Title: A Randomized, Double-blind, Placebo-Controlled, Phase 1 Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Single Ascending Dose and Multiple Doses with Titration of TAK-935 in Healthy Japanese Subjects

NCT Number: NCT04461483

Statistical analysis plan Approve Date: 20-NOV-2020

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If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-935-1004

A Randomized, Double-blind, Placebo-Controlled, Phase 1 Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Single Ascending Dose and Multiple Doses with Titration of TAK-935 in Healthy Japanese Subjects.

PHASE 1

Version: Second

Date: 20 Nov 2020

Prepared by:

PPD

Based on:

Protocol Version: Amendment 2

Protocol Date: 02 July 2020

1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUEC	area under the effect-time curve
BID	twice daily
BMI	body mass index
BP	blood pressure
CH24H	cholesterol 24-hydroxylase
CL/F	apparent clearance after extravascular administration
Cmax	maximum observed plasma concentration
CNS	central nerve system
C-QTc	concentration-QTc
CRF	case report form
C-SSRS	Columbia Suicide Severity Rating Scale
DEE	developmental epileptic encephalopathies
CCI	CCI
eCRF	electronic case report form
Emax	maximum drug-induced effect
Et	observed effect at time t
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDL	high density lipoprotein
HR	heart rate
ICH	International Conference on Harminsation of Technical Requirements for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDL	low density lipoprotein
LFT	liver function test
MD	multiple doses

MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
CCI	CCI
MMSE	mini mental state examination
MR	metabolic ratio
OTC	over the counter
PD	pharmacodynamics
PGx	pharmacogenomics
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PT	preferred term
PT/INR	prothrombin time / international normalized ratio
QD	once daily
QTcF	QT interval with Frederica correction method
Rac	accumulation ratio
RBC	red blood cells
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
t1/2z	terminal disposition phase half-life
Tmax	time of first occurrence of Cmax
TSH	thyroid stimulating hormone
ULN	upper limit of normal
Vz/F	apparent volume of distribution during the terminal disposition phase after extravascular administration
WBC	white blood cells
24HC	24*S*-hydroxycholesterol

4.0 OBJECTIVES

4.1 Primary Objectives

- The primary objective of the study is to evaluate the safety and tolerability of TAK-935 in healthy Japanese subjects when administered as single oral dose or multiple oral doses with titration.

4.2 Secondary Objectives

- The secondary objective of the study is to evaluate the PK of TAK-935 in healthy Japanese subjects when administered as single oral dose or multiple oral doses with titration.

4.3 CCI

CCI

[redacted]

4.4 Study Design

This study consists of 2 parts, which is a randomized, double-blind, placebo-controlled study to assess safety, tolerability, and PK and PD of TAK-935 when administered via oral administration in healthy Japanese subjects.

Part 1 is a SAD study, consisting of 3 cohorts containing 8 subjects each. On Day 1 of each dose level, a single dose of TAK-935 or placebo will be administered, and safety, PK and PD will be evaluated.

Part 2 is a MD with titration study within the same subjects. TAK-935 or placebo will be administered to the 9 subjects at the dose of 100 mg BID from Day 1 to Day 7, then 200 mg BID from Day 8 to Day 14, and finally 300 mg BID from Day 15 to Day 21, and safety, PK and PD will be confirmed. The planned dose levels of TAK-935 to be evaluated are outlined in Table 4.a

Table 4.a Outline of the Study Parts and Planned Dosing Cohorts

Part	Cohort	Daily dose level (mg)	Dosing regimen	Randomization
Part 1	1	200	Single oral dose under fasted condition	Subjects will be randomized to TAK-935 or placebo at a ratio of 6:2 in each cohort, double-blind. No stratification variables will be used for
	2	600		
	3	1200		

				randomization.
Part 2	4	Day 1-7: 200 (100 mg BID) Day 8-14: 400 (200 mg BID) Day 15-21: 600 (300 mg BID)	Multiple oral doses up/titration with TAK-935 for 7 days per each dose level within the same subjects under fasted condition	Subjects will be randomized to TAK-935 or placebo at a ratio of 6:3, double-blind. No stratification variables will be used for randomization.

BID: twice daily

Study Population

Study Population: Healthy Japanese subjects.

Planned Number of Subjects

Part 1 (SAD): Total of 24 subjects

- Cohort 1: 8 subjects
- Cohort 2: 8 subjects
- Cohort 3: 8 subjects

Part 2 (MD): Total of 9 subjects

- Cohort 4: 9 subjects (dose up/titration within the same subjects)

Key Study Procedure Overview

<Part 1>

After the screening visit, eligible participants will check-in on Day-2. On Day 1, eligible participants will be randomized 6:2 to TAK-935 or placebo in each dose group in a double-blinded fashion. No stratification variables will be used for randomization. On the same day, study drug will be administered by oral administration of a single dose to each subject at each dose level. The subjects will be discharged on Day 3. Intensive PK sampling will be performed from Day 1 to Day 3.

<Part 2>

After the screening visit, eligible participants will check-in on Day-2. On Day 1, eligible participants will be randomized 6:3 to TAK-935 or placebo in a double-blinded fashion. No stratification variables will be used for randomization. Study drug will be administered every day by oral administration of multiple dosing. The 3 subjects receiving placebo will receive placebo throughout the study. The other 6 subjects will receive TAK-935 with up-titration firstly at 100 mg BID from Day 1 to Day 7, then at 200 mg BID from Day 8 to Day 14, and finally at 300 mg BID from Day 15 to Day 21, successively. The subjects will be discharged on Day 24. Intensive PK sampling will be performed on Day 1, Day 7, Day 14 and Day 21.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

The primary endpoint of the study includes:

Safety endpoint:

- Percentage of subjects who experience at least 1 TEAE

5.2 Secondary Endpoints

Secondary endpoints include:

Pharmacokinetic endpoints:

- Maximum observed plasma concentration (Cmax).
- Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration (AUClast) (Part 1 only).
- AUC from time 0 to time of infinity (AUCinf) (Part 1 only).
- AUC from time 0 to 24 hours (AUC24) (Part 1 only).
- AUC during a dosing interval (AUCtau) at steady state (Part 2 only).

