Official Title:	An Open-label, 52-Week, Multicenter Trial Evaluating the Long-term Safety and Tolerability of Centanafadine Sustained-Release Tablets in Adults with Attention-Deficit/ Hyperactivity Disorder
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Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational Medicinal Product

Centanafadine (EB-1020)

An Open-label, 52-Week, Multicenter Trial Evaluating the Long-term Safety and Tolerability of Centanafadine Sustained-Release Tablets in Adults with Attention-Deficit/Hyperactivity Disorder

Protocol No. 405-201-00015
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Statistical Analysis Plan

Version: Final

Date: September 15, 2021

CONFIDENTIAL – PROPRIETARY INFORMATION

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1 Introduction

This statistical analysis plan (SAP) documents the statistical methodology and data analysis algorithms and conventions to be applied for statistical analysis and reporting of efficacy and safety data of study 405-201-00015. All amendments to the protocol are taken into consideration in developing this SAP.

2 Study Objectives

The primary objective of this trial is to assess the safety and tolerability of centanafadine SR tablets administered BID (400 mg TDD) in the treatment of adults with ADHD.

3 Study Design

This is a phase 3, 52-week, open-label, multicenter trial to assess the long-term safety and tolerability of centanafadine SR tablets (400 mg TDD) for the treatment of adults with ADHD. The trial population will include male and female subjects 18 to 55 years of age (inclusive) who meet Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for ADHD (including predominantly inattentive presentation, hyperactive presentation, and combined presentations) as confirmed by the Adult ADHD Clinical Diagnostic Scale (ACDS) Version 1.2. Subjects who rollover from the double-blind phase 3 trial (i.e., Trial 405-201-00013 or Trial 405-201-00014) and de novo subjects from selected sites are permitted to enroll in this trial.

This trial will have 3 periods for rollover subjects:

1. Baseline;
2. Open-label treatment; and
3. Follow-up.

The trial will have 4 periods for de novo subjects:

1. Screening and washout;
2. Baseline;
3. Open-label treatment; and
4. Follow-up.

The trial will be organized as follows:

Rollover Subjects from Double-blind Phase 3 Trial (i.e., Trial 405-201-00013 or Trial 405-201-00014)

Open-label Screening/Baseline: Subjects who completed one of the double-blind phase 3 trials may be eligible to enroll in this trial; subjects who discontinued will not be eligible. Subjects who complete both the 6-week double-blind treatment period and the 7-day follow-up visit are eligible to enroll into this trial. Subjects will be evaluated for eligibility at the 7-day follow-up visit of the double-blind phase 3 trial, and informed consent will be obtained before any procedures for the open-label trial are conducted. Therefore the assessments from the 7-day follow-up visit of the double-blind phase 3 trial may serve as the baseline assessments for the open-label trial.

CCI [redacted]

Open-label Treatment: Eligible subjects from the double-blind phase 3 trial will receive daily treatment with open-label centanafadine SR tablets as described in Section 3.2 of the protocol.

During the open-label treatment period, subjects will return to the clinic for evaluations at the end of Weeks 1, 2, 4, 8, 12, 16, 20, 26, 32, 38, 44, and 52/ET. A Week 48 visit will be conducted via telephone, web, or other acceptable means of contact.

Follow-up: If any subject discontinues the trial early, every effort should be made to complete the early termination (ET) evaluations as soon as possible and, whenever possible, prior to starting any new medication or treatment. All subjects (completers and early withdrawals) will be evaluated for safety during a 10-day follow up (follow-up telephone calls at 1, 3, and 5 days after the last dose of IMP, in-clinic visits 2 and 7 days after the last dose of IMP, and a follow-up telephone call [or web, or other acceptable means of contact] 10 days after the last dose of IMP).

De Novo Subjects

Screening and Washout: De novo subjects must meet the DSM-5 criteria for ADHD (including predominantly inattentive presentation, hyperactive presentation, and combined presentations) as confirmed by the ACDS Version 1.2. To confirm that ADHD is the primary diagnosis, the Mini International Neuropsychiatric Interview (MINI) will be used to identify and exclude other psychiatric conditions.

Subjects will be screened to establish eligibility for trial participation. The length of screening (Day –28 to Day –2) will include a washout period (if needed), which will range from 7 to 28 days. The investigator or his/her designee must obtain informed consent from the subject prior

to any trial-related procedures being performed. An identification (ID) number will be assigned for each subject with documented consent. Those subjects who meet eligibility requirements will undergo ADHD medication washout, if applicable. If subjects are taking disallowed medications and are able to taper appropriately and safely, they will do so during the screening period. If medication taken is for ADHD, a minimum of 7 days off stimulants and 21 days off nonstimulants will be required before baseline. A complete washout schedule, including common excluded medications and herbal preparations, is provided in Table 4.1-1 of the protocol. The screening visit may take place over multiple days to accommodate the subject's schedule, if needed.

Baseline: Following medication washout, subjects will return to the clinic for reassessment of eligibility criteria and establishment of baseline measurements. The interval between the first day of the screening visit (informed consent date) and the baseline visit (Day –1) must not exceed 28 days. Subjects who meet relevant entry criteria by the time they leave the clinic on the day of the baseline visit will be dispensed the trial medication.

CCI [redacted]

Open-Label Treatment: After completing the baseline assessments, eligible subjects will receive daily treatment with open-label centanafadine SR tablets during the open-label treatment period, as described in Section 3.2 of the protocol.

During the open-label treatment period, subjects will return to the clinic for evaluations at the end of Weeks 1, 2, 4, 8, 12, 16, 20, 26, 32, 38, 44, and 52/ET. A Week 48 visit will be conducted via telephone, the web, or other acceptable means of contact.

Follow-up: If any subject discontinues the trial early, every effort should be made to complete the Week 52/ET evaluations as soon as possible and whenever possible prior to starting any new medication or treatment. All subjects (completers and early withdrawals) will be evaluated for safety during a 10-day follow up (follow-up telephone calls at 1, 3, and 5 days after the last dose of IMP, in-clinic visits 2 and 7 days after the last dose of IMP, and a follow-up telephone call [or web, or other acceptable means of contact] 10 days after the last dose of IMP).

