Title: A Phase 1 Study to Assess Absolute Bioavailability of TAK-935 (OV935) and to Characterize Mass Balance, Pharmacokinetics, Metabolism, and Excretion of [14C]TAK-935 (OV935) in Healthy Adult Male Participants

NCT Number: NCT04992442

SAP Approve Date: 16 September 2020

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- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

STATISTICAL ANALYSIS PLAN

A Phase 1 Study to Assess Absolute Bioavailability of TAK-935 (OV935) and to Characterize Mass Balance, Pharmacokinetics, Metabolism, and Excretion of [^{14}C]TAK-935 (OV935) in Healthy Adult Male Participants

Protocol No: TAK-935-20-001 (OV935)
Final Protocol Date: 04 June 2020
Protocol Clarification Letter Date: 19 June 2020
Compound Name: Soticlestat (TAK 935, OV935)

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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Signature: PPD

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Signature PPD ____

Signature ____

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ABBREVIATIONS

%Dose	Percentage of the dose eliminated/recovered in a given collection interval
%Dose[f]	Percentage of the dose excreted in feces in a given interval
%Dose[u]	Percentage of the dose excreted in urine in a given interval
%F	Percent absolute bioavailability
$_z$; Kel	Terminal disposition phase rate constant
ABA; F	Absolute bioavailability
ADME	Absorption, distribution, metabolism, and excretion
Ae	Amount eliminated/recovered in a given collection interval
AE(s)	Adverse event(s)
Ae[f], Ae_{t1-t2}	Amount eliminated/recovered in feces in a given interval
Ae[u]; Ae_{t1-t2}	Amount eliminated/recovered in urine in a given interval
AMS	Accelerator mass spectrometry
ANOVA	Analysis of variance
AUC ; $AUC_{0-\infty}$; AUC0-inf	Area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration.
AUC_{0-t} Ratio	Ratio between plasma TAK-935, M-I, or [^{14}C]TAK-935 AUC_{0-t} and plasma total radioactivity AUC_{0-t}.
$AUCCL_R$	Area under the concentration time curve from time 0 to time of the last common time point at which an analyte is quantifiable in the urine and plasma of a given subject
$AUC_{extrap\%}$	Area under the curve from the last quantifiable concentration to infinity calculated using the observed value of the last quantifiable concentration, expressed as a percentage of $AUC_{0-\infty}$.
AUC_{last}; AUC_{0-last}	Area under the concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_t; AUC_{0-t}	Area under the concentration time curve from time 0 to time of the last common time point "t" for all participants at which an analyte (i.e., TAK-935, M-I, or [^{14}C]TAK-935) and total radioactivity are quantifiable in plasma.
BLQ	Below the limit of quantitation
C_{eoi}	Concentration at the end of the infusion

CIs	Confidence intervals
CL_R	Renal clearance
C_{max}	Maximum observed concentration
Combined Cum%Dose	Cumulative percentage of the dose eliminated/recovered in urine and feces combined
COVID-19	Novel coronavirus 2019
CRF	Case report form
CRU	Clinical research unit
CS	Clinically significant
CSR	Clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
Cum%Dose	Cumulative percentage of the dose eliminated/recovered in successive collection intervals
Cum%Dose[f]	Cumulative percentage of the dose eliminated/recovered in feces
Cum%Dose[u]	Cumulative percentage of the dose eliminated/recovered in urine
CumAe	Cumulative amount eliminated/recovered in successive collection intervals
CV%	Arithmetic percent coefficient of variation
$DNAUC_{0-\infty}300$; DNAUC0-inf300	$AUC_{0-\infty}$ normalized to a 300 mg dose
$DNAUC_{0-last}300$	AUC_{0-last} normalized to a 300 mg dose
ECG(s)	Electrocardiogram(s)
Geom CV%	Geometric percent coefficient of variation
Geom Mean	Geometric mean
GMRs	Geometric least-squares mean ratios
HPLC-MS/MS	High performance liquid chromatography-tandem mass spectrometry
HR	Heart rate
ICH	International Council for Harmonisation
IV	Intravenous
LLOQ	Lower limit of quantitation
LS	Least-squares
Mean	Arithmetic mean
MedDRA®	Medical Dictionary for Regulatory Activities
$MPRAUC_{0-}$	Metabolite-to-parent ratio of AUC_{0-}
MW	Molecular weight
n	Number of observations
NCS	Not clinically significant
Pharmacokinetic(s)	PK
PI	Principal Investigator
PT	Preferred Term
QTc	Corrected QT interval