5.3 CCI

CCI

CCI

6.0 DETERMINATION OF SAMPLE SIZE

The sample sizes of 8 subjects for each of the cohorts in Part 1 and 9 subjects for Part 2 (Part 1: 6 active 2 placebo in each cohort, Part 2: 6 active 3 placebo as total) are considered to be sufficient for the evaluation of safety, tolerability, and PK of each cohort. Sample sizes were not based on statistical power considerations.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

7.1.1 Study Definitions

The following definitions and calculation formulas will be used.

- Treatment-emergent adverse event (TEAE): An adverse event whose onset occurs on or after the start of study drug
- Pretreatment event (PTE): Any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of study drug
- Descriptive statistics: Number of subjects, mean, standard deviation, maximum, minimum, and quartiles
- Dose:
  - Part 1:
    - Placebo (cohort 1, 2, and 3 combined)
    - TAK-935 200 mg (cohort 1)
    - TAK-935 600 mg (cohort 2)
    - TAK-935 1200 mg (cohort 3)
  - Part 2:
    - Placebo
    - TAK-935
- Visit: Time point at which the assessment was made
- Coefficient of variation (CV) (%): Standard deviation / mean * 100
- Geometric CV (%): (exp(log-transformed standard deviation)^2 - 1) * 100
- QTcF interval (msec): QT interval (msec) / (RR interval (sec))$^{0.33}$ (rounded to the nearest whole number)
- Duration of study after baseline (days): Date of last visit/contact - date of first dose + 1
- Percent change from time-matched baseline: CCI [redacted] For Part 1, change from time-matched baseline will be calculated by subtracting the value of Day -1 from the value of Day 1 in the matching column in Table 7.a for each subject. For Part 2, change from

time-matched baseline will be calculated by subtracting the value of Day -1 from the value of Day 1 or later in the matching column in Table 7.b for each subject.

Table 7.a Percent Change from Time-Matched Baseline for Part 1

Day	Time postdose (hour)						
Day -1	Predose	1	4	8	12	24*	24*
Day 1	Predose	1	4	8	12	24	48

* : Just prior to dosing.

Table 7.b Percent Change from Time-Matched Baseline for Part 2

Day	Time postdose (hour)					
Day -1	Predose	1	4	8	12	24*
Day 1-18	Predose	-	-	-	-	-
Day 21	Predose	1	4	8	12	24

* : Just prior to dosing.

7.1.2 Definition of Study Visit Windows

There will be no new study visit windows defined for the summaries in this SAP. For all variables, evaluable data will be used as entered in the CRF according to the scheduled Study Time.

7.2 Analysis Sets

- Safety Analysis Set:
  All subjects who received at least 1 dose of study drug.
- Pharmacokinetic Analysis Set:
  All subjects who received at least 1 dose of study drug and had at least 1 estimable PK parameter.
- CCI
  CCI [redacted]

7.3 Disposition of Subjects

7.3.1 Study Information

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variable(s):

Date First Subject Signed Informed Consent Form

Date of Last Subject's Last Visit/Contact

MedDRA Version

SAS Version Used for Creating the Datasets

Analytical Method(s):

(1) Study Information

Study information shown in the analysis variables section will be provided.

7.3.2 Screen Failures

Analysis Set:

All Subjects Who Did Not Enter the Treatment Period

Analysis Variable(s):

Age (years)

Gender [Male, Female]

Analytical Method(s):

(1) Screen Failures

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

7.3.3 Subject Eligibility

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variable(s):

Eligibility Status

[Eligible for Randomization, Not Eligible for Randomization]

Primary Reason for Subject Not Being Eligible

[Adverse Event, Death, Lost to Follow-up, Protocol Deviation, Sample Size Sufficient, Screen Failure, Study Terminated by Sponsor, Withdrawal by Subject, Other]

Analytical Method(s):

(1) Eligibility for Randomization

Frequency distributions will be provided. When calculating percentages for the primary reasons for subject not being eligible, the total number of ineligible subjects will be used as the denominator.

7.3.4 Disposition of Subjects

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variable(s):

Study Completion Status

[Completed All Planned Study Visits, Did Not Complete All Planned Study Visits]

Reason for Discontinuation of Study Visits

[Adverse Event, Death, Lost to Follow-up, Protocol Deviation, Study Terminated by Sponsor, Withdrawal by Subject, Other]

Analytical Method(s):

(1) Disposition of Subjects

Frequency distributions will be provided by dose and overall for each of Part 1 and Part 2. When calculating percentages for the reasons for discontinuation, the total number of subjects who did not complete all planned study visits will be used as the denominator.

7.3.5 Study Completion Status

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variables:

Study Completion Status

[Completed Study, Prematurely Discontinued Study]

Reason for Discontinuation of Study

[Adverse Event, Death, Lost to Follow-up, Protocol Deviation, Study Terminated by Sponsor, Withdrawal by Subject, Other]

Categories:

Duration of Study after Baseline (days)

[0, 1<= - <=7, 8<= - <=14, 15<= - <=23, 24<= - <=Max]

Analytical Method:

(1) Study Completion Status

Frequency distribution will be provided for each category of duration of study period by dose and overall. This table will only be provided for Part 2.

7.3.6 Protocol Deviations and Analysis Sets

7.3.6.1 Protocol Deviations

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variable(s):

Significant Protocol Deviation

[Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol, Study Medication, Withdrawal Criteria, Major GCP Violations]

Analytical Method(s):

(1) Protocol Deviations

Frequency distribution will be provided by dose and overall for each deviation category for each of Part 1 and Part 2. A subject who has several deviations will be counted once in each appropriate category. A subject who has several deviations that can be classified into the same category will be counted only once.