Late rollover subjects (i.e., those who were unable to rollover from Trial 405-201-00013

or Trial 405-201-00014 due to the inability of an in-person baseline visit in

Trial 405-201-00015) will follow the de novo path (see details in the protocol addendum).

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See Figure 3-1 and Figure 3-2 for schematics of the trial design for rollover and de novo subjects, respectively.

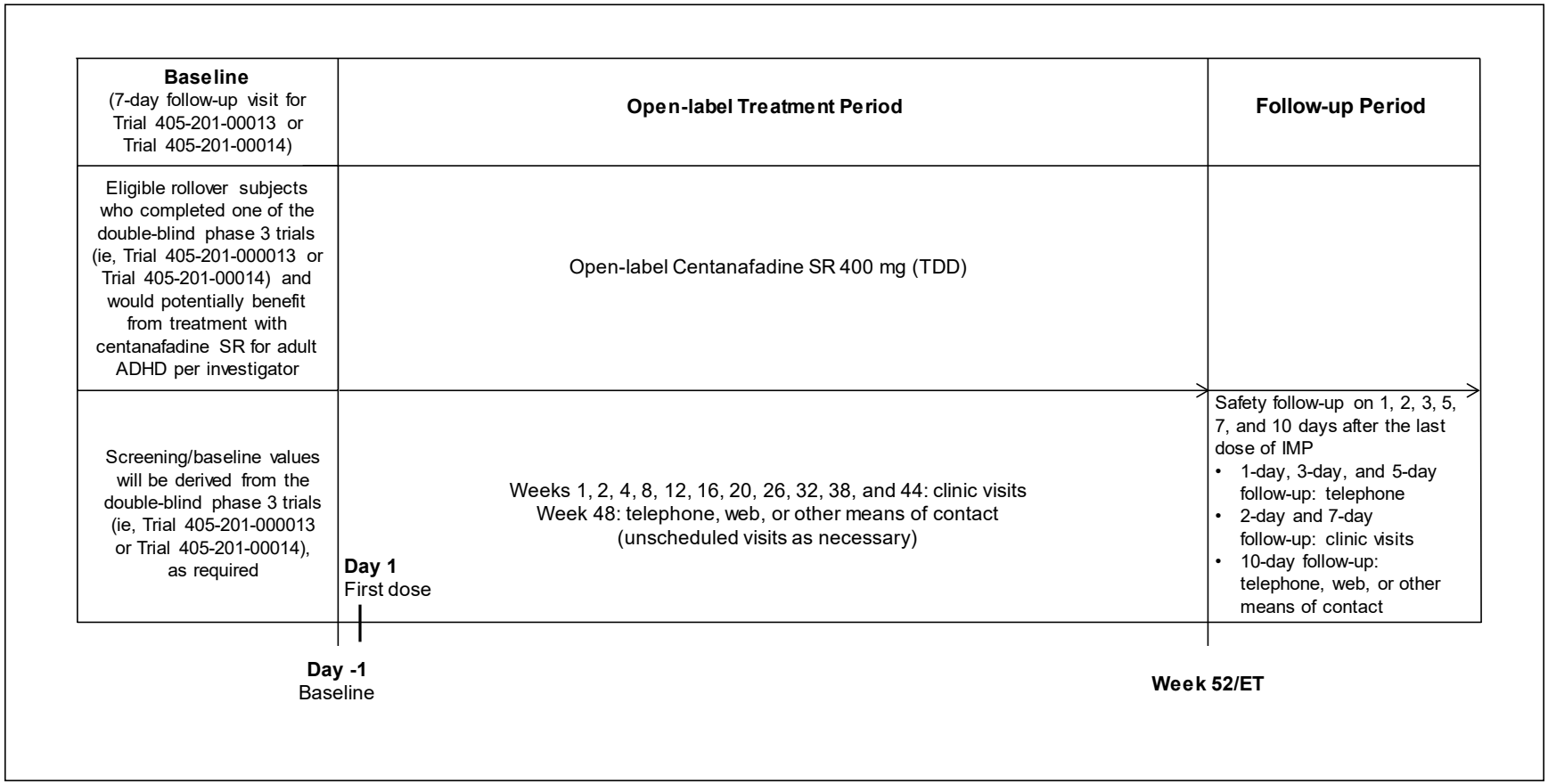

Figure 5.1 Trial Design Schematic - Rollover Subjects from Trial 405-201-00013 or Trial 405-201-00014