QT_cF	QT interval corrected using Fridericia's formula
R^2	Coefficient of determination
SAEs	Serious adverse events
SAP	Statistical analysis plan
SD	Standard deviation
SEM	Standard error of the mean
SOC	System Organ Class
$t_{1/2z}$	Terminal disposition phase half-life
TEAEs	Treatment-emergent adverse events
TFLs	Tables, figures, and listings
t_{max}	Time of first occurrence of C_{max}
ULOQ	Upper limit of quantitation
WHO	World Health Organization

1. INTRODUCTION

The following statistical analysis plan (SAP) provides the framework for the summarization of the data from this study. The SAP may change due to unforeseen circumstances. Any changes made from the planned analysis within protocol after locking the database will be documented in the clinical study report (CSR). The section referred to as Table Shells within this SAP describes the traceability of the tables, figures, and listings (TFLs) back to the data. Note that the header for this page will be the one used for the main body of the CSR.

Any additional exploratory analyses not addressed within this SAP and/or driven by the data, or requested by the SPONSOR, will be considered out of scope and must be described in the CSR.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary

Period 1 (ABA)

- To determine absolute bioavailability (ABA) of TAK-935 following a single microdose intravenous (IV) administration of 50 µg (~1 µCi) [^{14}C]TAK-935 and a single oral administration of 300 mg TAK-935.

Period 2 (ADME)

- To assess the mass balance (i.e., cumulative excretion of total radioactivity in urine and feces) following a single oral administration of 300 mg (~100 µCi) [^{14}C]TAK-935.
- To characterize the pharmacokinetics (PK) of TAK-935 and M-I in plasma and urine, and total radioactivity concentration equivalents in plasma and whole blood following a single oral administration of 300 mg (~100 µCi) [^{14}C]TAK-935.

Secondary

Period 1 (ABA)

- To determine the PK of [^{14}C]TAK-935 following a single IV administration of 50 µg (~1 µCi) [^{14}C]TAK-935 and the PK of TAK-935 following a single oral administration of 300 mg TAK-935.
- To determine fecal and urinary excretion of the parent [^{14}C]TAK 935 following a single IV administration of 50 µg (~1 µCi) [^{14}C]TAK-935.

Period 2 (ADME)

- To assess the metabolic profile of TAK-935 in plasma, urine, and feces following a single oral administration of 300 mg (~100 µCi) [^{14}C]TAK-935.

Periods 1 (ABA) and 2 (ADME)

- To assess the safety of TAK-935 during the ABA and ADME study periods.

Note: this SAP does not address the secondary objective of assessing the metabolic profile of TAK-935 in plasma, urine, and feces. This objective will be assessed by Takeda.

2.2 Endpoints

Primary

Period 1 (ABA)

- Absolute bioavailability (F) as percent F (%F) for TAK-935.

Period 2 (ADME)

- Percent of total radioactivity excreted in urine (Cum%Dose[u]) and feces (Cum%Dose[f]) relative to the administered radioactive dose (Combined Cum%Dose).
- Amount of total radioactivity excreted in urine (Ae[u]) and feces (Ae[f]) and the percent of administered radioactive dose excreted in urine and feces within a given collection interval (urine %Dose[u]) and feces (%Dose[f]).
- PK parameters C_{max}, t_{max}, $t_{1/2z}$, AUC_{∞}, AUC_t, and AUC_{last} for TAK-935 in plasma.
- PK parameters C_{max}, t_{max}, $t_{1/2z}$, AUC_{∞}, AUC_t, and AUC_{last} for total radioactivity concentration equivalents in plasma and whole blood.
- PK parameters for renal clearance (CL_R) for TAK-935 in urine.
- PK parameters for amount excreted in each collection interval (Ae_{t1-t2}) for TAK-935 in urine.
- The change over time in percentage of [^{14}C]-radioactivity in whole blood relative to plasma (i.e., whole blood:plasma partitioning ratio).