7.3.6.2 Analysis Sets

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variable(s):

Handling of Subjects

[Categories are based on the specifications in Subject Evaluability List]

Analysis Sets

Safety Analysis Set [Included]

Pharmacokinetic Analysis Set [Included]

CCI [redacted]

Analytical Method(s):

(1) Subjects Excluded from Analysis Sets

(2) Analysis Sets

Frequency distributions will be provided by dose for each of Part 1 and Part 2. For (1), a subject who has several reasons for exclusion will be counted once in each appropriate category. A subject who has several reasons for exclusion that can be classified into the same category will be counted only once.

7.4 Demographic and Other Baseline Characteristics

Analysis Set:

Safety Analysis Set

Analysis Variable(s):

Age (years)

Gender [Male, Female]

Height (cm)

Weight (kg)

BMI (kg/m^2)

Smoking Classification

[Never, Current, Former]

Alcohol Classification

[Daily, A Few Times Per Week, A Few Times Per Month, No]

Caffeine Classification [Yes, No]

Analytical Method(s):

(1) Summary of Demographics and Baseline Characteristics

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided by dose and overall for each of Part 1 and Part 2.

7.5 Medical History and Concurrent Medical Conditions

Not applicable.

7.6 Medication History and Concomitant Medications

Not applicable.

7.7 Study Drug Exposure and Compliance

Analysis Set:

Safety Analysis Set

Analysis Variable(s):

Number of Times the Study Drug was Taken

[1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14<= - <=Max]

Analytical Method(s):

(1) Study Drug Exposure

This table will only be provided for Part 2. Frequency distributions will be provided by dose for each dose level of Part 2 (i.e., Period 1 (100 mg BID), Period 2 (200 mg BID), and Period 3 (300 mg BID)).

7.8 Efficacy Analysis

Not applicable

7.8.1 Primary Efficacy Endpoint(s)

Not applicable.

7.8.2 Secondary Efficacy Endpoint(s)

Not applicable.

7.8.3 Additional Efficacy Endpoint(s)

Not applicable.

7.8.4 Statistical/Analytical Issues

7.8.4.1 Adjustments for Covariates

Not applicable.

7.8.4.2 Handling of Dropouts or Missing Data

For plasma concentrations and laboratory test results, values below the lower limit of quantification will be treated as zero when calculating the descriptive statistics. For laboratory test results, values above the upper limit of quantification will be treated as the upper limit value when calculating the descriptive statistics.

7.8.4.3 Multicenter Studies

Not applicable.

7.8.4.4 Multiple Comparison/Multiplicity

Not applicable.

7.8.4.5 Use of an "Efficacy Subset" of Subjects

Not applicable.

7.8.4.6 Active-Control Studies Intended to Show Equivalence or Non-Inferiority

Not applicable.

7.8.4.7 Examination of Subgroups

Not applicable.

7.9 Pharmacokinetic/[CCI redacted]

7.9.1 Pharmacokinetic Analysis

7.9.1.1 Plasma Concentrations

Part 1

Analysis Set:

Pharmacokinetic Analysis Set

Analysis Variable(s):

Plasma Concentrations of TAK-935 Analyte (TAK-935, [CCI redacted])

Visit:

Predose, 0.25, 0.5, 1, 1.5, 2, 4, 8, 10, 12, 16, 24 and 48 Hours Postdose

Analytical Method(s):

The following summaries will be provided by dose. Subjects who were administered placebo will be excluded from the analysis.

(1) Summary of Plasma Concentrations by Visit

Descriptive statistics and CV will be provided by visit.

(2) Case Plots of Plasma Concentrations

Plots over time for each subject will be provided. Visit will be plotted on the horizontal axis and the analysis variable will be plotted on the vertical axis. In addition to plots with the vertical axis as a normal scale, plots with the vertical axis as a common logarithmic scale will also be provided.

(3) Mean and Standard Deviation Plot of Plasma Concentrations

Mean and standard deviation will be plotted. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

(4) Mean Plot of Plasma Concentrations

Mean will be plotted. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a common logarithmic scale.

Part 2

Analysis Set:

Pharmacokinetic Analysis Set

Analysis Variable(s):

Plasma Concentrations of TAK-935 Analyte (TAK-935, [redacted])

Visit:

Predose, 0.25, 0.5, 1, 2, 4, 8, 10 and 12 Hours Postdose on Day 1, Day 7, Day 14 and Day 21

Analytical Method(s):

The following summaries will be provided. Subjects who were administered placebo will be excluded from the analysis.

(1) Summary of Plasma Concentrations by Visit

Descriptive statistics and CV will be provided by visit.

(2) Case Plots of Plasma Concentrations

Plots over time for each subject will be provided. Visit will be plotted on the horizontal axis and the analysis variable will be plotted on the vertical axis. In addition to plots with the vertical axis as a normal scale, plots with the vertical axis as a common logarithmic scale will also be provided.

(3) Mean and Standard Deviation Plot of Plasma Concentrations

Mean and standard deviation will be plotted. A separate plot will also be provided for each analysis variable for each day. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

(4) Mean Plot of Plasma Concentrations

Mean will be plotted. A separate plot will also be provided for each analysis variable for each day. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a common logarithmic scale.

7.9.1.2 Pharmacokinetic Parameters

Part 1

Analysis Set:

Pharmacokinetic Analysis Set

Analysis Variable(s):

Pharmacokinetic parameters of TAK-935:

Cmax, Tmax, AUClast, AUCinf, AUC24, T1/2z, Lambda z, CL/F, Vz/F

Pharmacokinetic parameters of [redacted]

Cmax, Tmax, AUClast, AUCinf, AUC24, T1/2z, Lambda z, MR

Analytical Method(s):

The following summaries will be provided by dose. Subjects who were administered placebo will be excluded from the analysis.

