia.[3] Increased dosage of the UBE3A contributes to epilepsy in Dup15q and it is thought to be the underlying cause of the autistic features of the syndrome as well. When UBE3A is elevated in glia, ATPα levels are reduced, thus increasing the concentration of K^+ in the extracellular space. Elevated extracellular K^+ leads to the neuronal dysfunction via NMDA receptor activation and has emerged as a potential cause

of epilepsy. The most devastating feature of Dup15q is difficult to control seizures.[4] Approximately 60% of the patients have seizures and the rate of seizures is higher in patients with idic15 form. The other most common seizure types are infantile spasm and generalized tonic–clonic seizures followed by atonic, myoclonic, focal-onset, and tonic seizures.[5] Poorly controlled seizures severely impact the quality of life of both affected individuals and their caregivers. Current treatment options for Dup15q-associated epilepsy are often ineffective. GABAergic promoting antiepileptics are typically ineffective while broad-spectrum antiepileptic medications such as valproic acid and rufinamide provide some relief.

3.2.2. CDKL5 Deficiency Disorder (CDD)

Patients with cyclin-dependent kinase-like 5 (CDKL5) mutations present with early epilepsy, starting from 10 days to 3 months after birth.[6] In particular, early drug-resistant epilepsy, usually starting in the first months of life, tends to be the most common feature. Seizures are in general highly polymorphic and many different seizure types can also occur in the same patient, changing with time. Complex partial seizures, infantile spasms, myoclonic, generalized tonic-clonic, and tonic seizures have all been reported. Stereotypic hand movements, severe hypotonia, and impaired psychomotor development are usually associated with CDKL5 mutations and common to the general clinical manifestation of Referral to Treatment patients. CDKL5 plays an important role in controlling postsynaptic localization of the GluN2B-SAP102 complex in the hippocampus and thereby regulates seizure susceptibility, and that aberrant NMDA receptor-mediated synaptic transmission underlies the pathological mechanisms of the CDKL5 loss-of-function.[7] CCI [redacted]

CCI [redacted]

The current study is designed to explore the effects of TAK-935 on seizure frequency using a seizure diary. An additional aim is to characterize the safety and tolerability of multiple-dose TAK-935 administration in patients with Dup15q or CDD.

4. STUDY OBJECTIVES AND ENDPOINTS

Study objectives and associated endpoints are presented in Section 4.1 and Section 4.2, respectively; the frequency and timing of study measurements is provided in the Schedule of Assessments (Table 2). Information regarding sample collection and safety data collection are presented in Section 8.

4.1. Objectives

4.1.1. Primary Objective

The primary objective of this study is:

- To investigate the effect of TAK-935 on the frequency of motor seizures for patients with Dup15q or CDD during the Maintenance Period.

4.1.2. Secondary Objectives

The secondary objectives of this study 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 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)
- To investigate the relationship between 24HC level and motor seizure frequency

4.1.3. Exploratory Objectives

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4.1.4. Safety Objectives

The safety objectives of this study 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

4.2. Endpoints

4.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint in this study is:

- Percent change from Baseline in median motor seizure frequency per 28 days in the patients with CDD during the Maintenance Period

OR

- Percent change from Baseline in motor seizure frequency per 28 days in the patients with Dup15q during the Maintenance Period

4.2.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints in this study are:

- Percent change from Baseline in motor seizure frequency per 28 days in the patients with CDD during the Treatment Period
- Percent change from Baseline in motor seizure frequency per 28 days in the patients with Dup15q during the Treatment Period
- Proportion of patients considered treatment responders for patients with CDD throughout the Maintenance Period, treatment responders are defined as those with:
  - Reduction of 25% or more in median motor seizures from baseline
  - Reduction of 50% or more in median motor seizures from baseline
  - Reduction of 75% or more in median motor seizures from baseline
  - Reduction of 100% in median motor seizures from baseline
- Proportion of patients considered treatment responders for patients with Dup15q throughout the Maintenance Period, treatment responders defined as those with:

  - Reduction of 25% or more in median motor seizures from baseline
  - Reduction of 50% or more in median motor seizures from baseline
  - Reduction of 75% or more in median motor seizures from baseline
  - Reduction of 100% in median motor seizures from baseline
- Percent change from Baseline in frequency of motor seizures longer than 5 minutes in patients with CDD
- Percent change from Baseline in motor seizure-free days frequency in patients with Dup15q or CDD during the Maintenance Period
- Change from baseline in CGI-S
- Assessment of ratings by clinician using the CGI-C
- Assessment of 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

4.2.3. Exploratory Efficacy Endpoints

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4.2.4. Safety Endpoints

The safety endpoints in this study are:

- Percentage of patients with at least 1 treatment-emergent adverse event (TEAE)
- 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 electrocardiogram (ECG) parameters after TAK-935 treatment
- Change from Baseline in clinical laboratory evaluations, vital signs, body weight, height, Columbia–Suicide Severity Rating Scale (C-SSRS), and ECG parameter values after TAK-935 treatment
- Percent of absence seizure free days in patients who report absence seizures during baseline

5. INVESTIGATIONAL PLAN

5.1. Summary of Study Design

Study TAK-935-18-002 (OV935; ARCADE Study) is a multicenter, open-label, 2-cohort study in patients (aged ≥2 and ≤55 years with Dup15q or CDD demonstrating ≥3 motor seizures (i.e., drop seizures, tonic-clonic, tonic, bilateral clonic, atonic, myoclonic-atonic, myoclonic-tonic-clonic, focal seizures with bilateral hyperkinetic motor features. Note - isolated myoclonic seizures are excluded) per month during the 3 months immediately prior to Screening (based on the Investigator's assessment).

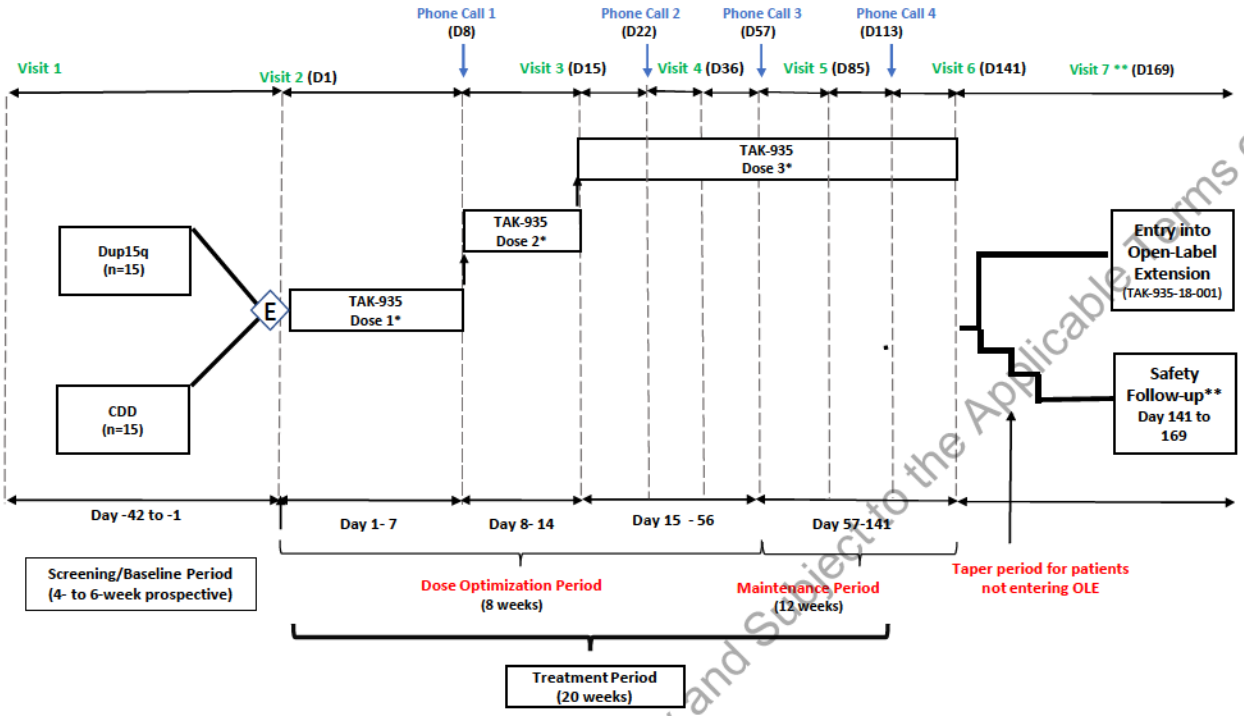
Approximately 30 total patients with Dup15q or CDD (approximately 15 patients in each syndrome) will be enrolled. This study consists of 2 main periods:

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

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.

Figure 1 illustrates the study design.

Figure 1: Study Design for Clinical Protocol TAK-935-18-002 (OV935; ARCADE Study)



* IP given as 2 divided doses BID (refer to Table 1 for weight-based dosing)
** Patients who do not enter the open-label extension study

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.

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 and safety follow-up visits). Refer to Section 7.2 for additional information.

The study will begin with a phased enrollment based on age:

- Two patients aged ≥9 years will be enrolled for assessment of safety and PK. The independent Data Monitoring Committee (iDMC) will review safety (adverse events 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.

5.1.1. End of Study Definition

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

5.1.2. Study Extension

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

Patients currently participating in this trial can immediately roll over to the open-label extension as long as they meet the criteria specified in the OLE study.

5.2. Selection and Timing of Doses in the Study

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

5.2.1. Modeling and Simulation of Clinical Data

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6. STUDY POPULATION

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened. Refer to Section 8.1.23 for additional information on recording screen failures.

Individuals may be re-screened for up to 2 times, after consultation with the Medical Monitor.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

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

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all the following criteria:

1. The patient has a documented diagnosis of Dup15q or CDD supported by:
   - Dup15q, diagnosed as per standard of care and consistent with literature described phenotype
   - CDD
     - A pathogenic or likely pathogenic variant in CDKL5
       OR
     - A variant of uncertain significance (VUS) in the kinase domain of CDKL5 that has been confirmed to be de novo. Unless both parents have been tested and found to not harbor the VUS, a patient with a VUS cannot be enrolled. Participants with a VUS found outside of the kinase domain will not be enrolled.
     - A patient with mosaicism for a CDKL5 variants is eligible.
2. The patient or patient's custodial parent or guardian are willing and able to read, understand, and sign the informed consent form and assent, if applicable
3. Male and female patients aged ≥2 and ≤55 years at the time of informed consent
4. A history of, on average, ≥3 motor seizures (excluding isolated myoclonic seizures) per month during the 3 months immediately prior to Screening based on the Investigator's assessment, and the patient has ≥3 motor seizures (excluding isolated myoclonic seizures) during the 4-week prospective Baseline Period
5. Weight of ≥10 kg at the Screening visit (Visit 1)
6. Currently taking 1 to 6 AEDs at a stable dose for 4 weeks prior to the Screening visit (Visit 1); benzodiazepines used chronically (on daily frequency) to treat seizures are considered AEDs. Antiepileptic drug treatment, (medical) marijuana, cannabidiol products, VNS settings, and ketogenic diet should not be altered during the study.
7. The use of cannabidiol products must be stable for 4 weeks prior to screening

8. If using a VNS, must have VNS placed at least 3 months prior to the Screening visit (Visit 1) with stable settings for >1 month; VNS parameters must remain constant throughout the study (VNS will not be counted as an AED)
9. If on a ketogenic diet, must have started the ketogenic diet at least 3 months prior to the Screening visit (Visit 1), diet should be stable for 4 weeks before the Screening visit (Visit 1); and should continue through the duration of the study (ketogenic diet will not be counted as an AED)
10. Failed to become and remain seizure free with trials of at least 2 AEDs
11. The patient or patient's legal representative (parents or legal guardian) is willing to keep the AED, (medical) marijuana and cannabidiol products, VNS, and ketogenic diet regimen(s) stable throughout the study
12. The patient is able to carry out all appropriate assessments and take study drug in the opinion of the Investigator and parent/caregiver
13. From signing of informed consent, throughout the duration of the study, and for 30 days after last dose of study drug, female patients of childbearing potential* who are sexually active with a nonsterilized male partner** must agree to use a highly effective/effective method of contraception (from the list below). In addition, they must not to donate ova during this period.

    * Females NOT of childbearing potential are defined as those who are prior to first menarche or who have been surgically sterilized (hysterectomy, bilateral oophorectomy, or tubal ligation) or who are postmenopausal (e.g., defined as ≥1 year since last regular menses with a follicle□stimulating hormone level >40 IU/L or ≥5 years since last regular menses, confirmed before any study drug is administered).