Secondary

Period 1 (ABA)

- PK parameters including concentration at the end of the infusion (C_{eoi}) (IV infusion), C_{max} (oral), t_{max} (oral), AUC_{∞}, AUC_t, AUC_{last}, and $t_{1/2z}$ for TAK 935, and [^{14}C]TAK-935 in plasma.

- Total radioactivity excreted and percentage of dose excreted in the feces (amount eliminated/recovered in feces [Ae(f)] and %Dose(f)) and amount eliminated/recovered in urine [Ae(u)] and %Dose(u)) as total radioactivity following IV administration.

Period 2 (ADME)

- Metabolic profile of TAK-935 in plasma, urine, and feces following a single oral administration of 300 mg (~100 µCi) [^{14}C]TAK-935.

Periods 1 (ABA) and 2 (ADME)

- Tabulated treatment-emergent adverse events (TEAEs) and summary statistics for clinically relevant 12-lead electrocardiograms (ECGs), vital signs, and clinical laboratory tests results.

Note: this SAP does not address the secondary endpoint of the metabolic profile of TAK-935 in plasma, urine, and feces. This endpoint will be determined by Takeda.

3. STUDY DESIGN

This was an open-label, 2-period, fixed-sequence, single-dose study in 6 healthy adult male participants.

On Day 1 of Period 1 (ABA Study Period), participants received a single oral 300 mg dose of unlabeled TAK-935 in tablet form (3 x 100 mg tablets). At 0.17 hours (10 minutes) post oral dosing (i.e., 15 minutes prior to the median t_{max} for the oral unlabeled dose [~ 0.42 hours or 25 minutes]), participants received a 15-minute IV infusion of a microdose of 50 µg (~1 µCi) [^{14}C]TAK-935. Serial blood sampling was performed up to 48 hours (Day 3) to determine the PK of TAK-935 and its M-I metabolite (and others, if applicable) in plasma for the oral dose and total radioactivity and PK of [^{14}C]TAK-935 in the plasma for the IV dose. Urine and fecal output were also collected up to 120 hours postdose to determine total radioactivity recovery. Collection of urine and fecal samples continued until one of the release criteria was met (i.e., 80% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples or the excretion of radioactivity in the urine and feces combined had declined to ≤ 1% of the total administered radioactivity for at least 2 consecutive intervals where both a urine and fecal sample were collected) or up to Day 8, but no less than Day 6, for total radioactivity excretion in urine and

feces. Participants who met release criteria before Day 8, but no less than Day 6, were to remain confined in the clinical research unit (CRU) until Day -1 of Period 2 and throughout Period 2 (until a Period 2 discharge criterion was met).

There was a washout period of at least 7 days between the last dose in Period 1 and the dose in Period 2.

On Day 1 of Period 2 (ADME Study Period), participants received a single oral dose of 300 mg (~100 μCi) [^{14}C]TAK-935 in solution. Serial blood sampling was performed and urine and feces were collected to determine the PK of TAK-935 and M-I in plasma and urine; and total radioactivity in plasma, whole blood, urine, and feces; and to characterize the metabolite profiles of TAK-935 in plasma, urine, and feces. Complete urinary and fecal output were collected during the confinement period until a discharge criterion was met.

In Period 2, participants were confined in the CRU for at least 5 days postdose (i.e., 120 hours) and until 90% or greater of the total dose of radioactivity administered was recovered in urine and fecal samples. If less than 90% of the total dose of radioactivity administered was recovered in urine and fecal samples, participants were to be confined in the clinic until a discharge criterion was met (i.e., 90% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples or the excretion of radioactivity in the urine and feces combined had declined to ≤ 1% of the total administered radioactivity per 24 hour interval for at least 2 consecutive intervals where both a urine and fecal sample were collected) or up to Day 11 (i.e., 240 hours). Release of participants who do not meet a discharge criterion by 240 hours (Period 2) was to be reviewed on a case-by-case basis. At all times, a participant may have been required to remain at the CRU for longer at the discretion of the Investigator or designee.