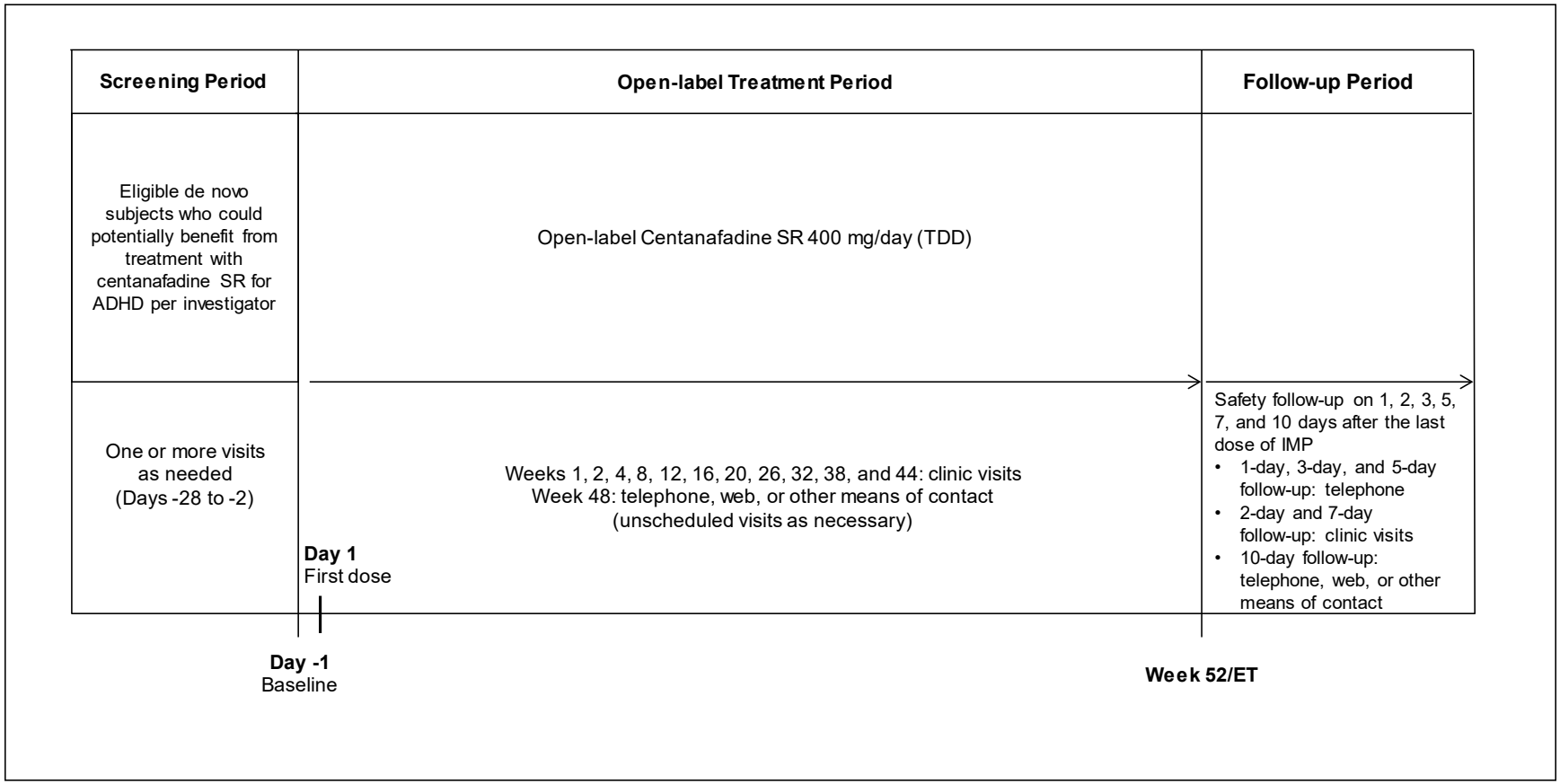

Figure 5.1 Trial Design Schematic - De Novo Subjects

4 Sample Size and Power Justification

The sample size is not based on statistical power considerations but on ICH/GCP requirements. The trial population will be derived from eligible subjects from the double-blind phase 3 trial (i.e., Trial 405-201-00013 or Trial 405-201-00014) and de novo subjects from selected sites. It is expected that approximately 560 completing rollover subjects from double-blind phase 3 trial (Trial 405-201-00013 or Trial 405-201-00014) and approximately 145 de novo subjects will be enrolled into this trial.

5 Data Sets for Analysis and Missing Data

5.1 Data Sets for Analysis

The following samples are defined for this trial:

- Enrolled Sample, which comprises all subjects who sign an eICF for the trial;
- Safety Sample, which comprises all subjects that will receive at least 1 dose of IMP;
- Efficacy Sample, which comprises those subjects in the Safety Sample who have at least 1 post baseline efficacy evaluation of AISRS Total Score

The observed case (OC) dataset will consist of the actual observations recorded at each visit and will be used to present summaries per trial week.

The last-observation-carried-forward (LOCF) data set will include data recorded at a given visit in the Treatment Phase or, if no observation is recorded at that visit, data carried forward from the previous visit in the Treatment Phase. Data collected prior to or on the first day of Treatment Phase dosing will not be carried forward or averaged with Treatment Phase data to impute missing values for the LOCF data set.

5.2 Handling of Missing Data

In order to assess the sensitivity of results due to missing data, 2 types of analyses will be performed: last observation carried forward (LOCF) and observed cases (OC). The OC dataset will consist of the actual observations recorded at each visit. The LOCF dataset will include data recorded at a scheduled visit, i.e., all OC data, or, if no observation is recorded at that visit, data will be carried forward from the previously scheduled visit. Baseline data will not be carried forward to impute missing values for the LOCF dataset. The OC dataset will be used for analyses at each trial visit and the LOCF dataset will be used for analyses at the last visit.

6 Study Conduct

Late rollover subjects will contribute as de novo subjects in the analyses as they could not rollover to 405-201-00015 due to the COVID-19 pandemic and they will follow the de novo path as described in the protocol addendum.

6.1 Subject Disposition, Completion Rate and Reasons for Discontinuation

Subject disposition will be summarized for the Enrolled Sample by parent study treatment group for rollover subjects, de novo subjects and overall.

Subject completion rate and reasons for discontinuation will be summarized for the Enrolled Sample by parent study treatment group for rollover subjects, de novo subjects and overall.

6.2 Treatment Compliance

For each subject, compliance in taking IMP is calculated by dividing the number of tablets taken by the total number of tablets the patients were scheduled to take during the study period. Compliance is calculated on the IMP for the study period. For lost-to-follow up patients, the last IMP end date record will be used as the treatment end date.

6.3 Protocol Deviation

Protocol deviations are summarized by center and type of deviation for enrolled subjects by parent treatment group. Listing of protocol deviation will list the treatment phases during which the deviations occurred.

7 Baseline Characteristics

7.1 Baseline Definition

Baseline is defined as the last available measurement prior to the first dose of open-label IMP in the open-label treatment period.

7.2 Demographic Characteristics

Baseline demographic characteristics including age, race, ethnicity, gender, weight, height, and body mass index (BMI) will be summarized by descriptive statistics (frequency, mean, median, standard deviation, maximum, minimum, and percentage when applicable) for the Enrolled Sample by parent study treatment group for rollover subjects, de novo subjects and overall.