    **Sterilized males should be ≥1-year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

    A highly effective method of contraception is defined as one that has no higher than a 1% failure rate per year when used consistently and correctly. In this study, the only acceptable methods of contraception are as follows:

    a. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
        - Oral
        - Intravaginal
        - Transdermal
    b. Progestogen-only hormonal contraception associated with inhibition of ovulation:
        - Oral
        - Injectable
        - Implantable
    c. Double-barrier methods (each time the patient has intercourse):

- Sponge (plus spermicidal cream or jelly) PLUS male condom with or without spermicidal cream or jelly.
- Cap (plus spermicidal cream or jelly) PLUS male condom with or without spermicidal cream or jelly.
- Diaphragm (plus spermicidal cream or jelly) PLUS male condom with or without spermicidal cream or jelly.

d. Intrauterine device (Copper T PLUS condom)

e. Intrauterine hormone-releasing system

f. Sterilization:

- Bilateral tubal occlusion
- Vasectomized partner (provided that the partner is the sole sexual partner of the patient and the absence of sperm in the ejaculate has been confirmed)

g. Sexual abstinence, if it is the preferred and usual lifestyle of the patient, will be considered an acceptable method of contraception on a case-by-case basis upon prior approval by the medical monitor. Patients practicing abstinence as a method of contraception must refrain from heterosexual intercourse throughout the duration of the study and for 30 days after last dose of study drug.

From signing of informed consent, throughout the duration of the study, and for 30 days after last dose of study drug, male patients (post-pubertal unless permanently sterilized**) who are sexually active with a female partner of childbearing potential* must agree to use barrier contraception (e.g., condom with or without spermicidal cream or jelly). In addition, they must not donate sperm during this period.

6.2. Exclusion Criteria

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

1. The patient has been admitted to a medical facility and intubated for treatment of status epilepticus 2 or more times in the 3 months immediately prior to the Screening visit
2. Patients with a history of confirmed cataract (untreated with surgery)
3. Unstable, clinically significant neurologic (other than the disease being studied), psychiatric, cardiovascular, ophthalmologic, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, immunologic, hematopoietic, or endocrine disease or other abnormality, which may impact the ability to participate in the study or that may potentially confound the study results. It is the responsibility of the Investigator to assess the clinical significance; however, consultation with the Medical Monitor may be warranted
4. Any history of alcohol, opioid, or other drug use disorder, as per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), within the 2 years immediately prior to the Screening Visit (Visit 1)

5. Suicide attempt within the last year, at significant risk of suicide (either in the opinion of the Investigator or defined as 'yes' to suicidal ideation question 4 or 5 on the C-SSRS at Screening) or appearing suicidal per Investigator judgment
6. Abnormal and clinically significant ECG abnormality at Screening; QT interval with Fridericia's correction method (QTcF) >450 ms (males) or >470 ms (females) or above upper limit of normal for age, confirmed with one repeat testing, at the Screening visit
7. Abnormal clinical laboratory test results at the Screening visit that suggest a clinically significant underlying disease that would compromise the well-being of the patient (if the patient has alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST] >2.5 × the upper limit of normal [ULN] for age, the medical monitor should be consulted)
8. Currently receiving a study drug or participated in a clinical study involving another investigational product in the previous month (or 5 half-lives of this investigational product, whichever is longer)
9. Received TAK-935 in a previous clinical study or as a therapeutic agent
10. Immediate family members, or in a dependent relationship with a study site employee who is involved in the conduct of this study (e.g., child, sibling)
11. Known hypersensitivity to any component of the TAK-935 formulation
12. Currently pregnant or breastfeeding or is planning to become pregnant within 30 days of the last dose of study drug

6.3. Discontinuations

6.3.1. Discontinuation of Patients

The criteria for enrollment must be followed explicitly. If the investigative site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the Sponsor must be notified immediately. A discussion must occur between the Sponsor and the Investigator to determine whether the patient may continue in the study, with or without study drug. Inadvertently enrolled patients may be maintained in the study and on study drug when the Sponsor agrees with the Investigator that it is medically appropriate for that patient. The patient may not continue in the study with or without study drug if the Sponsor does not agree with the Investigator's determination it is medically appropriate for the patient to continue. The Investigator must obtain documented approval from the Sponsor to allow the inadvertently enrolled patient to continue in the study with or without study drug.

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

- Liver Function Test (LFT) Abnormalities

  Study drug should be discontinued with appropriate clinical follow up (including repeat laboratory tests, until a subject's laboratory profile has returned to

normal/baseline status, see Section 8.1.10), if the following circumstances occur at any time during study drug treatment:

- ALT or AST >8 × ULN for age, or
- ALT or AST >5 × ULN for age and persists for >2 weeks, or
- ALT or AST >3 × ULN for age in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or
- ALT or AST >3 × ULN for age with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

- QTcF interval >500 ms that is confirmed with a repeat ECG

  Study drug should be discontinued with appropriate clinical follow up (including repeat ECG)

- Greater than a 100% increase in seizure frequency from the 4-week prospective Baseline Period and considered by the Investigator to be clinically significant worsening of the seizure frequency
- Not tolerating Dose 1 (the lowest dose) for their weight category
- Enrollment in any other clinical study involving a study drug or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Investigator Decision (Physician Decision)
  - The Investigator decides that the patient should be discontinued from the study
- Patient Decision (Withdrawal by Patient or Withdrawal by Parent/Guardian)
  - The patient or the patient's legal representative (i.e., parents or legal guardian) requests to be withdrawn from the study
- Sponsor Decision
  - The Sponsor or its designee discontinues the study or discontinues the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
  - The Sponsor or its designee stops the clinical study at a particular site
- Adverse Event
  - If the Investigator decides that the patient should be withdrawn because of an SAE or a clinically significant laboratory value, the study drug is to be discontinued and appropriate measures are to be taken; the Sponsor or its designee is to be alerted immediately (refer to Section 8.3)
- Depression and/or Suicidal Ideation
  - Study staff trained in the administration of the C-SSRS will assess patient suicidality using the C-SSRS, eliciting answers from the patient or the patient's

caregiver; ultimately, the determination of the presence of suicidal ideation or behavior depends on the clinical judgment of the investigator

Patients who discontinue the study drug and/or study early will have early termination procedures performed as shown in the Schedule of Assessments (Table 2).

6.3.2. Discontinuation of Study Sites/Site Terminated by Sponsor

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

6.3.3. Discontinuation of the Study/Study Terminated by Sponsor

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

7. TREATMENT

7.1. Materials and Supplies

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

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

7.1.1. Storage

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7.2. Treatments Administered

All patients will receive TAK-935 twice a day (BID) orally or via gastrostomy tube (G-tube)/ percutaneous endoscopic gastrostomy (PEG)-tube with or without food. Jejunostomy tube (J-tube) administration may be considered following approval by the Medical Monitor and Sponsor.

Patients enrolled in clinical sites in China are not to receive study drug via G-tube/PEG tube/J-tube.

For patients weighing <60 kg at Visit 1, the total daily dose of TAK-935 is calculated based on body weight at Visit 1 and will be given BID (Figure 1; Table 1) at Visit 2. 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 (100 mg BID) followed by 400 mg/day (200 mg BID), then 600 mg/day (300 mg BID) (Figure 1; Table 1). Study drug can be taken with or without food.

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

Patients will receive the initial dose of study drug, Dose 1, for the first 7 days starting at Visit 2 (Day 1). 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. Visit 3 [Day 8] will be an onsite visit only for the first two patients in each age range (i.e. the first two patients aged > 9 years and the first two patients aged > 2 to < 9 years). The maximum dose for any patient will be 600 mg/day (300 mg BID). 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. After reaching the maximum dose, an additional 6 weeks will be allowed to adjust the patient to the optimal dose level, 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 changed during the Dose Optimization Period in consultation with the Medical Monitor. 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.

The dose may be increased per Investigator's discretion with approval of the Medical Monitor to a maximum of Dose 3 (maximum 600 mg/day). All dose changes must be made during the Dose Optimization Period; dose changes during the Maintenance Period must be discussed and approved by the Sponsor.

Table 1: Dosing Schedule by Weight

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

[a] Total dose administered twice daily.

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

If a patient misses a dose, the missed dose should be skipped, and the patient should continue with his/her normal dosing schedule. The scheduled dose can be administered up to 4 hours after the scheduled time of dosing. If the patient/caregiver remembers after 4 hours of the scheduled time of dosing, the dose should then be skipped and reported as missed in their diary and on the next clinic visit. Skipped doses should be reported as missed doses.

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

For patients receiving study drug via G-tube/PEG tube/J-tube, study drug will be crushed, suspended in water, and the suspension will be administered via the G-tube/PEG tube/J-tube using a syringe. Other medications or enteral feeds should not be given concurrently with

TAK-935. Complete instructions will be provided to subjects/caregivers in a document provided outside of the protocol.

7.2.1. Dose Tapering

Following completion of the study, patients will have the option to enroll in a long-term, open-label extension study (under a separate protocol; see Section 5.1.1) 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.

7.2.2. Investigator Responsibilities for Drug Administration

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

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

Note: In some cases, sites may destroy the material if, during the Investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose clinical study materials.

Patients and/or their parent/custodian/legal representative will be instructed to contact the Investigator as soon as possible if he or she has a complaint or problem with the study drug so that the situation can be assessed.

All clinical trial material provided to the Investigator will be stored in a secure and locked place and allocated and dispensed by Interactive Voice/Web Response System (IxRS/IWRS). Detailed records of the amounts of the study drug received, dispensed, and remaining at the end of the study will be maintained.

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

7.3. Method of Assignment to Treatment

All subjects will receive the same treatment throughout the study. Patients who meet all criteria for enrollment will begin treatment at Visit 2 (Day 1). Assignment to treatment groups will be determined by the seizure syndrome: Dup15q or CDD.

7.4. Continued Access to Study Drug

TAK-935 may be made available after conclusion of the study to patients who are still receiving and benefitting from study treatment in an OLE study (under a separate protocol; see Section 5.1.1).

7.5. Blinding

This is an open-label study.

7.6. Concomitant Medications and Non-Pharmacologic Therapies and Procedures

Adjunctive AED treatment, VNS settings, and ketogenic diet should not be altered during the study. Concurrent treatment regimen data will be collected throughout the study.

All medications including vitamin supplements, over-the-counter medications, and herbal preparations including (medical) marijuana and cannabidiol products will be collected throughout the study. (Medical) Marijuana and cannabidiol products should not be altered during the study.

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Use of perampanel is prohibited during the study.

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

7.7. Treatment Compliance

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

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

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

8. STUDY ASSESSMENTS

The following sections describe the study procedures to be performed and data to be collected. For each procedure, patients are to be assessed by the same Investigator or site personnel whenever possible. Study procedures and their timing (including tolerance limits for timing) are summarized in the Schedule of Assessments (Appendix 1, Table 2).

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

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

8.1. Study Procedures

8.1.1. Informed Consent Procedure

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

8.1.1.1. Study Informed Consent Procedure

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

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

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

8.1.2. Demographics, Medical History, and Medication History Procedure

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

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

Medication history information to be obtained includes any medication relevant to eligibility criteria and the efficacy or safety evaluations stopped at or within 30 days before signing of informed consent. AED history will be collected as part of the medication history information.

8.1.3. Physical Examination Procedure

The physical examination will consist of the following body systems: (1) head, ears, nose, throat; (2) cardiovascular system; (3) respiratory system; (4) gastrointestinal system; (5) dermatologic system; (6) extremities; (7) musculoskeletal system; (8) lymph nodes; (9) psychiatric status; and

(10) other. All examinations are to be performed by the Investigator or a qualified site staff member. The physical examination must be captured in the source document and eCRF.

8.1.4. Neurological Examination Procedure

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

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8.1.5. Weight and Height

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

8.1.6. Vital Signs Procedure

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

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

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

8.1.7. Seizure Diary Procedure

The seizure diary is an observer-reported clinical outcome assessment measure that captures the total number and duration of motor seizures (i.e., drop seizures, tonic-clonic, tonic, bilateral clonic, atonic, myoclonic-atonic, myoclonic-tonic-clonic, focal seizures with bilateral hyperkinetic motor features. Note – exclude- isolated myoclonic seizures) by type, in accordance with the new seizure classification system.[9]

Patients and/or patients' caregivers will be the observers and reporters in the current study. Patients and/or patients' caregivers may record seizures throughout the day but must ensure that the daily diary assessment is completed each evening, even if no seizures occurred.

At the Screening visit (Visit 1) and at every clinic visit, the patient and/or patient's caregiver will be given a seizure diary and specific instructions to ensure compliance with the seizure recording. The seizure events will be recorded starting at the Screening/Baseline Period up until the Follow-up Visit and collected at each clinic visit. Prior to the first dose at Day 1 (Visit 2), seizure diaries must be sent to the Medical Monitors for review and approval. At all other visits,

the diary can be reviewed by the Investigator with the patient and/or patient's caregiver for proper recording and accountability.

8.1.8. Documentation of Study Drug

A Seizure diary with dosing form will be provided to the patient and/or caregiver at each clinic visit to record AM and PM study drug administration throughout the study, including changes in dosing regimen (de-escalation) that may occur between visits and during the de-escalation period of the study. These will be recorded into the electronic case report form (eCRF).

8.1.9. Documentation of Concomitant Medications

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

Antiepileptic drug treatment, (medical) marijuana, cannabidiol products, VNS settings, and ketogenic diet should not be altered during the study.

8.1.10. Procedures for Clinical Laboratory Samples

Blood and urine samples are to be collected at the time points stipulated in the Schedule of Assessments (Table 2). Samples will be collected in accordance with acceptable laboratory procedures. Details of these procedures and required safety monitoring will be given in the laboratory manual.

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

For an individual patient, the maximum volume of blood collected over the course of the study will be approximately 118.2 mL (Appendix 3).