Since up to an approximate 24-hour time lag was anticipated for radioactivity counting of samples, actual participant release from the CRU may have occurred 1 day after a discharge criterion was met.

In both periods, any participant who experienced emesis within 1-hour post oral dosing was to be excluded in the PK data analysis and may have been replaced with a new participant. If a participant discontinued in Period 2, the replacement participant was to complete Period 2 only. If a participant experienced emesis after dosing in Period 2, vomitus was to be collected throughout the study and assayed for total radioactivity.

The clinic was to contact all participants (including participants who terminated the study early) 30 ± 2 days after the last study drug administration to determine if any adverse events (AEs) had occurred since the last study visit.

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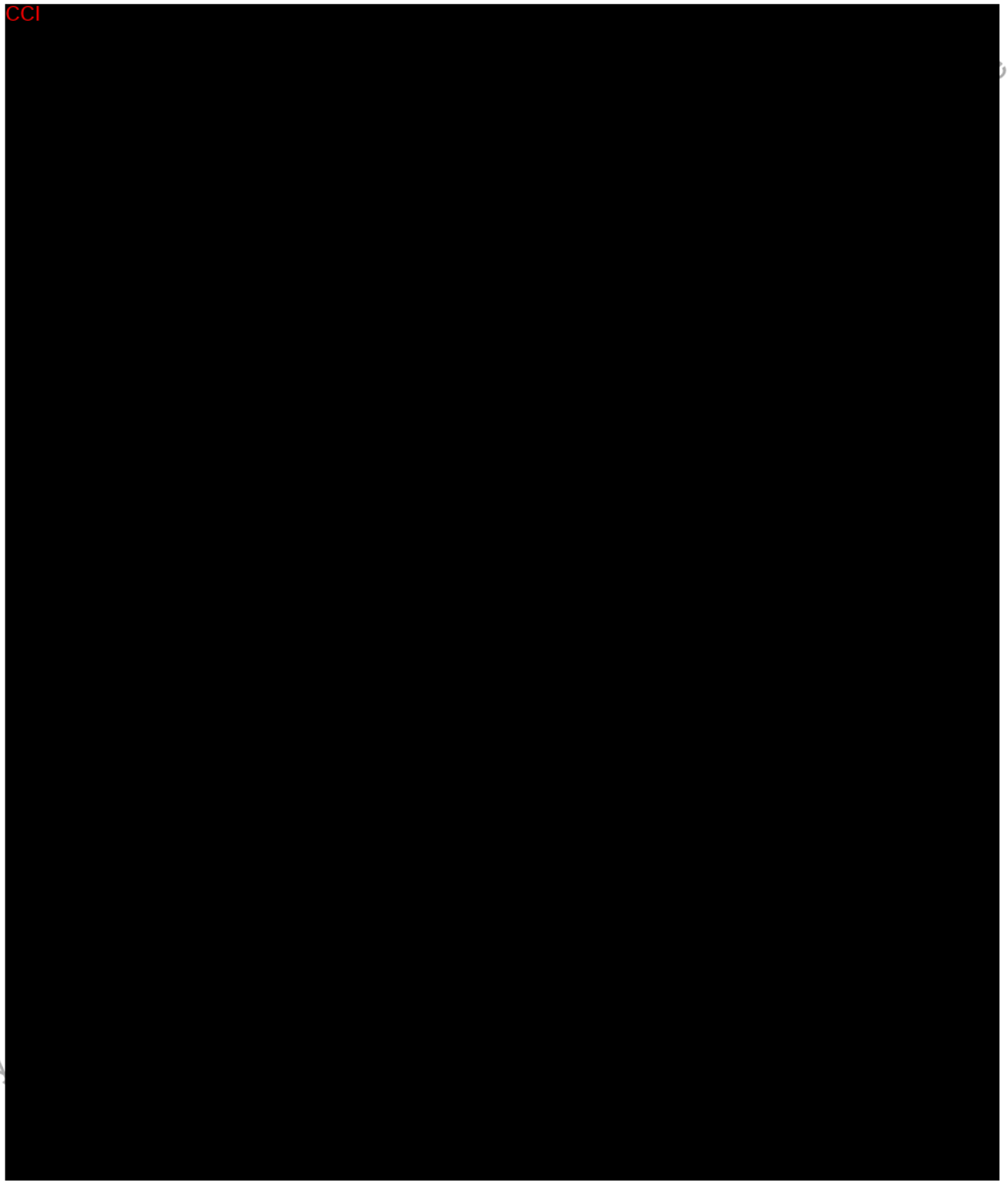