7.3 Medical and Psychiatric History

A summary of medical and psychiatric history will be presented for the Enrolled Sample by parent study treatment group for rollover subjects, de novo subjects and overall.

A summary of the Adult ADHD Clinical Diagnostic Scale (ACDS) at screening will also be presented for the Enrolled Sample (by parent study treatment group for rollover subjects, de novo subjects and overall). The number and percentage of patients with each response to items A23-A41 from Section A (Childhood ADHD Symptoms Summary), B22-B39 from Section B (Adult ADHD Symptoms Summary), and C1-C5 will be presented.

7.4 Baseline Psychiatric Evaluation

Baseline psychiatric scale evaluation for the open-label treatment period will be summarized for the Enrolled Sample by parent study treatment group for rollover subjects, de novo subjects and overall. The mean, median, range and standard deviation will be used to summarize the assessments of: AISRS total score, CGI - Severity of Illness Score (CGI-S), and ADHD Impact Module – Adult (AIM-A).

8 Efficacy Analysis

Exploratory (efficacy) endpoints for the open-label trial are:

- Change from baseline in AISRS Total Score, by trial visit and at the last visit (i.e., Week 52/ET);
- Change from baseline in CGI-S, by trial visit and at the last visit (i.e., Week 52/ET);
- Change from baseline in AIM-A Score by trial visit and at the last visit;
- CCI [redacted]

Descriptive statistics will be provided for each endpoint and will be summarized at each trial visit based on the Efficacy Sample using the OC dataset and at the last visit using the LOCF dataset. These summaries will be presented by parent study treatment group for rollover subjects, de novo subjects and overall. Baseline is defined as the last available measurement prior to the first dose of open-label IMP in the open-label treatment period.

For AIM-A, the following will be provided:

1) Change from baseline for Question 1 (Global Quality of Life) and Questions 9Aa – 9Ai and 9Ba – 9Bi (Impact of Symptoms) of AIM-A at scheduled visits during the open-label treatment period, separately at every visit

2) Proportion of subjects in each response for the following questions of AIM-A at scheduled visits during the open-label treatment period, separately at every visit

    a. Questions 2-4 (Global Quality of Life)

    b. Questions 5a-5j (Living with ADHD)

    c. Questions 6a-6k (General Well-Being)

    d. Questions 7a-7j (Work, Home and School Performance and Daily Functioning)

    e. Questions 8a-8h (Relationships and Communication)

    f. Economic impact (5 items)

    g. Questions 17-23 (Demographics/Medication Status)

The key outcome measures from the CANTAB assessments include the following:

CCI

CCI

[redacted]

8.1 COVID-19 Related Supplementary Analyses

Summary statistics for mean and mean change from baseline in AISRS Total Score, by trial visit and at the last visit (i.e., Week 52/ET) and by visit type (face-to-face vs. virtual) based on the Efficacy Sample will be provided by parent study treatment group for rollover subjects, de novo subjects and overall.

9 Safety Analysis

The primary safety endpoint analysis is the frequency and severity of AEs in the open-label treatment period (see Section 9.1). Other standard safety variables to be analyzed include clinical laboratory tests, vital signs, body weight, waist circumference, BMI, 12-lead electrocardiograms (ECGs), and physical examinations. In addition, data from the following safety scales will be evaluated: C-SSRS and Study Medication Withdrawal Questionnaire (SMWQ).

Safety analyses will be conducted based on the Safety Sample, and summary statistics will be provided by parent study treatment group for rollover subjects, de novo subjects and overall, unless otherwise indicated.

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Unless otherwise specified, in general, analysis of safety data will be performed on observed case and for last visit.

9.1 Adverse Events

All adverse events will be coded by System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA). AEs that are sex-specific, e.g., ovarian cancer, will have their incidence rates evaluated for the specific sex.

Treatment-emergent AEs (TEAEs) are defined as AEs with an onset date on or after the first dose of IMP. In more detail, TEAEs are all adverse events which started after start of IMP; or if the event was continuous from baseline and was worsening, serious, study drug related, or resulted in death, discontinuation, interruption or reduction of study therapy. Adverse events occurring up to 30 days after the last day of IMP will be included in the summary tables.

The incidence of the following events in the open-label treatment phase will be summarized using the Safety Sample:

a) Treatment-emergent AEs (TEAEs)

b) TEAEs by severity

c) TEAEs potentially causally related to the IMP

d) TEAEs with an outcome of death

e) Serious TEAEs

f) TEAEs leading to discontinuation of the IMP

g) Treatment-emergent Adverse Events of Special Interest (AESI)

h) Abuse-related TEAEs and TEAEs involving MHIs (Medication handling irregularities)

AEs will be classified by Primary SOC and PT according to the MedDRA. AEs that are gender-specific, e.g., ovarian cancer, will have their incidence rates evaluated for the specific gender.

Incidence of TEAEs will be summarized for the open-label treatment period. Incidence of TEAEs by SOC and MedDRA PT will be summarized for sex and race.

Adverse Events of Special Interest

Newly acquired skin eruptions that are non-traumatic will be considered AESIs. These may include but are not limited to eruptions such as skin rashes, skin irritations, skin reactions, or acneiform lesions. This does not include localized contact irritation at ECG lead sites due to application or removal of lead adhesive.

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Refer to the separate rash workup plan for complete details, including reporting forms, and extra measures that must be performed to characterize any skin AESI of a newly acquired skin eruption that is non-traumatic. The trial site will have a local designated dermatologist available for immediate consultation during the trial for these AESIs.

9.2 Clinical Laboratory Tests

Summary statistics for mean and mean change from baseline in the routine clinical laboratory measurements, HbA1c, TSH, and PT/INR will be provided. Potentially clinically relevant results in laboratory tests will also be summarized.

Potentially clinically relevant laboratory measurement test results in the open-label treatment period will be identified, summarized, and listed. Criteria for identifying laboratory values of potential clinical relevance are provided in Appendix 2.