Blood volume limitations will sometimes preclude the collection of all samples in a particular study visit. Appendix 3 enumerates the priorities for blood collection.

In general, existing guidelines for blood sample volume limits (maximum of 120 mL for each patient with maximum blood volume collected during a 30-day period of approximately 40 mL and maximum blood volume collected during a single visit of approximately 25 mL) are consistent with the limited evidence available on "minimal risk" to children. Examples of guidelines for blood draw limits in pediatrics can be found at: http://www.who.int/bulletin/volumes/89/1/BLT-10-080010-table-T2.html.

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

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

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

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

8.1.11. Contraception and Pregnancy Avoidance Procedure

Please refer to Section 6.1 for detailed contraception requirements.

Patients will be provided with information on acceptable methods of contraception as part of the patient informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study and for 30 days after the last dose of study drug. This may be signed by the legally authorized representative of the patient.

All sexually active female patients of childbearing potential must have a negative urine or serum human chorionic gonadotropin (hCG) pregnancy test at Screening (Visit 1) before receiving any dose of study drug. Additional pregnancy tests (urine only) may be performed throughout the study at the Investigator's discretion. During the study, patients will receive continued guidance with respect to the avoidance of pregnancy and ova or sperm donation as part of the study procedures. An additional serum hCG pregnancy test will be performed at the patient's last clinic visit.

Sexually active male patients (post-pubertal unless permanently sterilized by bilateral orchidectomy) must agree to use male contraception (condom) during the study and for 30 days following the last dose of study drug. Male patients must also not donate sperm during the Screening and Treatment Periods and for 30 days after the last dose of study drug. Females of childbearing potential who are partners of male patients are also advised to use additional contraception as shown in the list containing highly effective/effective contraception in Section 6.1.

8.1.12. ECG Procedure

A 12-lead ECG will be recorded at Screening (Visit 1) and at 30 minutes (± 10 minutes) after the morning dose at other visits. If the patient cannot tolerate being supine, a sitting ECG may be obtained. The Investigator (or a qualified observer at the study site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The interpretation of the ECG will be recorded in the source

documents and in the eCRF. The time that the ECG was performed will be recorded. The following parameters will be recorded on the eCRF from the patient's ECG trace: heart rate, respiration rate, PR interval, QT interval, QRS interval, and corrected QT interval. ECG traces recorded on thermal paper will be photocopied to avoid degradation of trace over time.

8.1.13. Clinical Assessment of Suicidal Ideation and Behavior

Suicidal ideation and behavior will be assessed in patients aged ≥6 years using 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, or aborted attempts at suicide).[10]

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

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

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

8.1.14. Vineland Adaptive Behavior Scale

The VABS, 3rd Edition Parent Caregiver Form (VABS-3 Parent Caregiver Form), is a parent-report questionnaire of adaptive functioning or how an individual behaves in their day-to-day life at home and in the community.[12] It assesses adaptive functioning across 4 domains: behavior, communication, daily living, socialization, and problem behavior. The interview takes about 20 minutes to complete.

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

8.1.15. Aberrant Behavior Checklist-Community (ABC-C)

Behavior will be assessed by the use of the ABC-C questionnaire, which is a rating scale that measures the severity of a range of problem behaviors commonly observed in individuals with intellectual and developmental disabilities.[11] It is completed by the caregiver. It is an empirically developed scale designed to measure psychiatric symptoms and behavioral disturbance exhibited by individuals across 5 domains with 58 items: irritability, agitation, and crying (15 items); lethargy, social withdrawal (16 items); stereotypy (7 items); hyperactivity/noncompliance (16 items); and inappropriate speech (4 items).

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

8.1.16. Documentation of Concurrent Medical Conditions

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

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

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.

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

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

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

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

8.1.18. Clinical Global Impression of Severity (CGI-S) and Clinical Global Impression – Change (CGI- C)

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

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

For the CGI-C, treatment response ratings should take account of both therapeutic efficacy and treatment-related AEs and range from 0 (marked improvement and no side-effects) and 4 (unchanged or worse and side-effects outweigh the therapeutic effects). Each component of the CGI is rated separately; the instrument does not yield a global score. The PI or designee will complete the CGI-S and CGI-C at the timepoints specified in Table 2 (Appendix 1).

8.1.19. Severity Assessment in CDKL5 Deficiency Disorder

The optional severity assessment will be conducted in only the CDD patients and captures degrees of severity associated with motor function, cognition, and vision and autonomic dysfunction. A copy of the questionnaire is provided in Appendix 5.

8.1.20. Exit Survey

An exit survey will be conducted at Visit 6 or at the early termination visit with Care GI-C, and it takes approximately 2 minutes. The survey captures with parent's (and caregivers') experiences with TAK-935 including impact of treatment with TAK-935 on daily life/functioning and on most important bothersome symptoms.

8.1.21. Pharmacokinetic Sample Collection and Analysis

8.1.21.1. Collection of Plasma Samples for TAK-935 PK Evaluation

CCI [redacted]

8.1.21.2. Bioanalytical Methods for TAK-935

CCI [redacted]

8.1.21.3. Pharmacokinetic Parameters

CCI [redacted]

8.1.22. Pharmacodynamic Sample Collection and Analysis

8.1.22.1. Collection of Plasma Samples for Pharmacodynamic Evaluation

CCI [redacted]

8.1.22.2. Bioanalytical Methods for 24HC

CCI [redacted]

8.1.22.3. Pharmacodynamic Parameters

The PD parameter of change from Baseline in plasma 24HC levels will be summarized. Additional PD parameters may be calculated and subjected to additional PK/PD modeling, as appropriate.

8.1.23. Documentation of Screen Failure

Investigators must account for all patients with a signed informed consent. If the patient is found to be ineligible for the study at Visit 2 (Day 1), the IxRS/IWRS should be contacted as a notification of screen failure.

The primary reason for screen failure is to be recorded in the eCRF.

Patients may be re-screened after approval of Medical Monitor and Sponsor.

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

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

8.1.24. Documentation of Study Entrance

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

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

8.2. Sample Collection and Testing

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

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

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

8.3. Safety Evaluations

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

The Investigator is responsible for the appropriate medical care of patients during the study.

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

8.3.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether considered related to this medicinal product.

The definition of an AE also covers medication errors and uses outside what is foreseen in the protocol only if an AE results from the error, including intentional misuse, abuse, and overdose of the product. Adverse events (including SAEs) associated with overdose should be reported

according to the procedure outlined in Section 8.3.1.3. In the event of drug overdose, the patient should be treated symptomatically.

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

Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be recorded as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

For the purpose of this study, reporting of seizures should meet the AE/SAE reporting requirements. As seizures are considered a baseline condition, seizures should be reported as an AE/SAE if: 1) there is a clear increase in the frequency of seizures compared to the subject's baseline, 2) there is an emergence of a new seizure type, or 3) the subject 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 evaluating risk:benefit. The sponsor will report the SAE events of seizure that meet these criteria in an aggregated unblinded report at the conclusion of the study.

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

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

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

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

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

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

8.3.1.1. Severity Assessment

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

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

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

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

8.3.1.2. Causality Assessment

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

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

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

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

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

8.3.1.3. Serious Adverse Events

Serious adverse event collection begins after the patient has signed 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.

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

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

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

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

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

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

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

8.3.1.4. Suspected Unexpected Serious Adverse Reactions

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

8.3.1.5. Reporting Adverse Events

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

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

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

Email: PPD

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

If an SAE is reported via the hotline, the site should first submit the SAE paper form and then enter the SAE in the eCRF. Any AE that meets SAE criteria (Section 8.3.1.3) must be entered into the electronic data capture (EDC) system immediately (i.e., within 1 business day) after site personnel first learn about the event in addition to faxing/emailing the SAE Report form. Once the qualifying SAE data are entered into EDC, Ovid will be notified by an email alert, which will contain high-level safety information.

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

8.3.1.6. Sponsor Reporting Requirements

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

8.3.1.7. Investigator Reporting Requirements

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

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

8.3.2. Exposure During Pregnancy and/or Lactation

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

If any patient is found to be pregnant during the study, she should be withdrawn and any sponsor□supplied drug should be immediately discontinued.

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

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

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

Exposure of an infant to a Sponsor product during breastfeeding must also be reported and any AEs experienced by the infant must be reported to the Sponsor Pharmacovigilance or designee via the same methods as SAE reporting (Section 8.3.1.5).

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

8.3.3. Safety Monitoring

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

8.3.3.1. Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST elevated >3 × ULN on 2 consecutive occasions, as specified in Section 8.1.10, the abnormality should be recorded as an AE.

If a subject is noted to have ALT or AST >3 × ULN and total bilirubin >2 × ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 8.3.1.5. The Investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or

other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 8.1.10 must also be performed.

8.4. Appropriateness of Measurements

All efficacy and safety assessments included in this study are generally regarded as reliable and accurate with respect to the efficacy and safety assessments in individuals and populations with Dup15q or CDD.

9. DATA QUALITY ASSURANCE

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

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

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

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

9.1. Data Collection and Storage

All clinical raw data will be recorded promptly, accurately, and legibly, either directly into the data capture system as e-source data, or indelibly on paper (e.g., ECG readings). A detailed list of the type (electronic or paper) and location for all source data will be included in the Trial Master File. When recorded electronically, case report forms will be electronically generated. All raw data will be preserved to maintain data integrity. The Investigator or designee will assume the responsibility of ensuring the completeness, accuracy, and timeliness of the clinical data.

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

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

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

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

10. STATISTICAL METHODS AND PLANNED ANALYSES

10.1. General Considerations

All statistical analyses will be performed using SAS® Version 9.4 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.

Efficacy Analyses

Motor seizure frequency per 28 days will be calculated at each specified interval as:

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

For all patients, motor seizure frequencies per 28 days for the 4-week prospective Screening/Baseline Period, each 4-week interval in the Maintenance Period, the Maintenance Period and the 20-week Treatment Period will be calculated. The percent change from Baseline to the Maintenance Period in motor seizure frequency per 28 days is the primary efficacy endpoint. The percent change from Baseline to the Treatment Period in motor seizure frequency per 28 days is the secondary efficacy endpoint.

Observed values, change from Baseline, and percent change from Baseline for the motor seizure frequency (per 28 days) will be summarized descriptively by analysis group for the following intervals: the three 4-week intervals in the Maintenance Period, the Maintenance Period, and the entire 20 weeks of Treatment Period. For each analysis group, the mean of primary endpoint (the percent change from Baseline to the Maintenance Period in motor seizure frequency per 28 days) will be presented along with its corresponding 90% confidence interval (CI). Histograms will be produced for the primary endpoint for each analysis group. The analysis will be repeated for all motor seizure types.

The time course of seizure frequencies (per 28 days) in consecutive 4-week intervals in the Maintenance Period will be displayed in a line graph by analysis group.

The proportion of treatment responders based on ≥25% worsening, <25% and >1% worsening, no change (Worsening of 1% to Reduction of 1%), ≥25% reduction, ≥50% reduction, ≥75% reduction, and 100% reduction from Baseline in motor seizure frequency during the Maintenance Period will be summarized at each 4-week interval, the Maintenance period, and the entire 20 weeks of the Treatment Period by analysis group.

Observed values and change from Baseline in CGI-S responses of Investigator-reported impression of efficacy and tolerability of study drug and in Care GI-C responses of parent/family reported impression of efficacy and tolerability of study drug will be analyzed descriptively at

each study visit. Ratings of CGI-C will be assessed at Day 36, Day 85 and Day 141. The relationship between motor seizure frequency and plasma 24HC will be explored.

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

Safety Analyses

All safety assessments will be summarized using descriptive statistics. All safety analyses will be based on observed data only, and no missing values will be imputed. Reported AE terms will be coded using MedDRA and summarized by preferred term and system organ class categories. Serious AEs and AEs leading to study discontinuation will also be summarized.

Observed values and change from baseline in laboratory parameters, vital signs, and ECG parameters will be summarized by study visit. The number and percentage of patients who have met potentially clinically significant criteria at any post baseline visit will be summarized for laboratory, vital signs, and ECG parameters. The number and percentage of patients with shifts in laboratory will be summarized. The number and percentage of patients with C-SSRS assessments of suicidal ideation and behavior will also be summarized.

Prior and concomitant medication use will be summarized by WHO-ATC classification system.

Exploratory Analyses

CCI

[redacted]

10.2. Determination of Sample Size

A formal sample size calculation was not performed for this study. Given the rare occurrence of these epileptic encephalopathy syndromes and based on prior clinical development programs for treatment of rare diseases, the current sample size is deemed appropriate to evaluate the efficacy and safety of TAK-935in patients with Dup15q or CDD.

10.3. Analysis Sets

10.3.1. Modified Intent-to-Treat Analysis Set

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 will be included in the modified intent-to-treat (mITT) analysis set.

10.3.2. Efficacy Analysis Set

All mITT subjects whose assessments are compliant with Protocol Amendment 1 will be included in the efficacy analysis population. Efficacy analyses for primary and secondary efficacy endpoints will be based on the efficacy analysis population, and those for exploratory efficacy endpoints will be based on the mITT set.

10.3.3. Safety Analysis Set

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

10.3.4. Analysis Groups

All analyses will be performed by 2 analysis groups: theDup15q group and the CDD group.