(1) Summary of Pharmacokinetic Parameters

For Cmax, AUClast, AUCinf, and AUC24, descriptive statistics, geometric mean, CV, and geometric CV will be provided. For Tmax, descriptive statistics will be provided. For all other variables, descriptive statistics and CV will be provided.

(2) Summary of Pharmacokinetic Parameters Normalized by Dose

For Cmax, AUClast, and AUCinf that have been normalized by dose, descriptive statistics, geometric mean, CV, and geometric CV will be provided.

Part 2

Analysis Set:

Pharmacokinetic Analysis Set

Analysis Variable(s):

Pharmacokinetic parameters of TAK-935:

Cmax, Tmax, AUClast, AUCtau, T1/2z, Lambda z, CL/F, Vz/F, Rac(AUC), Rac(Cmax)

Pharmacokinetic parameters of [redacted]

Cmax, Tmax, AUClast, AUCtau, T1/2z, Lambda z, Rac(AUC), Rac(Cmax), MR

Visit:

Rac(AUC), Rac(Cmax): Day 7

For all other parameters: Day 1, Day 7, Day 14, Day 21

Analytical Method(s):

The following summaries will be provided. Subjects who were administered placebo will be excluded from the analysis.

(1) Summary of Pharmacokinetic Parameters

For Cmax, AUClast, and AUCtau, descriptive statistics, geometric mean, CV, and geometric CV will be provided. For Tmax, descriptive statistics will be provided. For all other variables, descriptive statistics and CV will be provided.

(2) Summary of Pharmacokinetic Parameters Normalized by Dose

For Cmax, AUClast, and AUCtau that have been normalized by dose, descriptive statistics, geometric mean, CV, and geometric CV will be provided.

7.9.1.3 Assessment of Dose Proportionality in Pharmacokinetic Parameters

Part 1

Analysis Set:

Pharmacokinetic Analysis Set

Analysis Variable(s):

Pharmacokinetic parameters of TAK-935 and CCI

Cmax, AUClast, AUCinf, AUC24

Analytical Method(s):

The following summaries will be provided. Subjects who were administered placebo will be excluded from the analysis.

(1) Scatter Plot for Pharmacokinetic Parameters and Dose

Scatter plots will be provided with dose plotted on the horizontal axis and each of the analysis variables plotted on the vertical axis.

(2) Regression Analysis of Pharmacokinetic Parameters on Dose

A power regression analysis will be performed for each analysis variable using the power model:

$y = a * (dose)^b * e,$

where y is the analysis variable, a and b are the regression parameters, and e is the error term of the power equation.

Parameter estimates for a and b, and their two-sided 90% confidence intervals will be provided.

Part 2

Analysis Set:

Pharmacokinetic Analysis Set

Analysis Variable(s):

Pharmacokinetic parameters of TAK-935 and CCI

Cmax, AUClast, AUCtau

Visit:

Day 7, Day 14, Day 21

Analytical Method(s):

The following summaries will be provided. Subjects who were administered placebo will be excluded from the analysis.

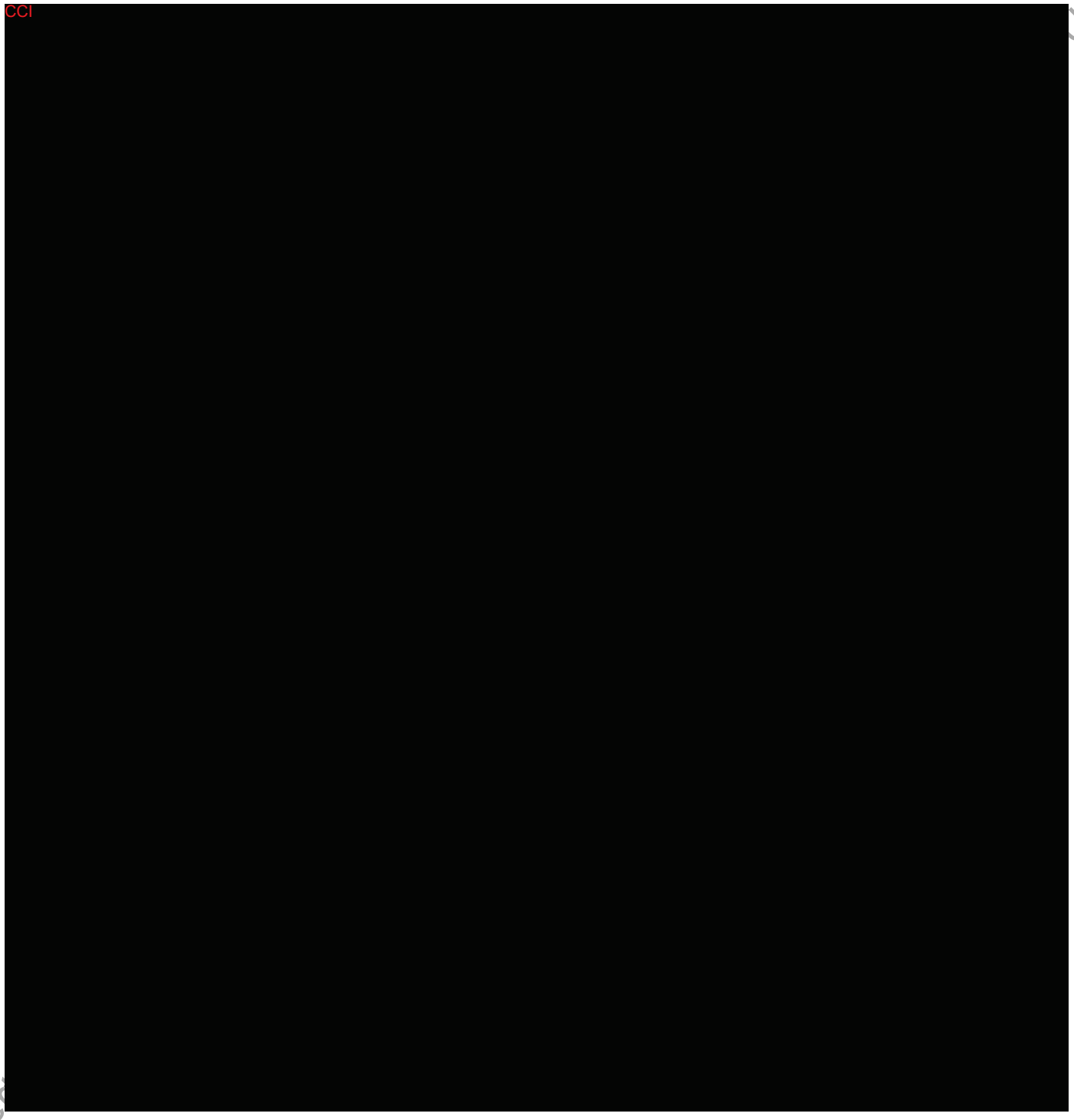
(1) Scatter Plot for Pharmacokinetic Parameters and Visit