9.2.1 Drug Induced Liver Injury (DILI)

Total bilirubin level should be checked for any subject with increased ALT or AST levels ≥ three times the upper normal limits (ULN) or baseline.

- Reporting all DILI as SAE to the FDA based on Hy's Law:
  - AST or ALT ≥ 3 x ULN or baseline and
  - T_Bili ≥ 2 x ULN or baseline

A separate incidence table will be provided for DILI cases, and the corresponding listing will be provided for Safety Sample during the open-label treatment period.

9.3 Physical Examination and Vital Signs

Summary statistics for changes from baseline in vital signs will be provided for the Safety Sample. By-patient listings will be provided for physical examination.

Potentially clinically relevant vital signs measurements identified in the open-label treatment phase for the Safety Sample will be listed and summarized. Criteria for identifying vital signs of potential clinical relevance are provided in Appendix 1.

In addition, the change from baseline in weight, BMI, and waist circumference, and potentially clinically relevant abnormalities in weight, will also be summarized.

9.4 Electrocardiogram (ECG) Data

Summary statistics and incidence of potentially clinically relevant changes will be provided for ECG parameters.

For the analysis of QT and QTc, data from three consecutive complexes (representing three consecutive heart beats) will be measured to determine average values. The following QT corrections will be used for reporting purposes in the clinical study report:

1) QTcB is the length of the QT interval corrected for heart rate by the Bazett formula: $QTcB=QT/(RR)^{0.5}$ and
2) QTcF is the length of the QT interval corrected for heart rate by the Fridericia formula: $QTcF=QT/(RR)^{0.33}$
3) QTcN is the length of the QT interval corrected for heart rate by the FDA Neuropharm Division formula: $QTcN=QT/(RR)^{0.37}$

Potentially clinically relevant changes in the 12-lead ECG identified in the open-label treatment phase for the Safety Sample will be listed and summarized. Criteria for identifying ECG measurements of potential clinical relevance are provided in Appendix 3.

Categorical changes in ECG parameters during the open-label treatment period will be summarized based on the following criteria:

Categorical Change Criteria in QT/QTc Parameters

Classification	Category	Criteria
QT	New Onset (> 450 Msec)	New onset (>450 msec) in QT means a subject who attains a value > 450 msec during treatment period but not at baseline.
QTc *	New Onset (> 450 Msec)	New onset (> 450 msec) in QTc means a subject who attains a value > 450 msec during treatment period but not at baseline.
	New Onset (> 450 Msec) And > 10% Increase	New onset (> 450 msec) and > 10% increase in QTc means a subject who attains a value > 450 msec and > 10% increase during treatment period but not at baseline
	New Onset (> 500 Msec)	New onset (> 500 msec) in QTc means a subject who attains a value > 500 msec during treatment period but not at baseline.
	Increase 30 - 60 Msec	Increase from baseline value > 30 and ≤ 60 msec in QTc
	Increase > 60 Msec	Increase from baseline value > 60 msec in QTc

* QTc categorical change criteria apply to QTcB, QTcF and QTcN.

9.5 Suicidality Data

Suicidality will be monitored during the study using the C-SSRS and will be summarized as number and percentage of subjects reporting any suicidal behavior, ideation, behavior by type (4 types), ideation by type (5 types) and treatment emergent suicidal behavior and ideation. Summary will be provided for the open-label treatment period for the Safety Sample.

Suicidality is defined as report of at least one occurrence of any type of suicidal ideation or at least one occurrence of any type of suicidal behavior during assessment period (count each person only once).

Treatment emergent suicidal behavior and ideation is summarized by four types: Emergence of suicidal ideation, Emergence of serious suicidal ideation, Worsening of suicidal ideation, Emergence of suicidal behavior.

Emergence of suicidal behavior/ideation is defined as report of any type of suicidal behavior/ideation during treatment when there was no baseline suicidal behavior/ideation.

Emergence of serious suicidal ideation is defined as observation of suicidal ideation severity rating of 4 or 5 during treatment when there was no baseline suicidal ideation.

Worsening of suicidal ideation is defined as a suicidal ideation severity rating that is more severe than it was at baseline.

For the open-label treatment period analyses, the last available measurement prior to the first dose of open-label IMP is being used as “Baseline”.

9.6 SMWQ

Medication withdrawal symptoms assessed by SMWQ total scores at the scheduled visits during the open-label treatment period and follow-up period will be summarized for the Safety Sample by parent study treatment group for rollover subjects, de novo subjects and overall. The number of patients, mean, median, range and standard deviation will be presented.

9.7 Medication Handling Irregularities (MHIs) and Events Subject to Additional Monitoring (ESAMs)

MHIs and ESAMs will be summarized for the Safety Sample by treatment group and overall. By-patient listings will be provided.

9.8 Concomitant Medications

Number and proportion of patients taking concomitant medications prior to the open-label treatment phase, during the open-label treatment phase, and after study therapy are tabulated by

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drug classification using the World Health Organization (WHO) drug dictionary for the Safety Sample.

9.9 Extent of Exposure

The start date of the open-label study therapy - centanafadine - will be the first day of dosing during the open-label treatment phase. The number and percentage of patients who receive study medication during the open-label treatment phase, will be presented by week. Each dosing week will be based on the actual week; i.e., Day 1-7 in Week 1, Day 8-14 in Week 2, etc. This summary will be performed on the Safety Sample.

The mean daily dosage will be summarized by week using descriptive statistics. The mean daily dosage per patient per week will be determined for each week of the study. This will be calculated by dividing the sum of individual total doses by the number of days in the week interval. The summary will contain the number of patients receiving study medication during the open-label treatment phase, and the mean and range of the mean daily dose for each week

10 Conventions

10.1 Study Visit Windows

Study visit windows will be used to map visits using study day intervals. This visit window convention applies to tables and listings for all efficacy and safety scales (AISRS, CGI-S, AIM-A, CGI Change from Baseline, CCI [redacted]). This derived study window variable will be named as WEEK and will be footnoted. In listings it will be listed along with the eCRF study visit.