10.4. Demographics and Baseline Characteristics

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

10.5. Patient Disposition

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

10.6. Concomitant Medications and Non-Pharmacologic Therapies and Procedures

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

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

10.7. Treatment Compliance

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

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

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

10.8. Efficacy Analyses

10.8.1. Primary Efficacy Analyses

For all patients the following will be calculated: motor seizure frequencies per 28 days for the 4-week prospective Screening/Baseline Period and the Maintenance Period.

Motor seizure frequency per 28 days will be calculated at each specified interval as:

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

Percent change from Baseline to the motor seizure frequency during the Maintenance Period (per 28 days) will be summarized using descriptive statistics.

10.8.2. Secondary Efficacy Analyses

Percent change from Baseline to the motor seizure frequency during the Treatment Period will be summarized for each analysis group.

The proportion of treatment responders based on ≥25% worsening, <25% and >1% worsening, no change (Worsening of 1% to Reduction of 1%), ≥25% reduction, ≥50% reduction, ≥75% reduction, and 100% reduction from Baseline in motor seizure frequency for the entire 20-week Treatment Period will be summarized.

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

The relationship between motor seizure frequency and plasma 24HC will be explored.

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

10.8.3. Exploratory Analysis

CCI

[redacted]

10.9. Safety Analyses

All safety assessments will be summarized using descriptive statistics. All safety analyses will be based on observed data only, and no missing values will be imputed. Reported AE terms will be coded using MedDRA and summarized by preferred term and system organ class categories. Serious AEs and AEs leading to study discontinuation will also be summarized.

Observed values and change from baseline in laboratory parameters, vital signs, and ECG parameters will be summarized by study visit. The number and percentage of subjects who have met potentially clinically significant criteria at any post baseline visit will be summarized for laboratory, vital signs, and ECG parameters. The number and percentage of subjects with shifts in laboratory will be summarized. Supporting listings will be provided. The number and percentage of subjects with C-SSRS assessments of suicidal ideation and behavior will also be summarized.

Prior and concomitant medication use will be summarized by WHO-ATC classification system. Listings will be provided for all concomitant medications.

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

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

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

Data listings will be provided.

10.9.2. Clinical Laboratory Tests

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

Listings of patients with abnormal results will be provided.

10.9.3. Adverse Events

The following definitions will be used for AEs:

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

The incidence of TEAEs, discontinuations due to TEAEs, drug-related, serious, and severe TEAEs will be summarized. All AEs will be coded using MedDRA and will be summarized by system organ class (SOC) and preferred term (PT) and treatment group. Detailed listings of AEs, SAEs, infusion-associated reactions (IARs), related AEs, and discontinuations due to AEs will be provided.

10.10. Pharmacokinetic/Pharmacodynamic Analyses

CCI [redacted]

10.11. Other Statistical Issues

10.11.1. Significance Levels

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

10.11.2. Missing or Invalid Data

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

10.12. Interim Analyses

Ad hoc analyses can be performed based on the discretion of the Sponsor for planning purposes in further designing of the TAK-935 development program. Final analyses will be performed after the last patient completes the study and the database is locked.

11. INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

11.1. Informed Consent

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

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

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

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

11.2. Data Monitoring Committee

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

11.3. Ethical Review

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

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

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

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

11.4. Regulatory Considerations

This study will be conducted in accordance with:

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

The Investigator or designee will promptly submit the protocol to applicable IRB/IEC(s).

Some of the obligations of the sponsor may be assigned to a Third-Party Organization.

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

11.4.1. Confidentiality

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

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient and/or patient's custodial parent or guardian, except as necessary for monitoring and auditing by the sponsor, its designee, FDA, Health Authorities, Ethics Committees, and/or IRBs.

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

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

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

11.4.2. Investigator Information

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

11.4.3. Protocol Signatures

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

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

11.4.4. Final Report Signature

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

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

11.5. Publication Policy

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

12. LIST OF REFERENCES

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

Table 2: Schedule of Assessments

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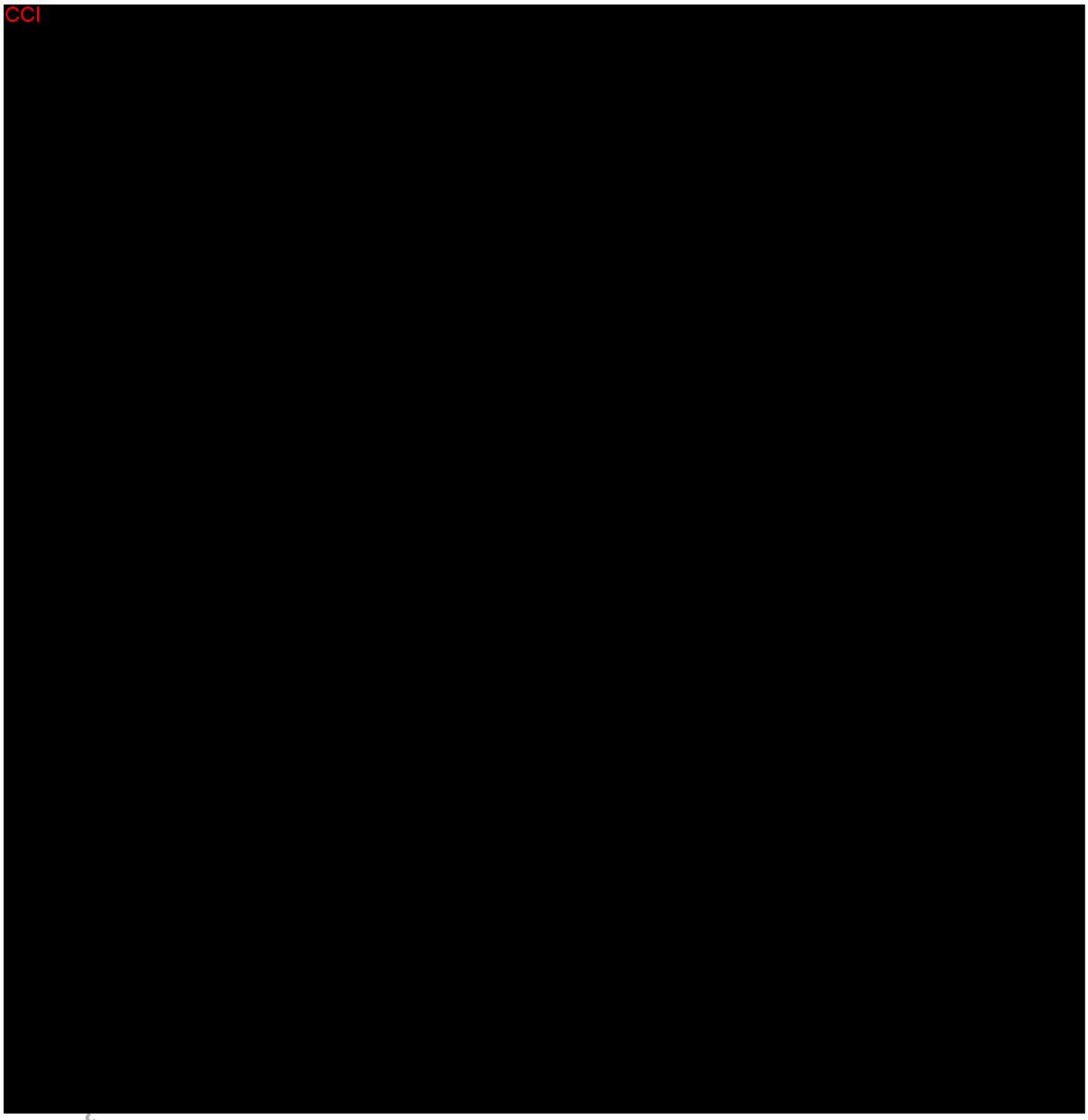

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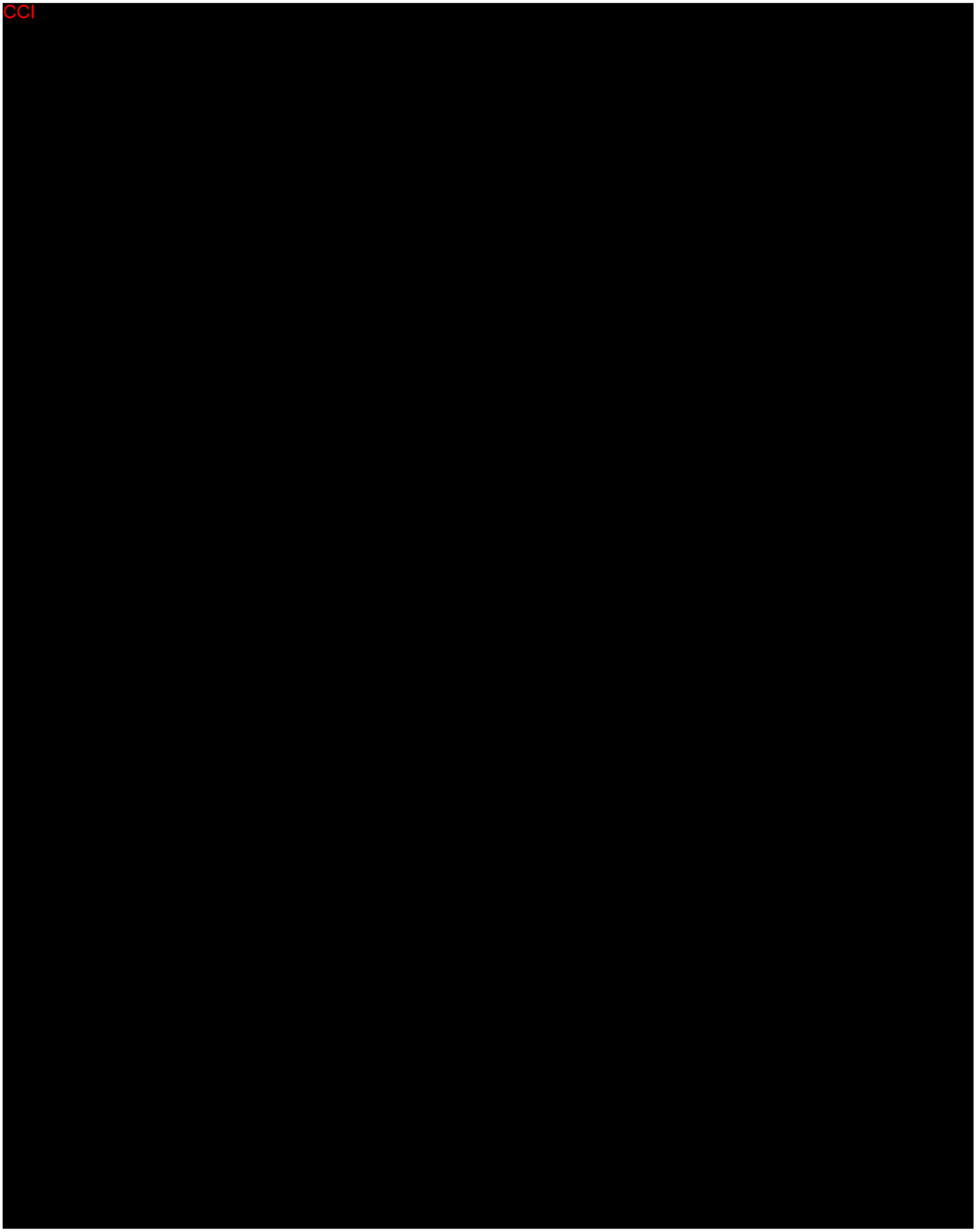
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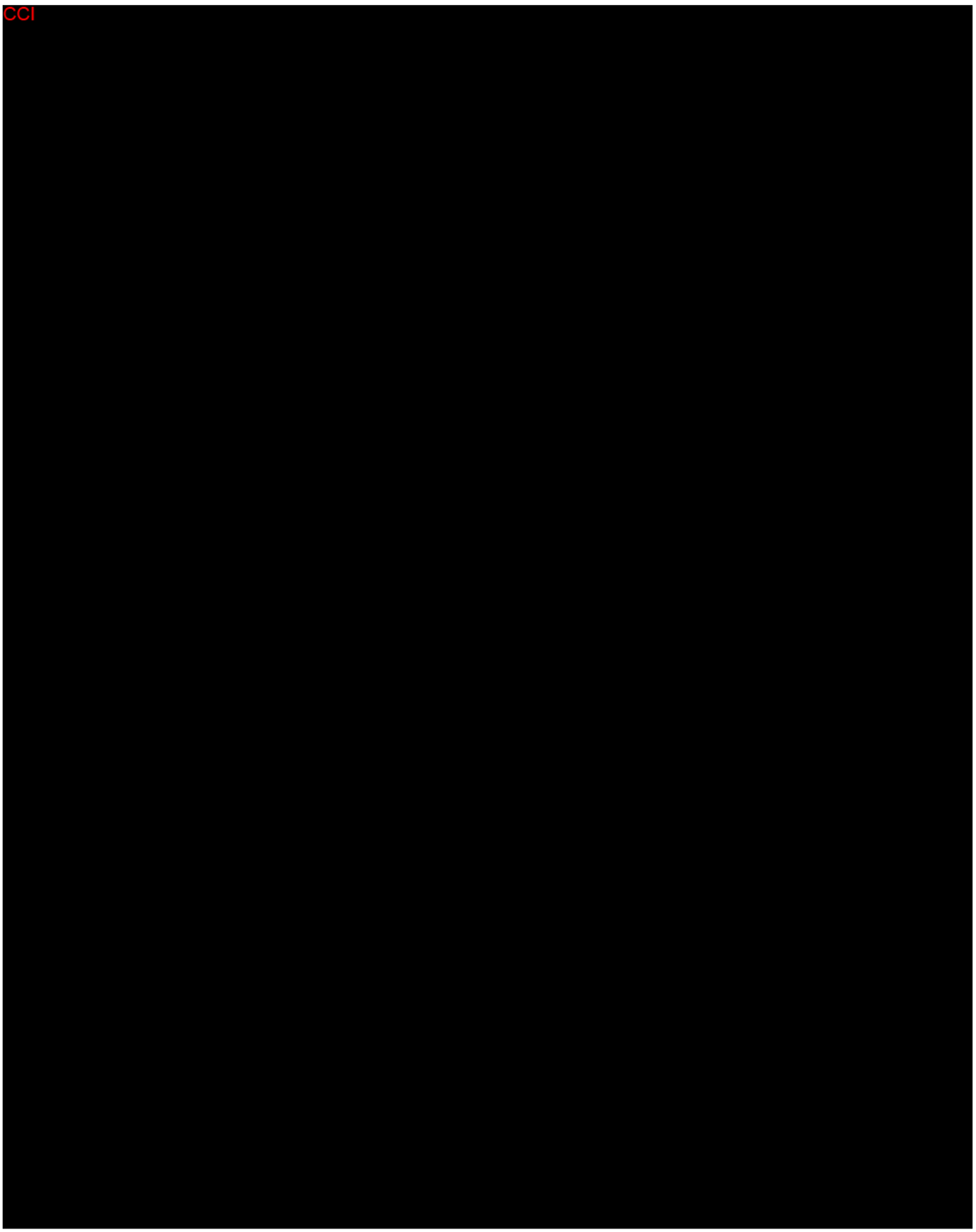