Scatter plots will be provided with visit plotted on the horizontal axis and each of the analysis variables plotted on the vertical axis.

7.9.2 CCI

CCI

CCI



7.9.2.2 CCI [redacted]

CCI [redacted]

CCI

7.9.2.3 CCI

CCI

CCI

[redacted]

7.10 Other Outcomes

Not applicable.

7.11 Safety Analysis

7.11.1 Adverse Events

7.11.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set:

Safety Analysis Set

Analysis Variable(s):

TEAE

Categories:

Relationship to Study Drug	[Related, Not Related]
Intensity	[Mild, Moderate, Severe]

Analytical Method(s):

The following summaries will be provided by dose for each of Part 1 and Part 2.

(1) Overview of Treatment-Emergent Adverse Events

1) All Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
2) Relationship of Treatment-Emergent Adverse Events to study drug (number of events, number and percentage of subjects)
3) Intensity of Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
4) Treatment-Emergent Adverse Events leading to study drug discontinuation (number of events, number and percentage of subjects)
5) Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
6) Relationship of serious Treatment-Emergent Adverse Events to study drug (number of events, number and percentage of subjects)
7) Serious Treatment-Emergent Adverse Events leading to study drug discontinuation (number of events, number and percentage of subjects)
8) Treatment-Emergent Adverse Events resulting in death (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below. Percentages will be based on the number of subjects in the safety analysis set. The primary endpoint of this study is the percentage of subjects who experience at least 1 TEAE.

Number of subjects

- Summaries for 2) and 6)

  A subject with occurrences of TEAE in both categories (i.e., Related and Not Related) will be counted once in the Related category.

- Summary for 3)

  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.

- Summaries other than 2), 3), and 6)

  A subject with multiple occurrences of TEAE will be counted only once.

Number of events

For each summary, the total number of events will be calculated

7.11.1.2 Displays of Treatment-Emergent Adverse events

Analysis Set:

Safety Analysis Set

Analysis Variable(s):

TEAE

Categories:

Intensity	[Mild, Moderate, Severe]
Time of Onset	[Period 1 (100 mg BID), Period 2 (200 mg BID), Period 3 (300 mg BID)]

Analytical Method(s):

The following summaries will be provided using frequency distribution by dose for each of Part 1 and Part 2. Summary table for (10) will only be provided for Part 2.

TEAEs will be coded using the MedDRA and will be summarized using SOC and PT.

SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by System Organ Class only or PT only.

(1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(2) Treatment-Emergent Adverse Events by System Organ Class

(3) Treatment-Emergent Adverse Events by Preferred Term

(4) Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(5) Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(6) Intensity of Drug-Related Treatment-Emergent Adverse Events by System Organ Class, and Preferred Term

(7) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term

(8) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(9) Treatment-Emergent Adverse Events of Special Interest by System Organ Class and Preferred Term

(10) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Over Time

The frequency distribution will be provided according to the rules below. Percentages will be based on the number of subjects in the safety analysis set.

Number of subjects

- Summary tables other than (5), (6), and (10)

  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT.

- Summary tables for (5) and (6)

  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity.

- Summary tables for (10)

  A subject with a TEAE that occurs in more than one interval is counted in all the intervals that the TEAE occurs. For each time interval, a subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once in that SOC or PT.
  When calculating percentages for each time interval, the number of subjects at risk (i.e., subjects who either have an exposure or have an occurrence of TEAE, during or after the corresponding time interval) will be used as the denominator. The number of subjects whose onset of any one of the TEAEs is within the time interval will be used as the numerator.

7.11.1.3 Displays of Pretreatment Events

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variable(s):

PTE

Analytical Method(s):

The following summaries will be provided using frequency distributions for each of Part 1 and Part 2.

PTEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

(1) Pretreatment Events by System Organ Class and Preferred Term

(2) Serious Pretreatment Events by System Organ Class and Preferred Term

The frequency distribution will be provided according to the rules below.