Table 10-1 shows classifications for study day intervals in the open-label treatment period. The variable “target day” is defined using the number of days since the start of open-label dosing in the open-label treatment period. The first day of open-label dosing is defined as “Day 1”.

If more than one observation falls within a particular study day interval, then the last observation within that interval is used. Evaluations occurring more than three days after the last open-label dosing date and evaluations occurring during the follow-up period will not be mapped into study visit windows and will be excluded from the open-label treatment period analysis.

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Table 10-1: Study Day and Visit Windows in the Open-label Treatment Period

Week	Target Day [a]	Study Day Interval [a]
1	7	2-10
2	14	11-21
4	28	22-42
8	56	43-70
12	84	71-98
16	112	99-126
20	140	127-161
26	182	162-203
32 [c]	224	204-245
38 [c]	266	246-287
44 [c]	308	288-336
52 [c]	364	337-385 [b]

[a] Relative to the first day of open-label IMP in the open-label treatment period.

[b] Evaluations occurring more than three days after the last open-label dosing date and evaluations occurring during the follow-up period will be excluded from the open-label treatment period analyses.

10.2 Scales: Rules for Scoring and Handling of Missing Data

10.2.1 Adult ADHD Investigator Symptom Rating Scale (AISRS)

The AISRS is a modified version of the ADHD Rating Scale that reflects the impact and severity of ADHD among adults and will be administered at each scheduled visit in the open-label treatment period, and at 2 and 7 days after the last dose of IMP in the follow-up period. It is a clinician-administered scale that measures the 18 symptoms of adult ADHD using a Likert scale: 0 (none); 1 (mild); 2 (moderate); and 3 (severe) and uses a semi-structured interview methodology with suggested prompts for each item to improve interrater reliability. The scale's 18 items directly correspond to the 18 DSM-5 symptoms of ADHD where 9 inattentive items alternate with 9 hyperactive impulsive items. The maximum total score for the scale is 54 points, with 27 points for each subscale. The total score is the sum of both the Inattentive and Hyperactive Impulsive subscales.

The AISRS inattentive subscale score and hyperactive-impulsive subscale score, as well as the AISRS total score is set to be missing if more than one item of a subscale is missing for inattentive subscale or hyperactive-impulsive subscale, separately. If one item is missing for a given subscale (inattentive or hyperactive-impulsive), then the subscale score is derived as the

mean of scores from the 8 non-missing items multiplied by 9. All imputed scores are rounded to the first decimal place. The 9 inattentive items consist of the 9 odd numbered items and the 9 hyperactive impulsive items consist of the 9 even numbered items.

10.2.2 Clinical Global Impression Severity of Illness Scale – Modified for Attention-Deficit Hyperactivity Disorder

The CGI-S modified is an observer-rated scale that will be used to measure symptom severity. To perform this assessment, the investigator or rater will respond to the following question: "Considering your total clinical experience with adult ADHD, how mentally ill is the patient at this time?" Response choices include: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill patients. CGI-S is assessed at each scheduled visit in the open-label treatment period.

10.2.3 Attention-Deficit Hyperactivity Disorder Impact Module – Adult (AIM-A)

The AIM-A is a subject self-report questionnaire which assesses quality of life in adults with ADHD. The questionnaire has 4 global quality of life items, 5 economic impact items, and 5 multi-item scales that assess the following key concepts: Living with ADHD, General Well-Being, Work, Home and School Performance and Daily Functioning. Additionally, Relationships and Communication, and Impact of Symptoms are also included.

10.2.4 Study Medication Withdrawal Questionnaire (SMWQ)

The SMWQ is a questionnaire to assess withdrawal symptoms. The SMWQ is a modification of the Amphetamine Withdrawal Questionnaire in which the terms "amphetamines and methamphetamine" are replaced with the term "the study medication." The SMWQ is assessed at Week 52/ET in the open-label treatment period and at 1, 2, 3, 5, 7, and 10 days after the last dose of IMP in the follow-up period.

10.2.5 Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidality will be monitored during the trial using the C-SSRS. The C-SSRS is a semi-structured interview that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The interview includes definitions and suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior has occurred. The interview and rating for the C-SSRS must be completed by a licensed clinician who has been successfully trained to rate this scale by the sponsor or a designee and is medically responsible for the subject. Documentation of trial training should be maintained in the investigational site's files.

This trial will use the “Baseline/Screening” and “Since Last Visit” versions of the scale. The “Baseline/Screening” version, which assesses the life-time experience of the subject with suicide events and suicidal ideation and the occurrence of suicide events or ideation within a specified time period prior to entry into the trial, will be completed for all de novo subjects at the screening visit to determine the eligibility. Any subject with active suicidal ideation within the last 30 days, suicidal behaviors within the last year, or who in the clinical judgment of the investigator presents a serious risk of suicide should be excluded from the trial. The “Since Last Visit” C-SSRS form will be completed at all other in-clinic visits for all subjects (rollover and de novo).

The C-SSRS is assessed at each scheduled visit in the screening period (for de novo subjects), the open-label treatment period and at 2 and 7 days after the last dose of IMP in the follow-up period.

11 Potential Clinical Relevance Criteria from Protocol

Appendix 1 Criteria for Identifying Vital Signs of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Heart Rate[b]	> 100 bpm < 50 bpm	≥ 10 bpm increase ≥ 10 bpm decrease
Systolic Blood Pressure[b]	≥ 140 mmHg < 90 mmHg	≥ 20 mmHg increase ≥ 20 mmHg decrease
Diastolic Blood Pressure[b]	≥ 90 mmHg < 60 mmHg	≥ 10 mmHg increase ≥ 10 mmHg decrease
Orthostatic Hypotension	≥ 30 mmHg decrease in systolic blood pressure and/or a ≥ 20 mmHg in diastolic blood pressure after at least 3 minutes of standing compared to the previous supine blood pressure.	Not Applicable (baseline status not considered)
Orthostatic Tachycardia	≥ 25 bpm increase in heart rate from supine to standing	Not Applicable (baseline status not considered)
Weight	-	≥ 7% increase ≥ 7% decrease

[a] In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

[b] As defined in "Supplementary Suggestions for Preparing an Integrated Summary of Safety Information in an Original NDA Submission and for Organizing Information in Periodic Safety Updates," FDA Division of Neuropharmacological Drug Products draft (2/27/87).