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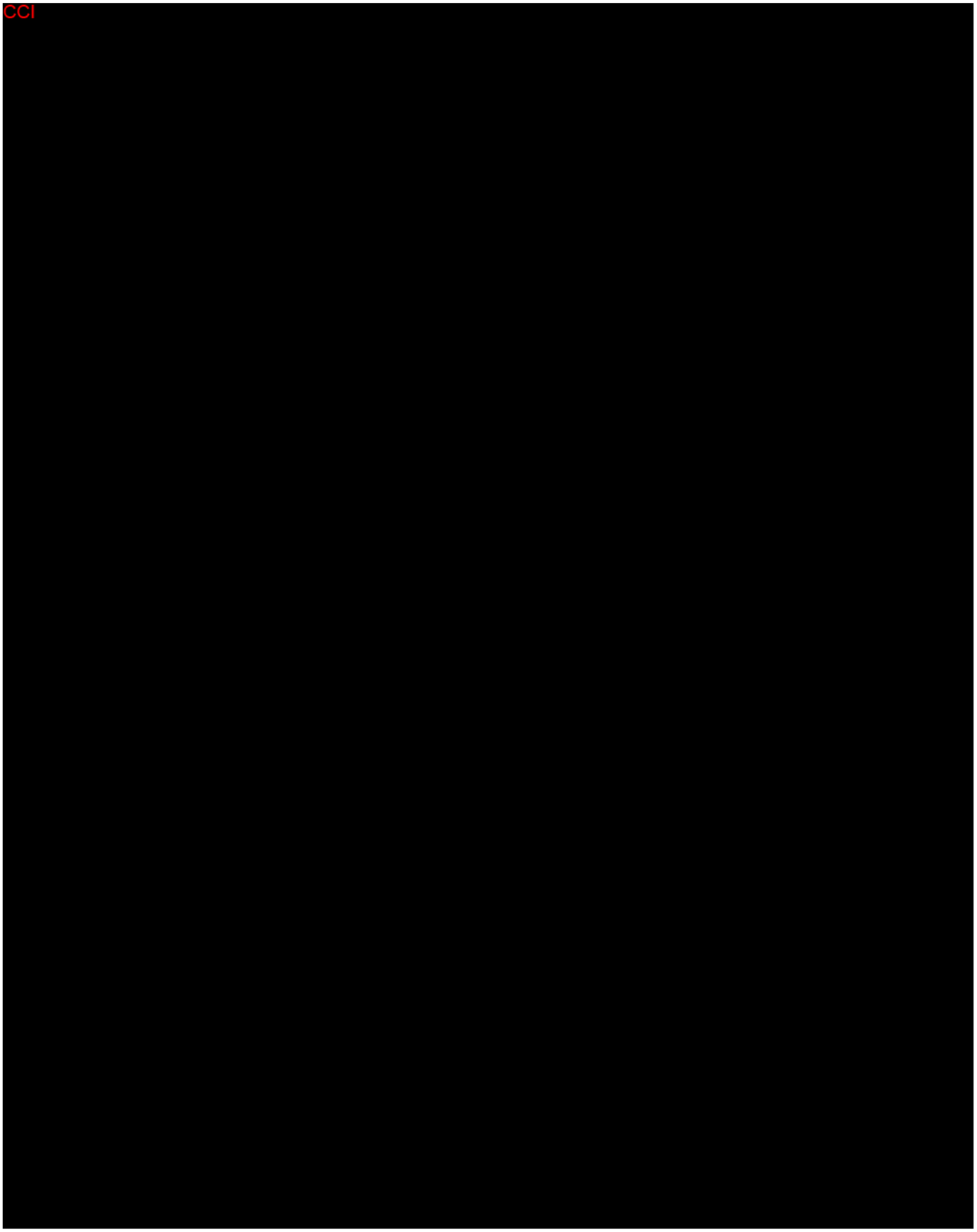

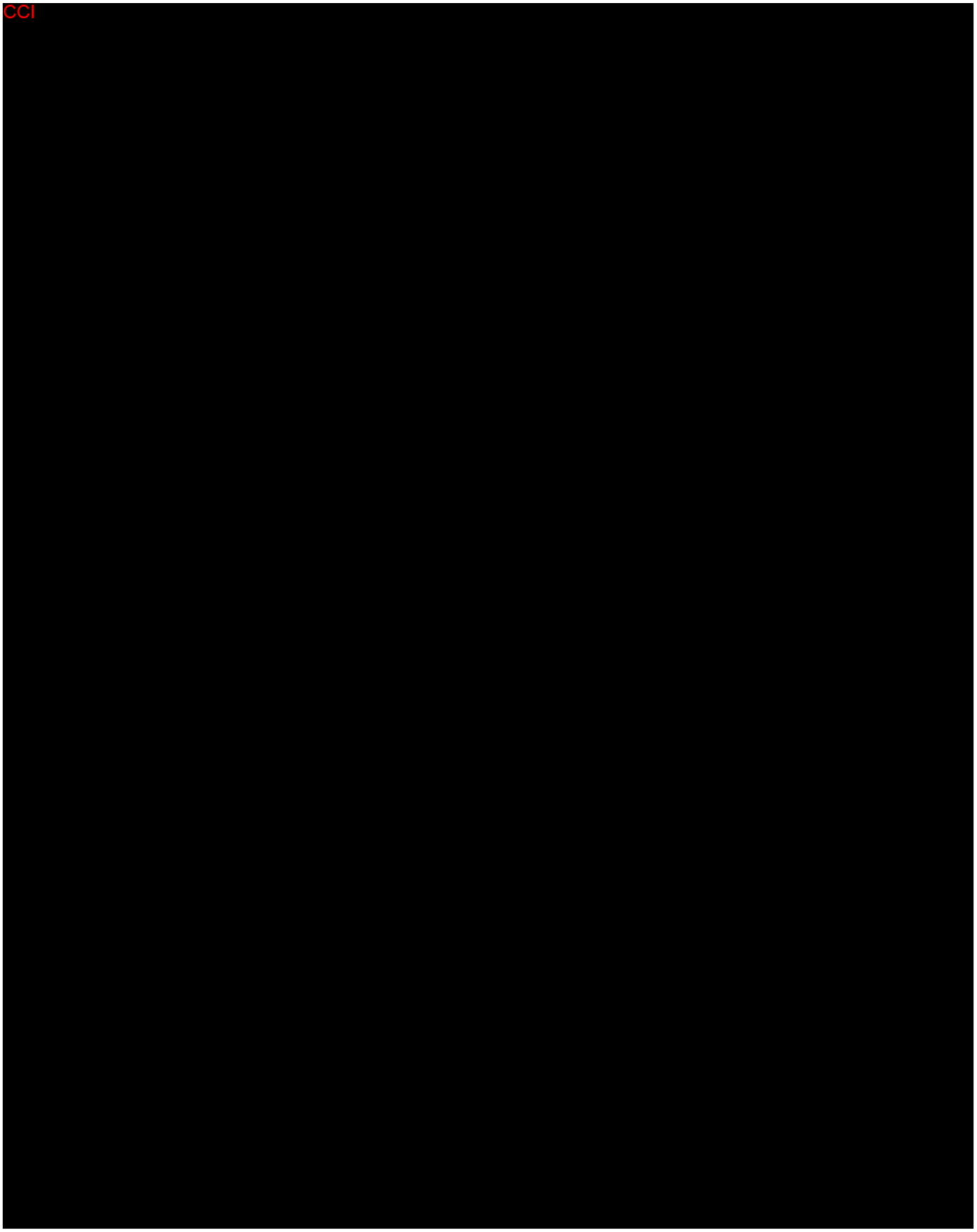
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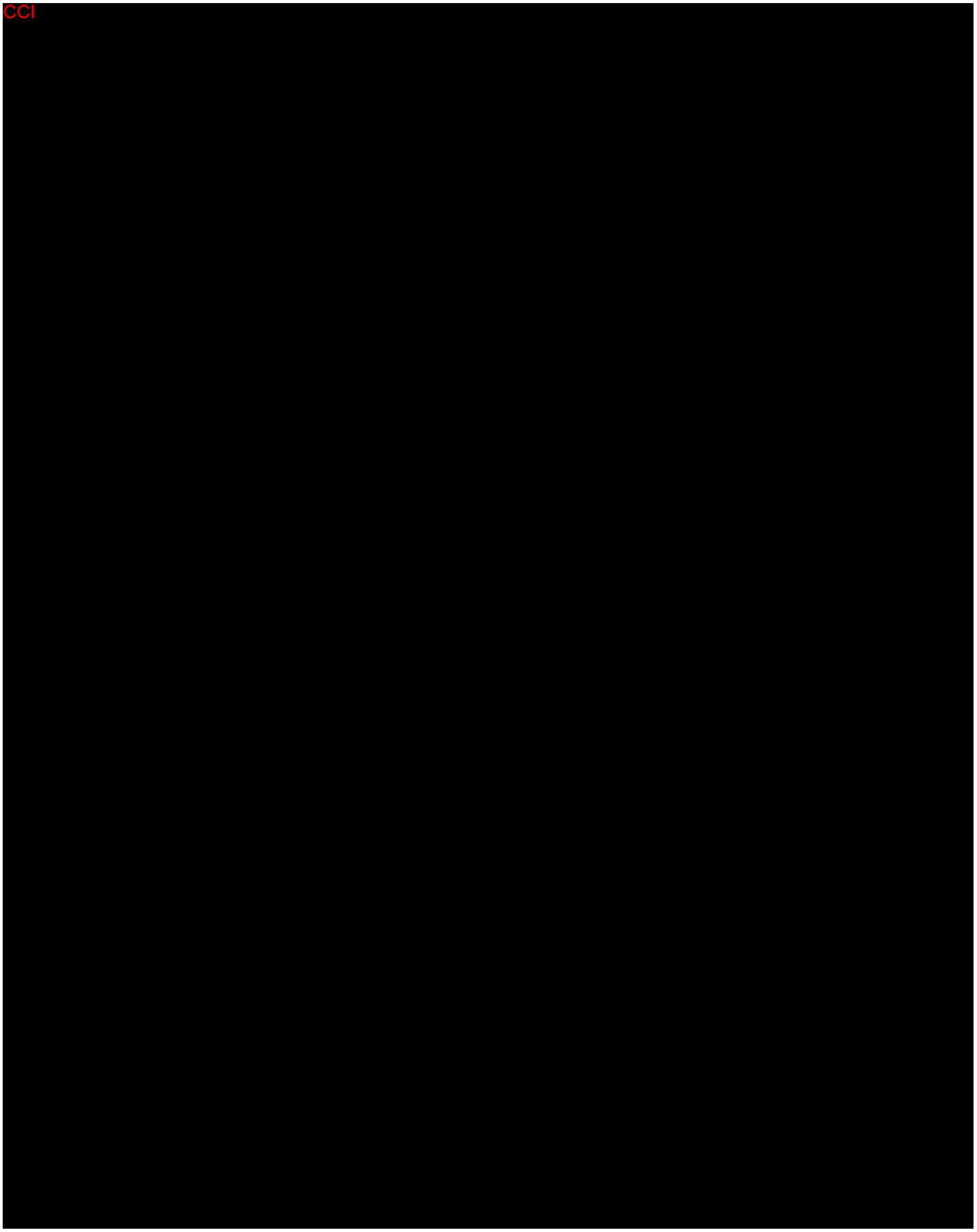