Number of subjects

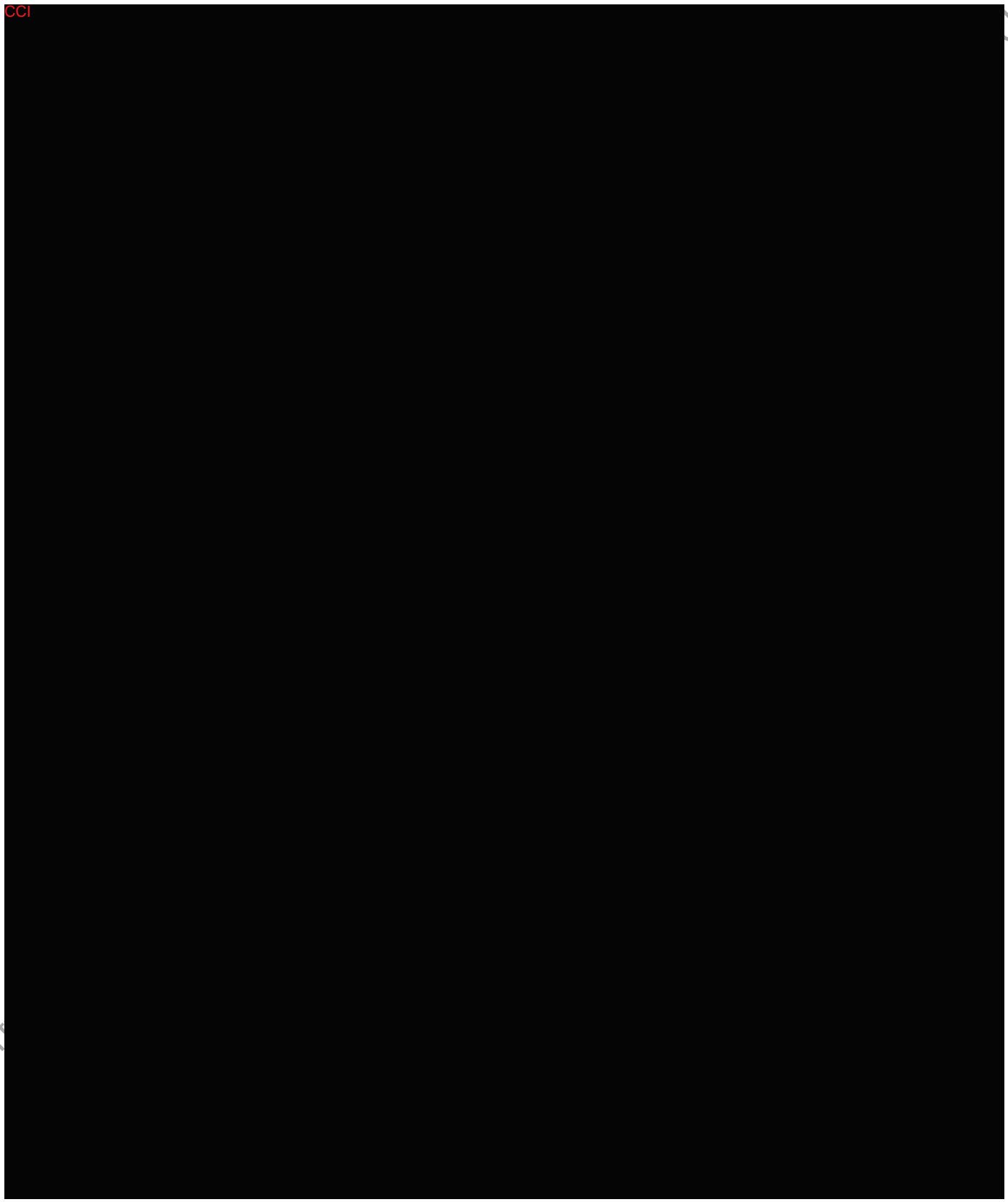
A subject with multiple occurrences of PTE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of PTE within a PT will be counted only once in that PT.

7.11.2 CCI

CCI

[redacted]

CCI



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7.11.3 CCI and Weight

Analysis Set:

Safety Analysis Set

Analysis Variable(s):

CCI

[redacted]

Weight

Visit:

CCI

[redacted]

<Weight>

Part 1: Day -2, Day 3

Part 2: Day -2, Day 24

(Value from Day -2 will be used as the baseline)

Analytical Method(s):

The following summaries will be provided by dose for each of Part 1 and Part 2.

(1) Summary of CCI and Change from Baseline by Visit

Descriptive statistics for observed values and changes from baseline (each post-baseline visit - baseline) will be provided by visit.

7.11.4 CCI

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[redacted]

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[redacted]

7.11.5 Other Observations Related to Safety

Not applicable

7.12 Interim Analysis

Not applicable.

7.13 Changes in the Statistical Analysis Plan

From the SAP Initial version, the following parts were updated.

Before the change

7.9.1 Pharmacokinetic Analysis

Section 7.9.1.1 Plasma Concentrations

Part 2

Analytical Method(s):

The following summaries will be provided. Subjects who were administered placebo will be excluded from the analysis.

(1) Summary of Plasma Concentrations by Visit

Descriptive statistics and CV will be provided by visit.

(2) Case Plots of Plasma Concentrations

Plots over time for each subject will be provided. Visit will be plotted on the horizontal axis and the analysis variable will be plotted on the vertical axis. In addition to plots with the vertical axis as a normal scale, plots with the vertical axis as a common logarithmic scale will also be provided.

(3) Mean and Standard Deviation Plot of Plasma Concentrations

Mean and standard deviation will be plotted. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

(4) Mean Plot of Plasma Concentrations

Mean will be plotted. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a common logarithmic scale.

After the change

7.9.1 Pharmacokinetic Analysis

Section 7.9.1.1 Plasma Concentrations

Part 2

Analytical Method(s):

The following summaries will be provided. Subjects who were administered placebo will be excluded from the analysis.

(1) Summary of Plasma Concentrations by Visit

Descriptive statistics and CV will be provided by visit.

(2) Case Plots of Plasma Concentrations

Plots over time for each subject will be provided. Visit will be plotted on the horizontal axis and the analysis variable will be plotted on the vertical axis. In addition to plots with the vertical axis as a normal scale, plots with the vertical axis as a common logarithmic scale will also be provided.

(3) Mean and Standard Deviation Plot of Plasma Concentrations

Mean and standard deviation will be plotted. A separate plot will also be provided for each analysis variable for each day. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

(4) Mean Plot of Plasma Concentrations

Mean will be plotted. A separate plot will also be provided for each analysis variable for each day. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a common logarithmic scale.