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Appendix 2 Criteria for Identifying Laboratory Values of Potential Clinical Relevance

Laboratory Tests	Criteria
Chemistry	
AST (SGOT)	≥ 3 x upper limit of normal (ULN)
ALT (SGPT)	≥ 3 x ULN
Alkaline phosphatase	≥ 3 x ULN
BUN	≥ 30 mg/dL
Creatinine	≥ 2.0 mg/dL
Uric Acid	
Men	≥ 10.5 mg/dL
Women	≥ 8.5 mg/dL
Bilirubin (total)	≥ 2.0 mg/dL
Creatine Phosphokinase (CPK)	> 3 x ULN
Hematology	
Hematocrit	
Men	≤ 37 % and decrease of ≥ 3 percentage points from Baseline
Women	≤ 32 % and decrease of ≥ 3 percentage points from Baseline
Hemoglobin	
Men	≤ 11.5 g/dL
Women	≤ 9.5 g/dL
White blood count	≤ 2,800/ mm^3 or ≥ 16,000/ mm^3
Eosinophils	≥ 10%
Neutrophils	≤ 15%
Absolute neutrophil count	≤ 1,500/ mm^3
Platelet count	≤ 75,000/ mm^3 or ≥ 700,000/ mm^3
Urinalysis	
Protein	Increase of ≥ 2 units
Glucose	Increase of ≥ 2 units
Additional Criteria	
Chloride	≤ 90 mEq/L or ≥ 118 mEq/L
Potassium	≤ 2.5 mEq/L or ≥ 6.5 mEq/L
Sodium	≤ 126 mEq/L or ≥ 156 mEq/L
Calcium	≤ 8.2 mg/dL or ≥ 12 mg/dL
Glucose	
Fasting	≥ 100 mg/dL
Non-Fasting	≥ 200 mg/dL
Total Cholesterol, Fasting	≥ 240 mg/dL
LDL Cholesterol, Fasting	≥ 160 mg/dL
HDL Cholesterol, Fasting	
Men	< 40 mg/dL
Women	< 50 mg/dL
Triglycerides, Fasting	≥ 150 mg/dL

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Appendix 3 Criteria for Identifying ECG Measurements of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Rate		
Tachycardia	≥ 120 bpm	increase of ≥ 15 bpm
Bradycardia	≤ 50 bpm	decrease of ≥ 15 bpm
Rhythm		
Sinus tachycardia[b]	≥ 120 bpm	increase of ≥ 15 bpm
Sinus bradycardia[c]	≤ 50 bpm	decrease of ≥ 15 bpm
Supraventricular premature beat	all	not present → present
Ventricular premature beat	all	not present → present
Supraventricular tachycardia	all	not present → present
Ventricular tachycardia	all	not present → present
Atrial fibrillation	all	not present → present
Atrial flutter	all	not present → present
Conduction		
1° atrioventricular block	PR ≥ 200 msec	increase of ≥ 50 msec
2° atrioventricular block	all	not present → present
3° atrioventricular block	all	not present → present
Left bundle-branch block	all	not present → present
Right bundle-branch block	all	not present → present
Pre-excitation syndrome	all	not present → present
Other intraventricular conduction block[d]	QRS ≥ 120 msec	increase of ≥ 20 msec
Infarction		
Acute or subacute	all	not present → present
Old	all	not present → present ≥ 12 weeks post study entry
ST/T Morphological		
Myocardial Ischemia	all	not present → present
Symmetrical T-wave inversion	all	not present → present
Increase in QTc	QTcF ≥ 450 msec (men) QTcF ≥ 470 msec (women)	

[a] In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

[b] No current diagnosis of supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, atrial flutter, or other rhythm abnormality.

[c] No current diagnosis of atrial fibrillation, atrial flutter, or other rhythm abnormality.

[d] No current diagnosis of left bundle branch block or right bundle branch block.