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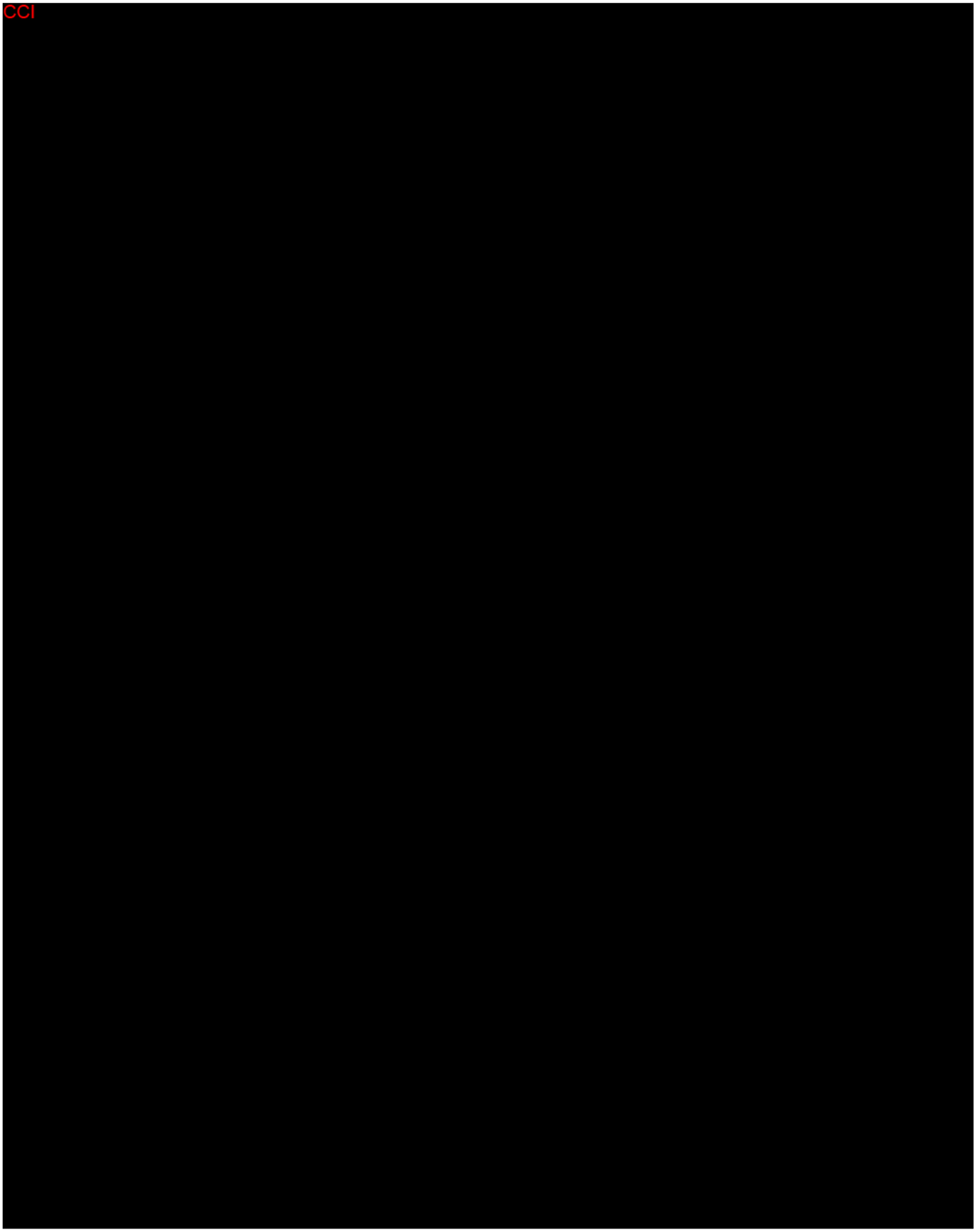

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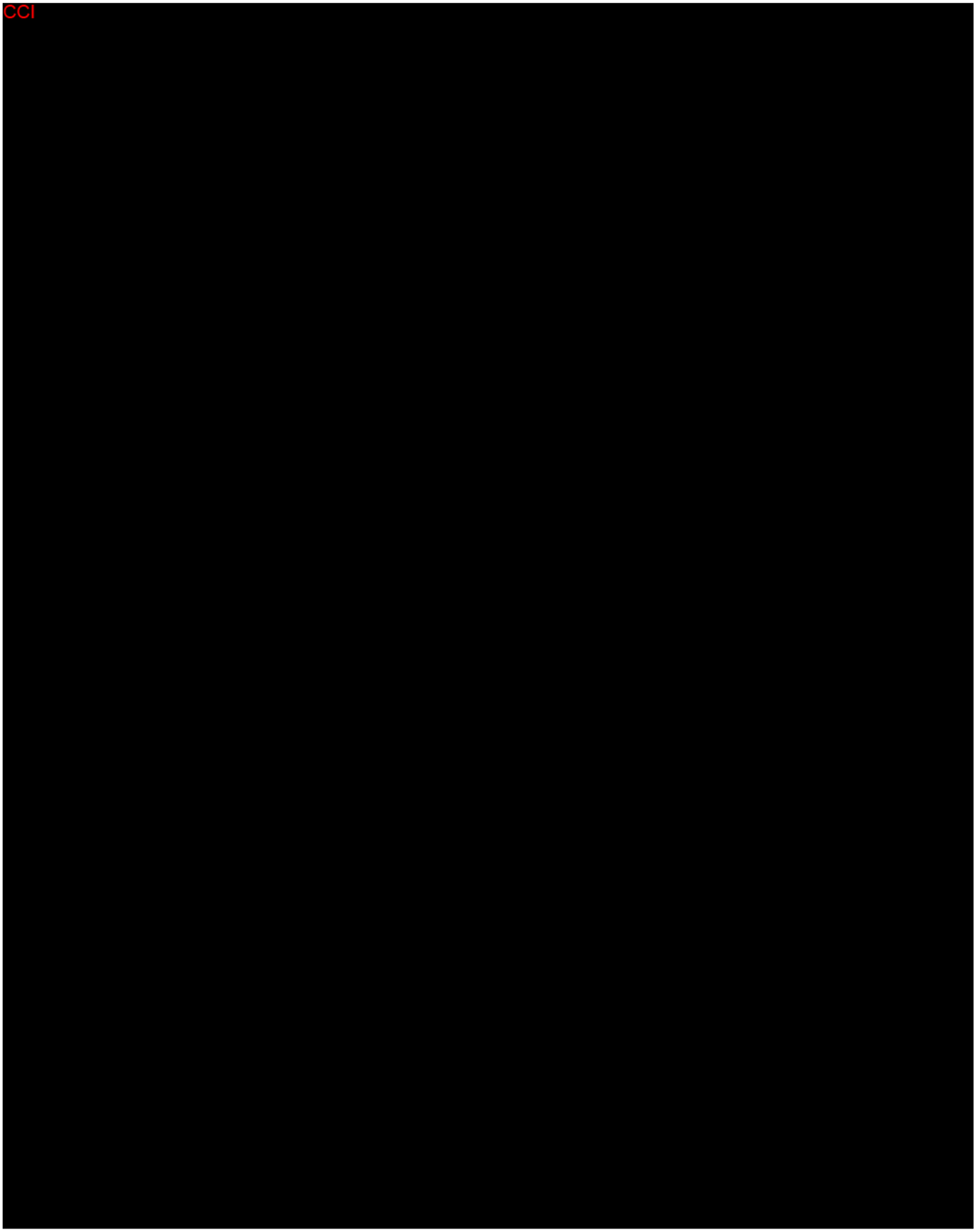

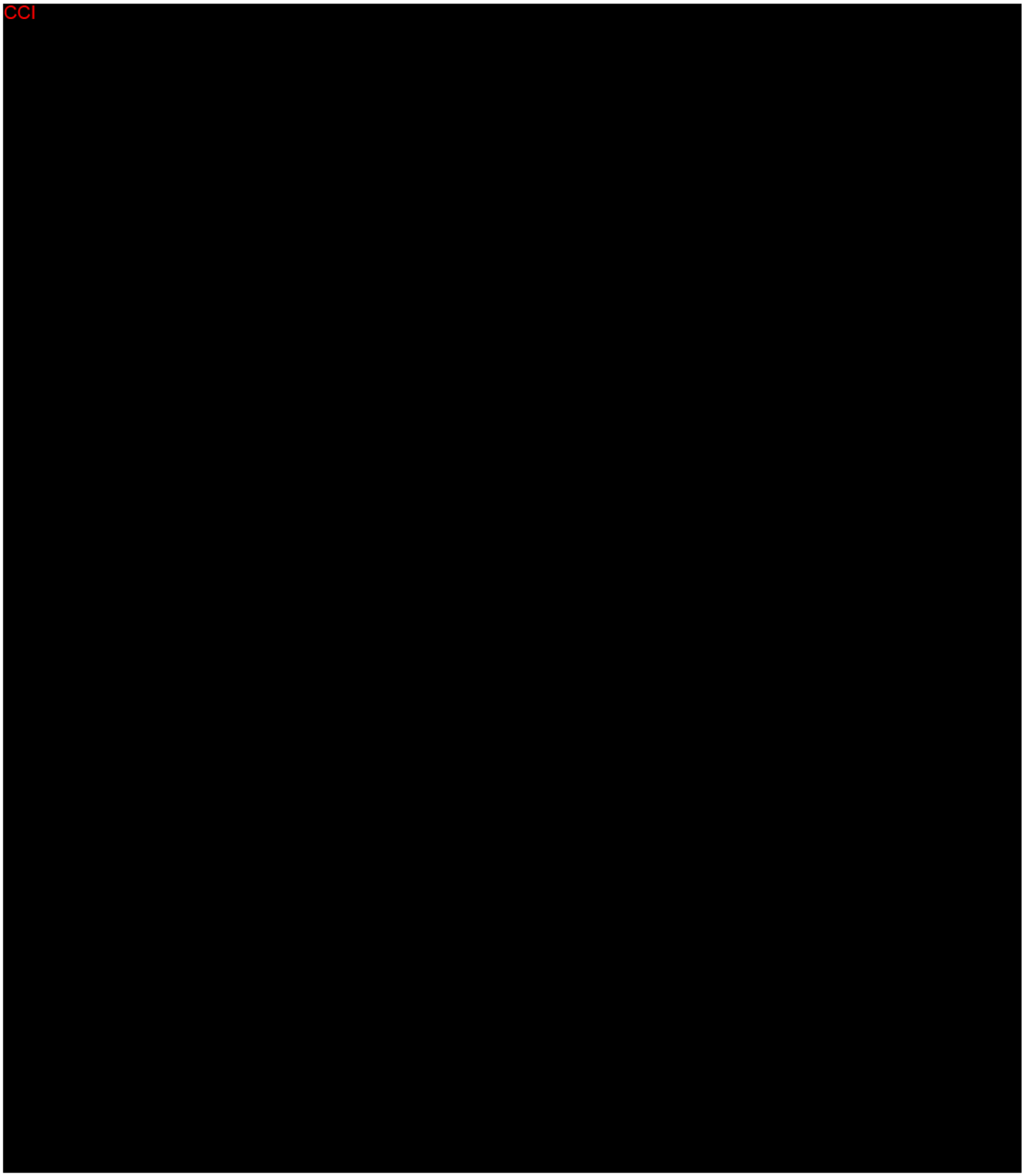
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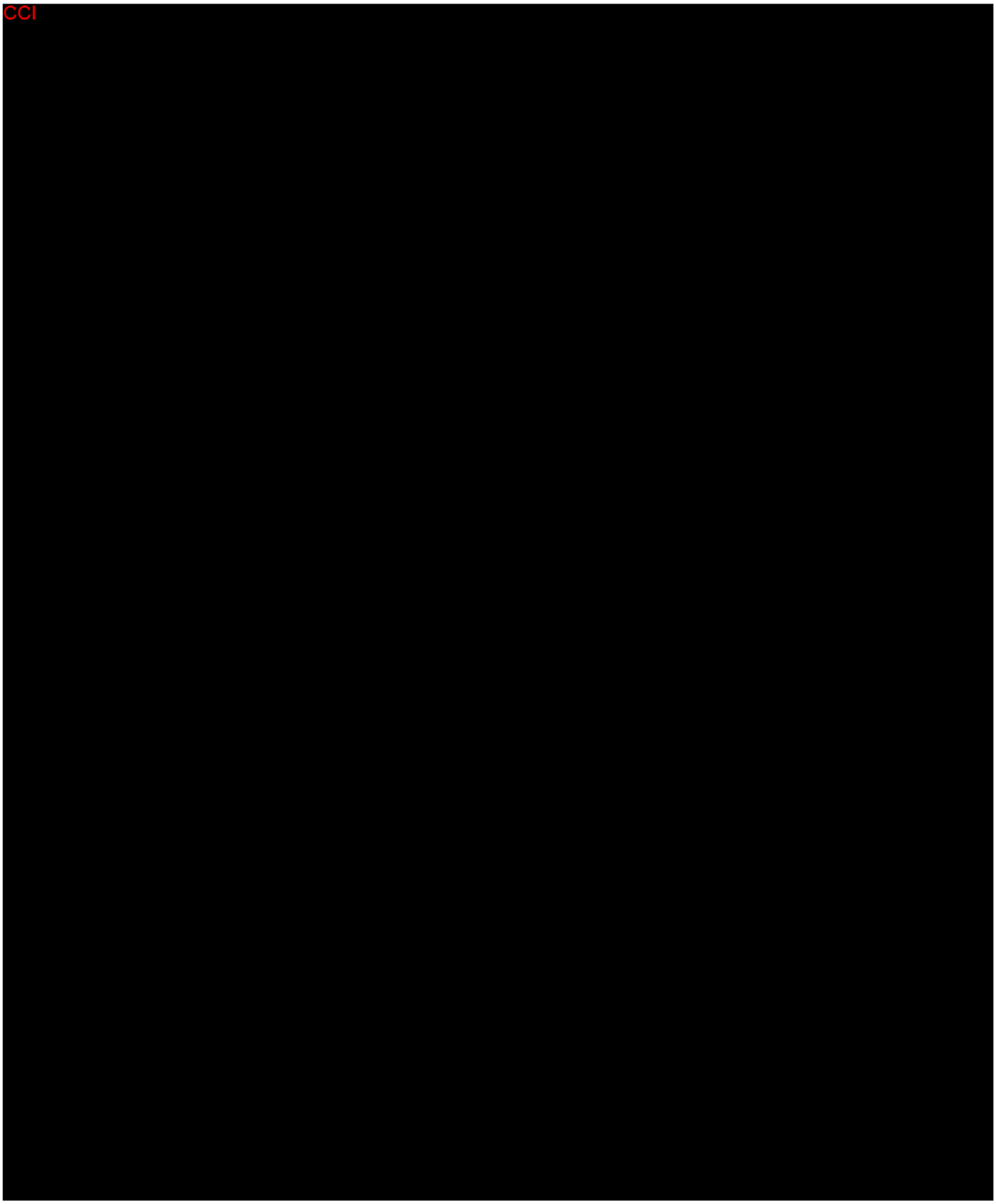