Reason for the change

To meet another department request.

cci

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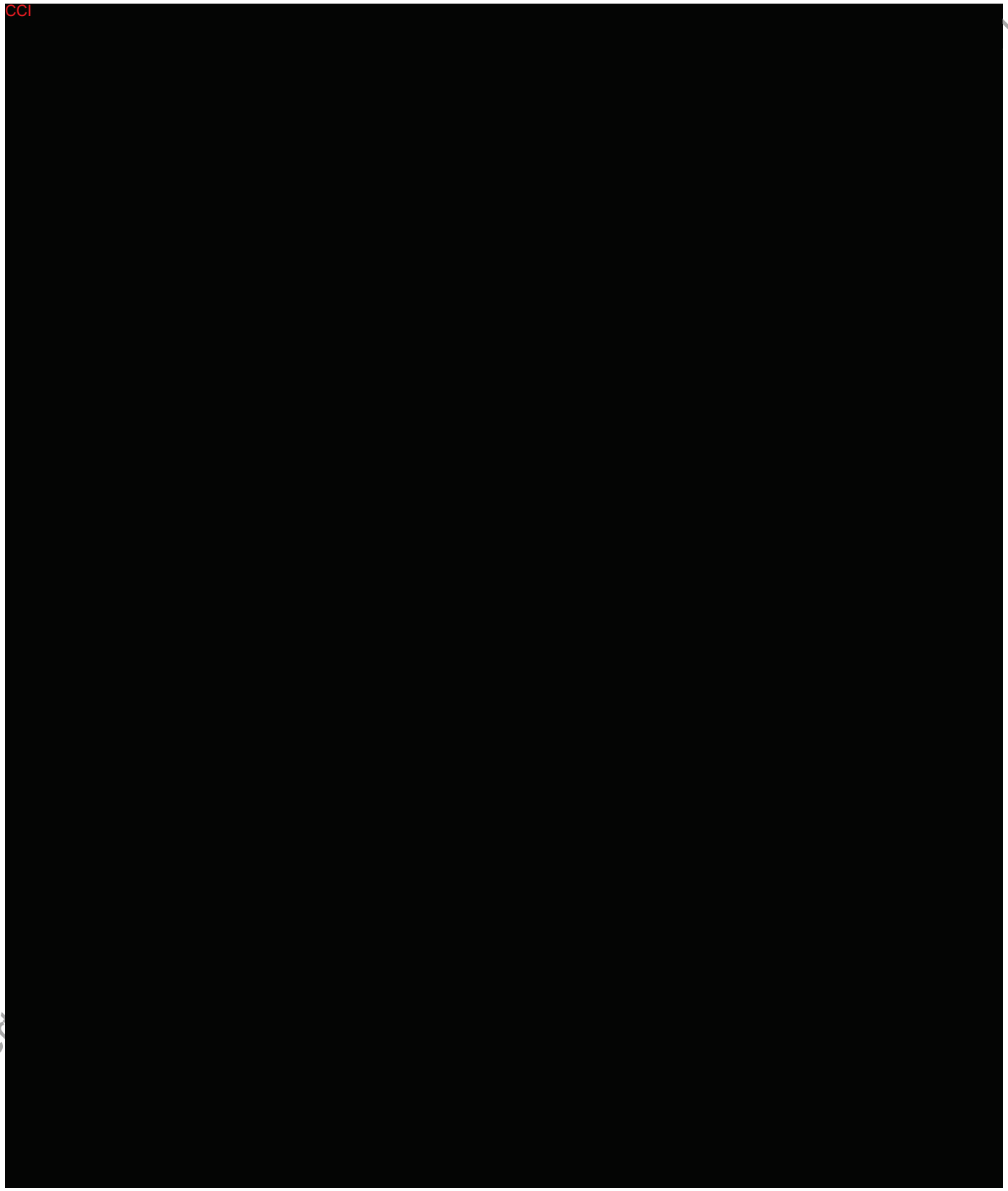

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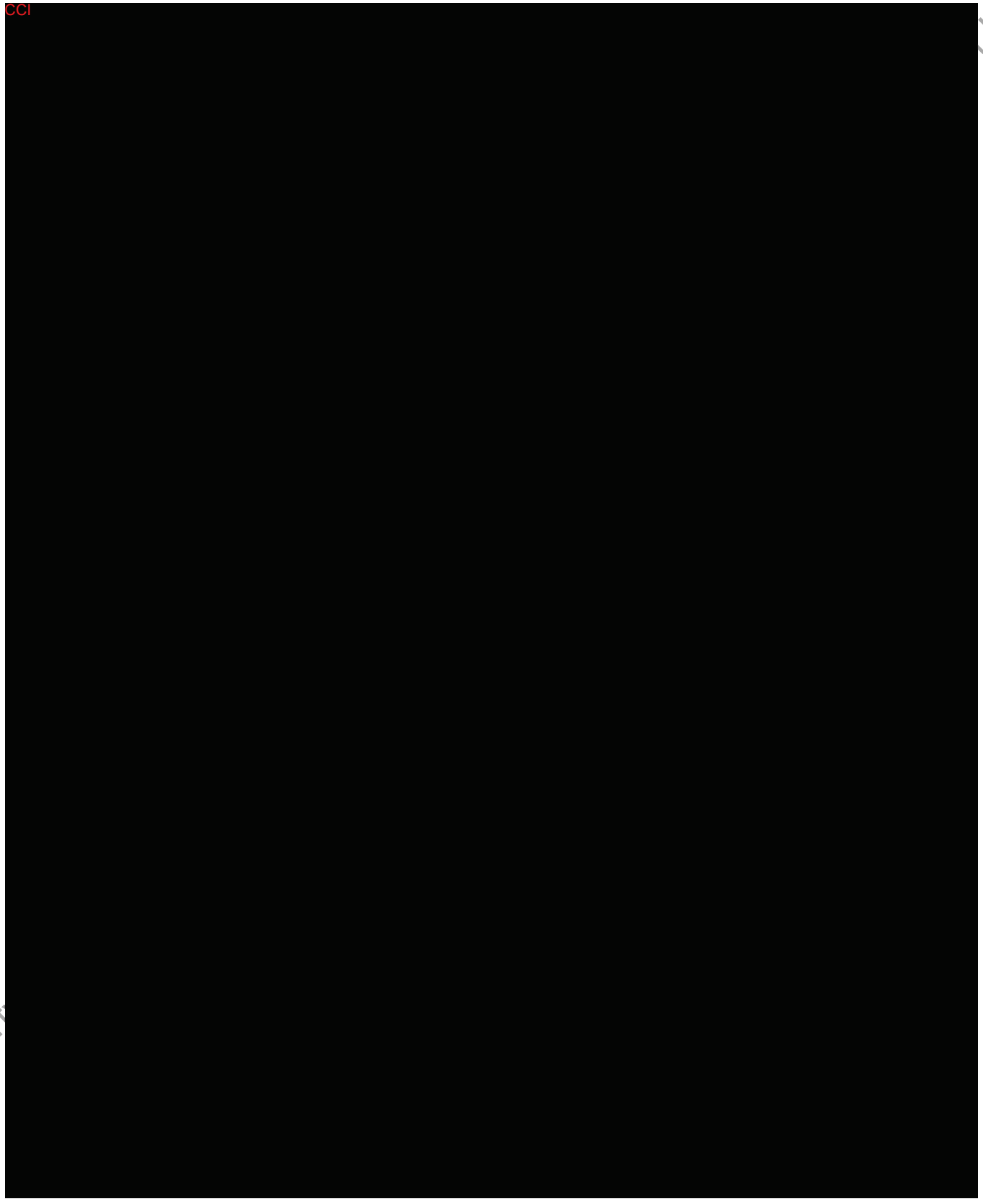