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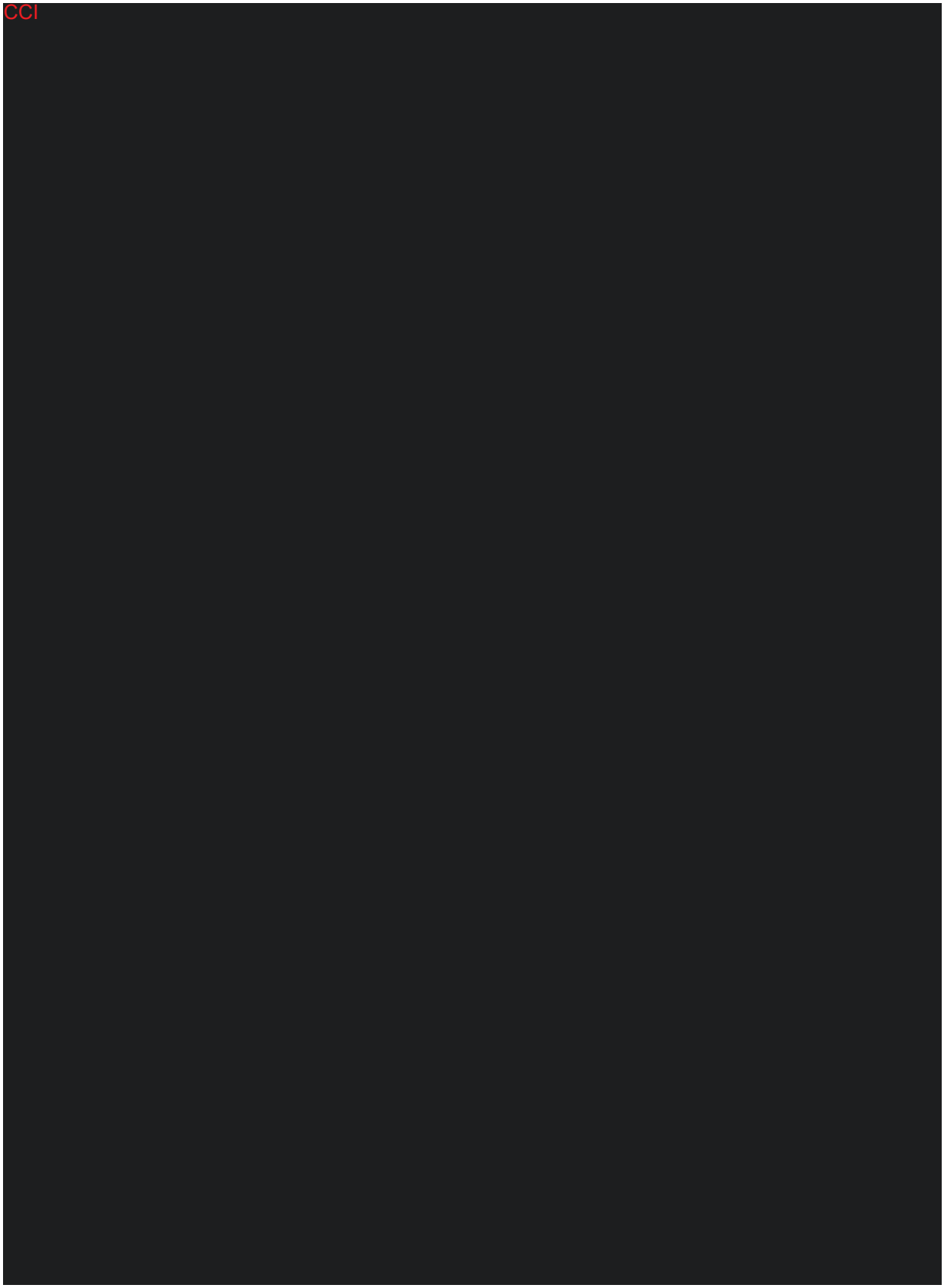

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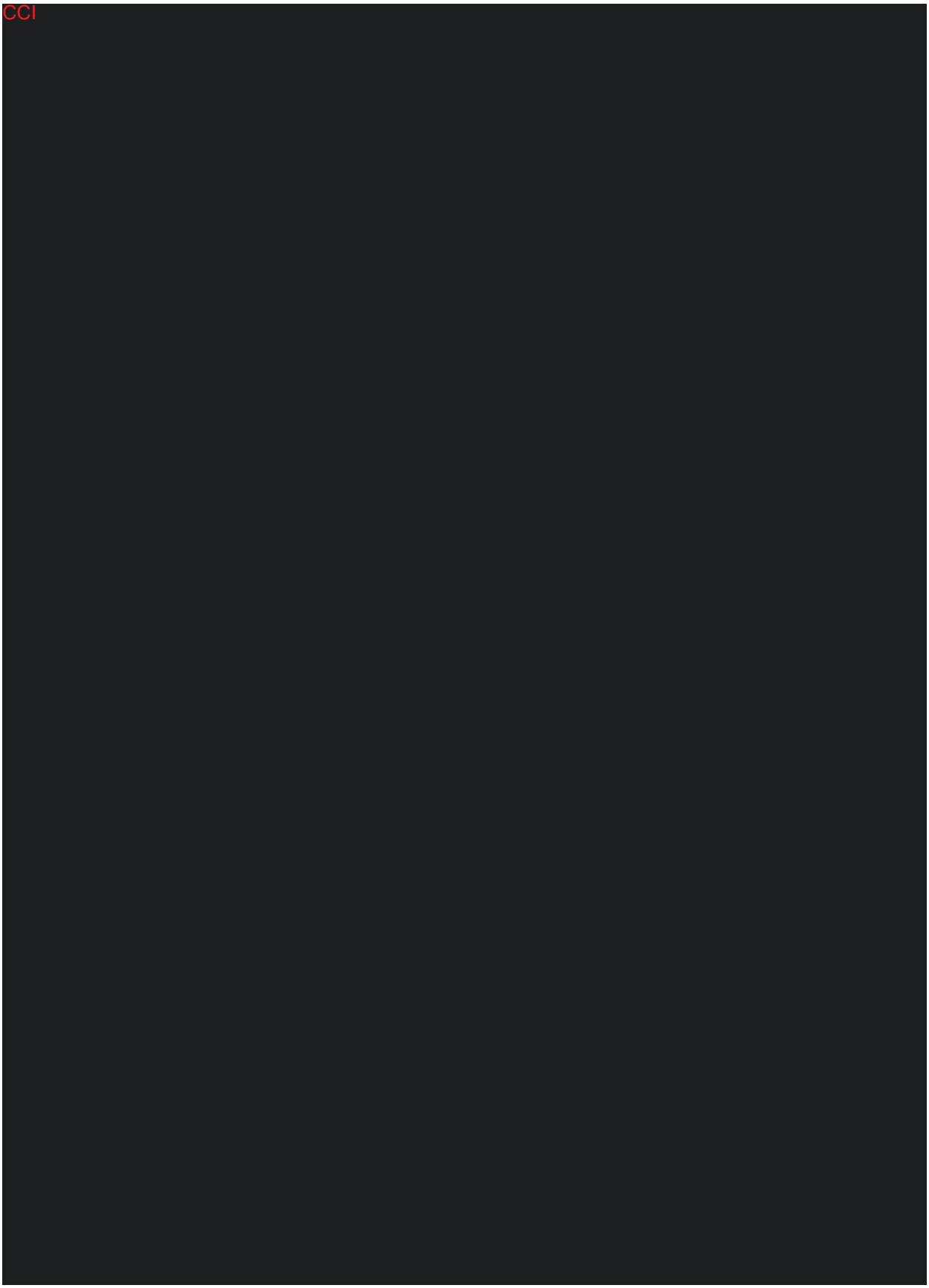

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