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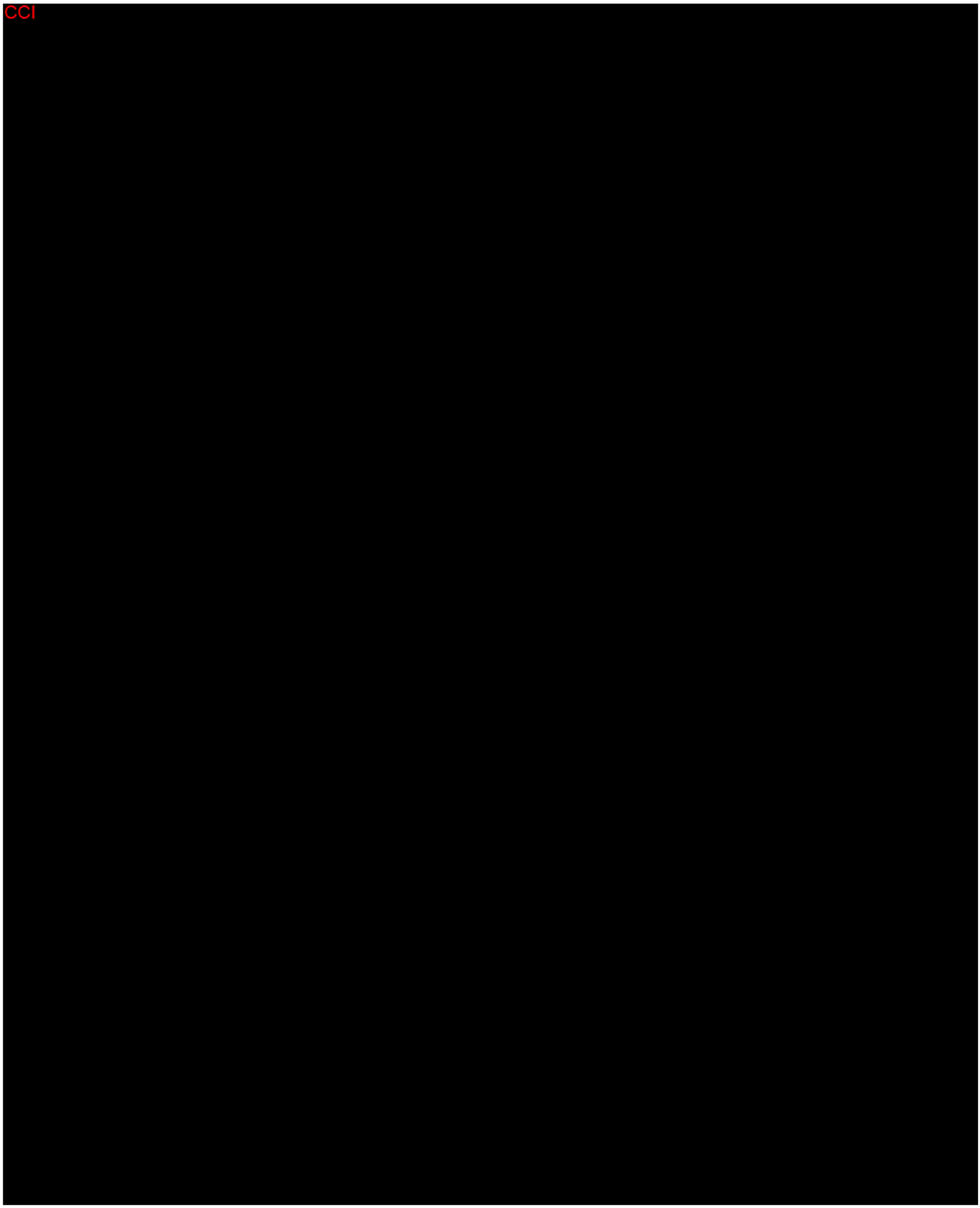

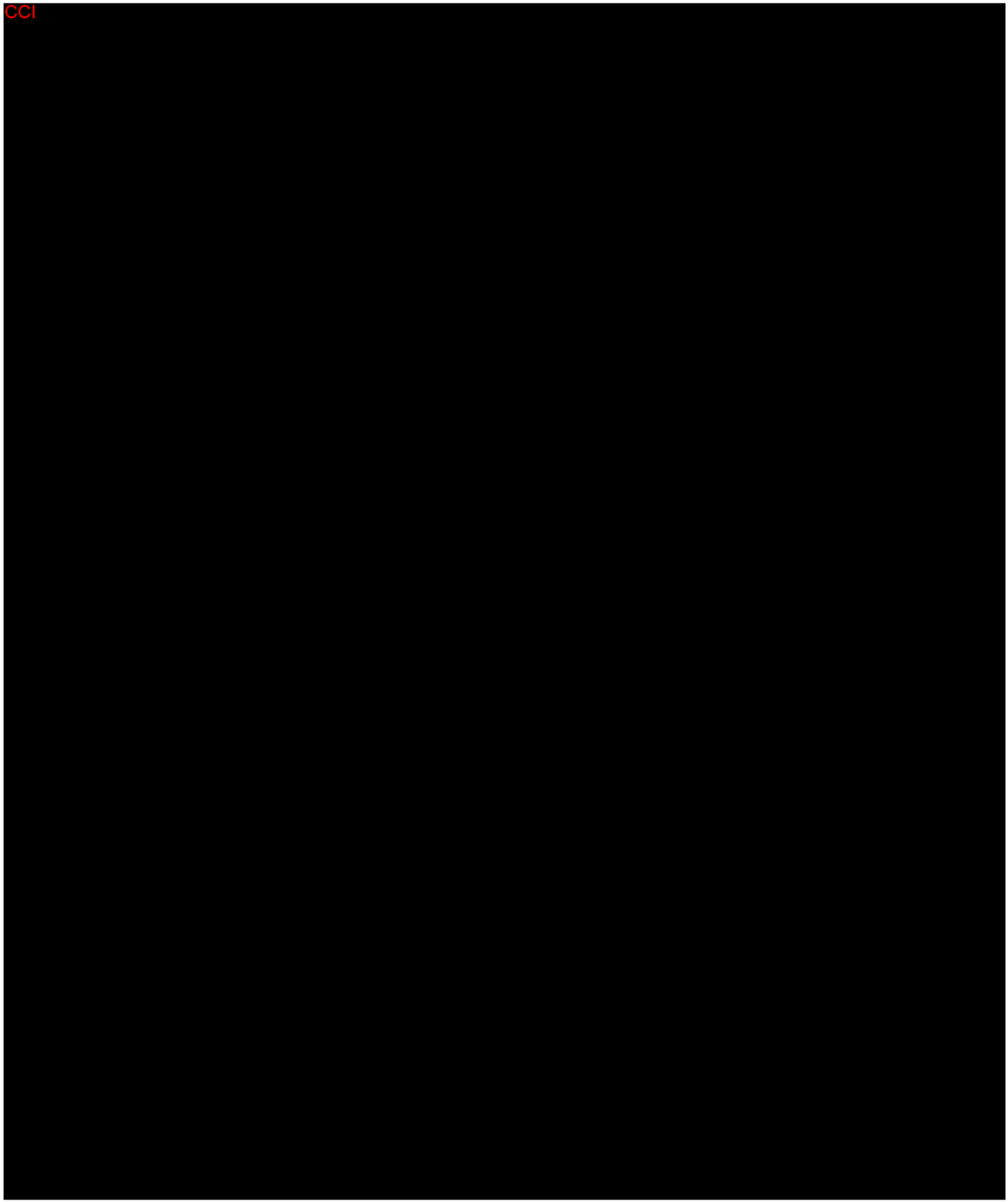
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APPENDIX 6. OVERVIEW OF MAJOR CHANGES IMPLEMENTED BY AMENDMENTS

Amendment 1

1. The study design is revised

Description of Change: The study duration is extended from 12 to 20 weeks (8-week Dose Optimization period and 12-week Maintenance Period)

Rationale for Change: [redacted]

Sections Impacted:

- Synopsis
- Section 5.1
- Section 7.2
- Figure 1
- Appendix 1

2. The titration period is now referred to as the Dose Optimization period

Description of Change: Description of Change: With the change is the length of the treatment period, dose optimization better defines this period

Rationale for Change: [redacted]

Sections Impacted:

- Synopsis
- Section 5.1
- Section 7.2
- Section 10.1
- Section 10.8.2
- Section 10.11.2
- Appendix 1

3. The primary and secondary objectives are revised

Description of Change:

- The primary objective is revised to change the assessment from the treatment period to the maintenance period.
- The secondary objective to investigate the effect of TAK-935 on the frequency of motor seizures is changed from the maintenance period to the treatment period.
- The secondary objectives to investigate the frequency of patients considered treatment responders are changed from the treatment period to the maintenance period. Treatment responders are defined as those with:
  - Worsening of 25% or more in motor seizures from baseline
  - Worsening of 1% to 25% in motor seizures from baseline
  - No change in motor seizures from baseline
  - Reduction of 25% or more in motor seizures from baseline
  - Reduction of 50% or more in motor seizures from baseline
  - Reduction of 100% in motor seizures from baseline

Rationale for Change: The change is made to address the findings from Study TAK-935-2001 and to better understand the effect of the drug on duration of seizures and on duration of seizure freedom.

Sections Impacted:

- Synopsis
- Section 4.1.1
- Section 4.1.2
- Section 4.1.3

4. Two secondary objectives are added

Description of Change:

- To investigate the effect of TAK-935 on the duration of motor seizures for patients with CDKL5 deficiency disorder throughout the Treatment Period
- To investigate the effect of TAK-935 on duration of seizure freedom in patients with CDKL5 deficiency disorder in patients with CDKL5 deficiency disorder during the Maintenance Period.

Rationale for Change: The objectives of the study have been expanded to understand the effect of the drug on duration of seizures and on duration of seizure freedom

Sections Affected:

- Synopsis
- Section 4.1.2

5. Exploratory objectives are revised

CCI

[redacted]

6. The primary and secondary endpoints are revised

Description of Change:

- The primary efficacy endpoint is changed from during the treatment period to during the maintenance period.
- The secondary efficacy endpoints for percent change from baseline in motor seizure frequency per 28 days are changed from during the maintenance period to during the treatment period.
- The secondary endpoints for proportion of patients considered treatment responders are changed from during the treatment period to during the maintenance period. treatment responders are defined as those with:
  - Worsening of 25% or more in motor seizures from baseline
  - Worsening of 1% to 25% in motor seizures from baseline
  - No change in motor seizures from baseline
  - Reduction of 25% or more in motor seizures from baseline
  - Reduction of 50% or more in motor seizures from baseline
  - Reduction of 100% in motor seizures from baseline

Rationale for Change: The preliminary data from the TAK-935-2001 study in adult patients with epileptic encephalopathy may indicate that full effects of TAK-935 are observed after 8 weeks of treatment. Accordingly, since treatment duration is extended to 20 weeks and to observe the full effects, the primary and secondary endpoints are changed.