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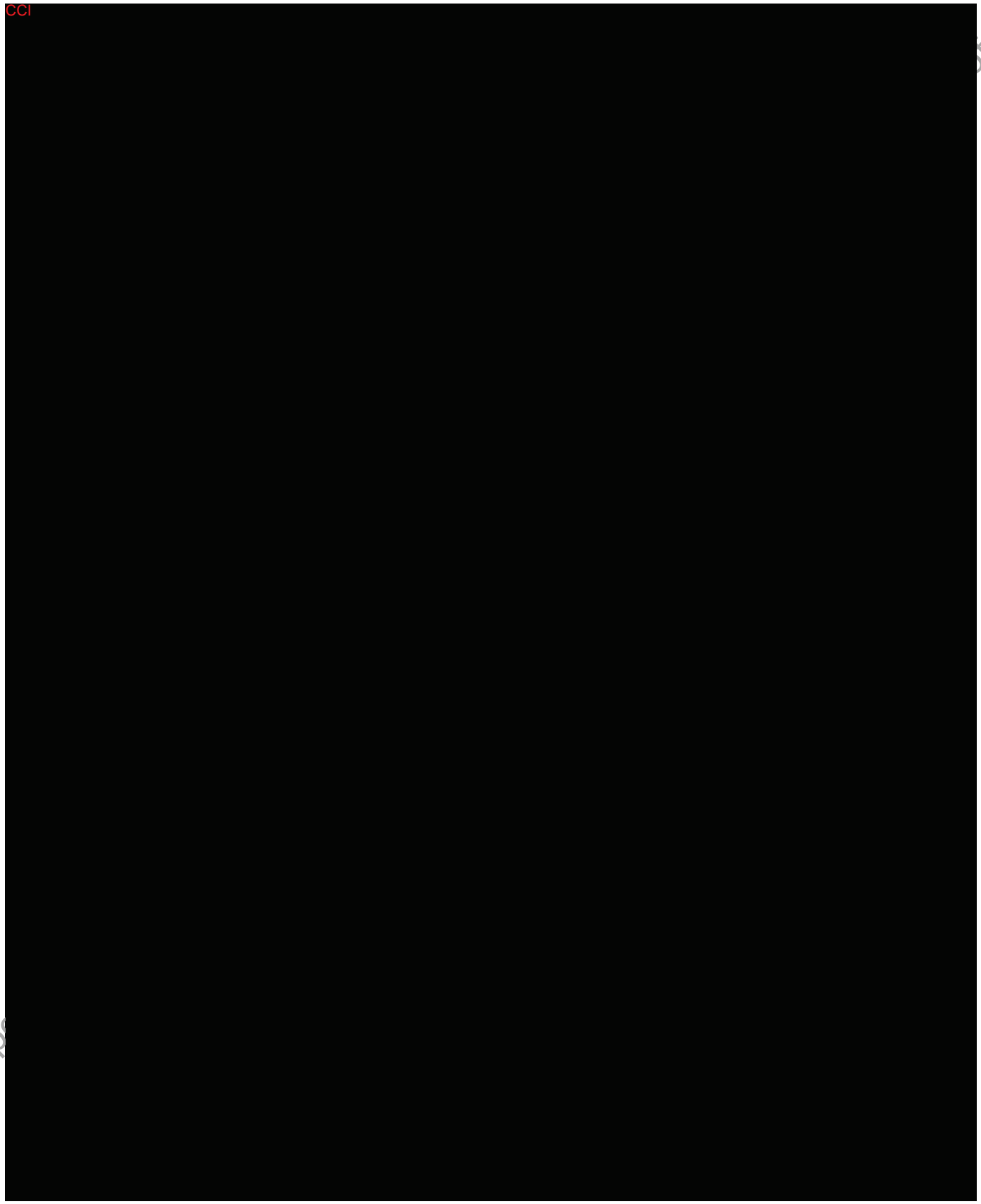

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8.0 REFERENCES

Not applicable.