4. ANALYSIS POPULATIONS

4.1 Analysis Populations

Pharmacokinetic Set

All participants who complied sufficiently with the protocol and displayed an evaluable PK profile (e.g., exposure to treatment, availability of measurements and absence of major protocol violations) will be included in the statistical analyses.

Safety Population

All participants who received at least one dose of the study drug will be included in the safety evaluations.

4.2 Preliminary Data and Interim Analysis

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5. TREATMENT DESCRIPTIONS

The treatments administered will be described in the PK tables and figures as follows:

Treatment	Description
300 mg TAK 935 PO:	a single oral dose of 300 mg TAK-935 in Period 1
50 µg (~1 µCi) [^{14}C]TAK-935 IV:	a single intravenous infusion of 50 µg (~1 µCi) [^{14}C]TAK-935 administered over 15 minutes from 10 to 25 minutes after the oral dose of TAK-935 in Period 1
300 mg (~100 µCi) [14C]TAK-935 PO:	a single oral dose of 300 mg (~100 µCi) [^{14}C]TAK-935 in Period 2

For safety tables and listings, due to spacing limitation, treatments will be coded using A and B with the follow footnotes:

Treatment A: 300 mg TAK-935 (3 x 100 mg tablets) administered orally at Hour 0 on Day 1 followed by 50 µg (~1 µCi) [^{14}C]TAK-935 IV solution administered at Hour 0.17 (10 minutes post oral dosing) for 15 minutes

Treatment B: 300 mg (~100 µCi) [^{14}C]TAK-935 administered as an oral solution at Hour 0 on Day 1