Sections Impacted:

- Synopsis
- Section 4.2.1
- Section 4.2.2

7. Secondary endpoints are added

- **Description of Change:** The following endpoints are added:
  - Percent change from Baseline in frequency of motor seizures longer than 5 minutes in patients with CDKL5 deficiency disorder
  - Percent change from Baseline in motor seizure-free days frequency in patients with 15q duplication syndrome during the Maintenance Period
  - To characterize plasma 24HC levels and change in motor seizure frequency in patients treated with TAK-935 as an adjunctive therapy

Rationale for Change: The secondary endpoints are added to address the secondary objectives.

Sections Affected:
- Synopsis
- Section 4.2.2

8. One exploratory objective/endpoint is added

CCI [redacted]

Description of Change: Study visits are changed as follows:

- Study visits at Days 8 and 57 are changed to phone contacts
- Study visit at Day 85 is changed from end of treatment visit to a treatment period visit
- The end of study visit is changed to Day 141
- Phone contacts are added at Days 22 and 113
- The safety follow-up visit is at Day169

Rationale for Change: Because the duration of treatment is changed to 20 weeks, additional study visits are incorporated.

Sections Impacted:
- Appendix 1

10. Timepoints for collection of samples for pharmacokinetic analysis are clarified

Description of Change: Five (5) PK blood draws will occur at these following timepoints on the first study day: 30 minutes (± 10 minutes), 1, 2, and 4 hours (± 10 minutes) post-first dose. On other study visit days, two PK blood draws will be collected; one within 1 hour prior to the morning dose (pre-dose) and the other at 30 minutes (± 10 minutes) post-morning dose.

Rationale for Change: These timepoints will better characterize PK profile of the drug in a pediatric population.

Sections Affected:

- Synopsis
- Section 8.1.22.1

11. The age for participation is increased to 35 years

Description of Change: The upper age limit is changed from 17 years to 35 years

Rationale for Change: Both dup 15Q syndrome and the CDKL5 deficiency disorder occur in childhood and continue into adulthood; thus, current clinical sites have indicated potential older patients in their clinical practice for this study

Sections Impacted:

- Synopsis
- Section 5.1
- Section 6.1

12. Route of administration is expanded to include G-tube/PEG tube/J-tube at all sites except those in China.

Description of Change: Study drug may be administered orally or via G-tube/PEG tube/J-tube. J-tube administration requires approval by the Medical Monitor and Sponsor. Patients enrolled in clinical sites in China are not to receive study drug via G-tube/PEG tube/J-tube.

Rationale for Change: Change is necessary to accommodate patients unable to take study drug orally.

Sections Impacted:

- Synopsis
- Section 5.1
- Section 7.2

13. Perampanel is added as a prohibited medication

Description of Change: Perampanel is a prohibited medication

Rationale for Change: [redacted]

Sections Impacted:

- Synopsis
- Section 6.1
- Section 7.6

14. The use of traditional Chinese medicines is clarified

Description of Change: The use of traditional Chinese medicines should be approved by the Medical Monitor at screening.

Rationale for Change: This clarification is added due to inclusion of sites in China.

Sections Impacted:
- Synopsis
- Section 7.2
- Section 7.6

15. Inclusion criterion 1 is revised to clarify the definition of CDKL5 deficiency disorder

Description of Change: CDKL5 deficiency disorder is defined as:

- A pathogenic or likely pathogenic variant in CDKL5

  OR

  A variant of uncertain significance (VUS) in the kinase domain of CDKL5 that has been confirmed to be de novo. Unless both parents have been tested and found to not harbor the VUS, a patient with a VUS cannot be enrolled. Participants with a VUS found outside of the kinase domain will not be enrolled.

  A patient with mosaicism for a CDKL5 variants is eligible.

Rationale for Change: This clarification is added to ensure consistency across sites.

Sections Impacted:
- Synopsis
- Section 6.1

16. Inclusion criteria 6 and 7 are revised to clarify the chronic use of benzodiazepines as antiepileptic drugs and to include stable use of cannabidiol products

Description of Change: Chronic use of benzodiazepines is defined as daily frequency to treat seizures and the use of cannabidiol products must be stable for 4 weeks prior to screening.

Rationale for Change:

- Based on inquiries from clinical sites, further clarification was needed to better define the "chronic" use.
- With current use of legal medical marijuana and the availability of cannabidiol products as AEDs, this inclusion was added to allow eligible patients using these products to enroll.

Sections Impacted:
- Synopsis
- Section 6.1

17. Exclusion criterion 1 is revised regarding the treatment of status epilepticus

Description of Change: The change removed the average number of episodes that could be allowed per week and that status epilepticus is defined as a seizure or repeated seizures that lasts 5 minutes or longer and required rescue therapy OR a seizure or repeated seizures that lasts 15 minutes or longer without rescue therapy. The new exclusion requires the patient has been admitted to a medical facility for treatment of status epilepticus 2 or more times in the 3 months immediately prior to the screening visit

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

Sections Impacted:

- Synopsis
- Section 6.2

18. Exclusion criterion 8 is deleted (positive findings in the screening C-SSRS assessment)

Description of Change:

Rationale for Change: This exclusion was confusing since there are a number of symptoms from the C-SSRS assessment that may not necessarily disqualify patients from entering the study.

Sections Impacted:

- Synopsis
- Section 6.2

19. An optional severity assessment for CDKL5 deficiency syndrome is added

Description of Change: The optional severity assessment is conducted in only the CDKL5 deficient patients.

Rationale for Change: This assessment will capture degrees of severity associated with motor function, cognition, and vision and autonomic dysfunction.

Sections Impacted:

- Section 8.1.19

20. Handling of missed doses is clarified

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

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

Sections Impacted:

- Section 7.2

21. Requirement is added to discontinue a patient if he/she exhibits signs of suicidal ideation

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

Rationale for Change: This change provided consistency between Section 8.1.14 and Section 6.3.1.

Sections Impacted:

- Section 6.3.1
- Section 8.1.13

CCI

[redacted]

23. Two additional timepoints are added for collection of plasma 24HC

Description of Change: Day 141 and Follow-up visit (Day 169)

Rationale for Change: These timepoints are added to correlate 24HC blood level with change in seizure frequency

Sections Impacted:

- Appendix 1

24. Amount of blood samples is changed to reflect additional visits

Description of Change: The total maximum amount of blood collected during the study per patient is 120.2 mL.

Rationale for Change: Increase based on additional study visits

Sections Impacted:

- Synopsis
- Section 8.1.10
- Appendix 3

25. Change in dose during the study is clarified

Description of Change: Patients will be contacted by phone within first two days following escalation to the maximum dose to assess safety and tolerability of the study drug. After reaching the maximum dose, an additional 6 weeks will be allowed to adjust the patient to the optimal dose level, 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 changed during the Dose Optimization Period in consultation with the medical monitor.

Rationale for Change: This change will allow flexibility to achieve optimal dose during the Optimization Period.

Sections Impacted:

- Synopsis
- Section 7.2

26. Weight-based dosing is updated to reflect the administration of 100 mg tablets

Description of Change: The number of tablets by weight group is added as the original table only showed the number of mini-tablets.

Rationale for Change: The study is amended to include adults

Sections Impacted:

- Synopsis
- Section 7.2

27. Use of an EEG charter is removed

Description of Change: A detailed description of the EEG parameters evaluated, and eligibility criteria will be further discussed in with the Sponsor's Medical Monitor.

Rationale for Change: The Sponsor medical monitor will discuss the EEG parameters with the clinical sites, so a charter is no longer required.

Sections Impacted:

- Synopsis
- Section 8.1.21

28. An additional ECG assessment is added

Description of Change: An additional assessment is included at Day 15

Rationale for Change: Assessment added due to the study duration extension

Sections Impacted:
Appendix 1

29. Clarification is added for rolling over from the antecedent trial to the open-label extension

Description of Change: To clarify that Patients currently participating in this trial can immediately roll over to the open-label extension as long as they meet the criteria specified in the OLE study.

Rationale for Change: To add clarity

Sections Impacted:
- Section 5.1.2

30. Oxcarbazepine is added to the assay for concomitant AEDs

Description of Change: Oxcarbazepine is added to the assay for concomitant AEDs

Rationale for Change: This assay was omitted in the previous version of the protocol.

Sections Impacted:
- Appendix 3

31. An analysis population (Efficacy Analysis Population) is added

Description of Change: The population is defined as All mITT subjects whose assessments are compliant with Protocol Amendment 1 will be included in the efficacy analysis population. Efficacy analyses for primary and secondary efficacy endpoints will be based on the efficacy analysis population, and those for exploratory efficacy endpoints will be based on the mITT set.

Rationale for Change: Only a modified ITT population had initially been proposed.

Sections Impacted:
- Synopsis
- Section 10.1

32. Statistical analyses are revised

Description of Change: Timepoints are changed to either maintenance period or treatment period based on changes to the study endpoints

Rationale for Change: Analyses are revised to reflect changes in study endpoints

Sections Impacted:
- Synopsis
- Section 10.8.1
- Section 10.8.2

33. Confidentiality of subject information is clarified

Description of Change: All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient and/or patient's custodial parent or guardian, except as necessary for monitoring and auditing by the sponsor, its designee, FDA, Health Authorities, Ethics Committees, and/or IRBs.

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

Rationale for Change: The clarification is based on local regulatory and IRB requirements

Sections Impacted:

- Section 11.4.1

34. The length of time subjects must avoid pregnancy, donation of ova, and sperm donation after the last dose of study drug is clarified and instructions are included if urine cannot be collected at Visit 2

Description of Change: Months are changed to days and instructions are provided if urine cannot be collected at Visit 2

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

Sections Impacted:

- Synopsis
- Section 6.1
- Section 8.1.12

35. End of study definition is added

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

Rationale for Change: To clarify the end of study for a patient and the end of the overall study.

Sections Impacted:

- Section 5.1.1

36. Description of the dosing card is added

Description of Change: A dosing card will be provided to the patient and/or caregiver at each clinical visit to record actual time of the last 2 dose administrations prior to PK sample collection and change in dosing regimen (de-escalation) that may occur between visits and during the de-escalation period of the study; these will be recorded in the patient's source documents and transcribed into the eCRF.

Rationale for Change: To clarify for sites the use of the dosing card.

Sections Impacted:

- Section 8.1.8

Amendment 2

1. The age for participation is increased to 55 years

Description of Change: The upper age limit is changed from 35 years to 55 years

Rationale for Change: Both Dup15q and the CDD occur in childhood and continue into adulthood; thus, current clinical sites have indicated potential older patients in their clinical practice for this study

Sections Impacted:

- Synopsis
- Section 5.1
- Section 6.1

2. Inclusion Criteria for diagnosis expanded

Description of Change: Removed the word "isodicentric" and included provision for diagnosis per standard of care and per literature described phenotype

Rationale for Change: To allow patients with a diagnosis of interstitial Dup15q.

Sections Impacted:

- Synopsis
- Section 6.1

3. The primary and secondary endpoints are revised

Description of Change: Secondary endpoints CGI-S/C (nomenclature) separated into CGI-S and CGI-C and percent change modified to change. Percent change also modified to change from Care-GI-C. CCI [redacted]

Rationale for Change: To provide clarification related to the analyses of these endpoints (CGI). CCI [redacted]

Sections Impacted:

- Synopsis
- List of Abbreviations and Definitions of Terms
- Section 4.1.2
- Section 4.2.2
- Section 8.1.18
- Section 8.1.20
- Section 10.1
- Section 10.8.2
- Appendix 1. Schedule of Assessments

4. Addition of ad hoc analyses

Description of Change: Added the provision that ad hoc analyses may be performed at the discretion of the Sponsor

Rationale for Change: These analyses may be necessary for planning purposes in further designing of the TAK-935 development program

Section Impacted:

- Section 10.12

5. Addition of J-tube and description

Description of Change: Clarification that Jejunostomy tube (J-tube) may be considered following approval by the Sponsor and Medical Monitor. Patients enrolled in clinical sites in China are not to receive study drug via J-tube.

Rationale for Change: May be necessary to accommodate patients unable to take study drug orally.

Sections Impacted:

- Synopsis
- Section 5.1
- Section 7.2

6. Corrections made to the Schedule of Assessments

Description of Change: Separated CGI-S from CGI-C separated into 2 rows and seizure diary collection removed from Phone Visit days

Rationale for Change: Assessments separated for clarity and removal of diary entries to correct error

Sections Impacted:

- Appendix 1. Schedule of Assessments

7. Revised contraception language

Description of Change: Contraception and exposure during pregnancy language updated to current Ovid Therapeutics standards. Includes currently accepted methods.

Rationale for Change: To make current and consistent with other studies sponsored by Ovid Therapeutics

Sections Impacted:

- Section 6.1 Inclusion Criteria
- Section 8.1.11 Contraception and Pregnancy Avoidance Procedures
- Section 8.3.2 Exposure During Pregnancy and/or Lactation

8. Removed optional blood sample for research

Description of Change: The optional blood sample was removed

Rationale for Change: to minimize the collection of blood samples and there are no current planned analyses for the sample

Sections Impacted:

- CCI [redacted]
- Appendix 3 Sampling Summary