6. PHARMACOKINETIC ANALYSIS

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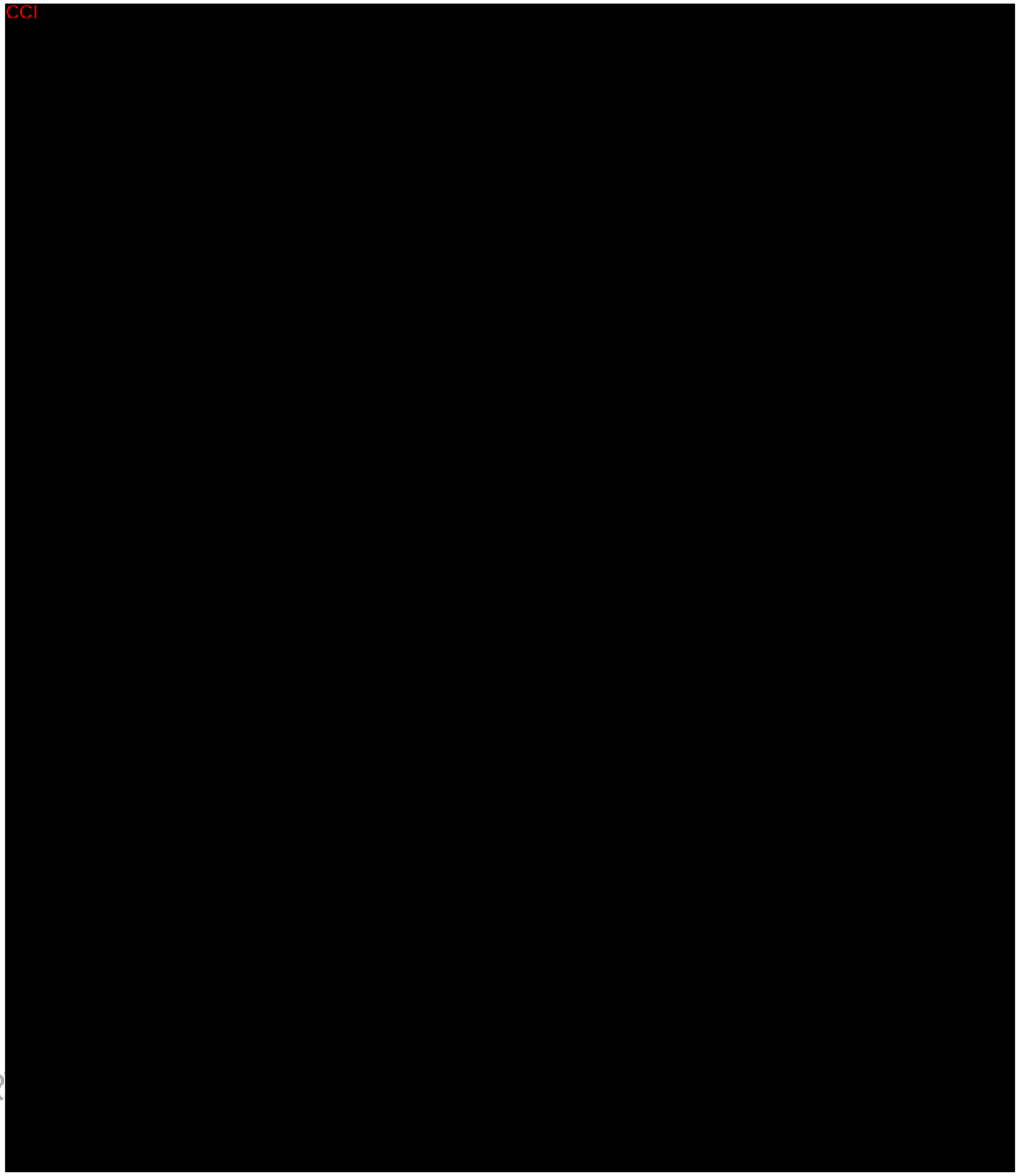
All concentration data will be included in the calculation of the individual PK parameters, the individual concentration versus time plots (based on actual sample times), and the mean concentration versus time, individual and mean whole blood:plasma partitioning ratio versus time, and individual and mean cumulative percentage of the dose recovered versus time plots (based on nominal sample times). However, if there are any significant deviations from nominal sample times, some concentration data may be excluded from mean concentration-time plots and/or additional concentration-time plots of the mean data may be provided. All deviations and excluded data will be provided and discussed in the CSR.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6.3.1 TAK-935 and M-I

Plasma will be analyzed for TAK-935 and M-I concentrations following a single oral dose of 300 mg TAK-935 in Period 1. Plasma, urine, and feces will be analyzed for [^{14}C]TAK-935 concentrations following a single microdose of 50 µg (~1 µCi) [^{14}C]TAK-935 administered via a 15-minute IV infusion from 10 to 25 minutes after the oral dose of TAK-935 in Period 1. Urine will be analyzed for TAK-935 and M-I concentrations following a single oral dose of 300 mg (~100 µCi) [^{14}C]TAK-935 in Period 2. CCI [redacted].

6.3.2 Total Radioactivity

Plasma, urine, and feces will be analyzed for total radioactivity following a single microdose of 50 µg (~1 µCi) [^{14}C]TAK-935 administered via a 15-minute IV infusion from 10 to 25 minutes after the oral dose of TAK-935 in Period 1. Whole blood, plasma, urine, and feces will be analyzed for total radioactivity following a single oral dose of 300 mg (~100 µCi) [^{14}C]TAK-935 in Period 2. Concentrations of total radioactivity in all matrices will be measured in dpm/mL or dpm/g of sample, and these will be converted to TAK-935 equivalent concentrations (ng eq TAK-935/mL or ng eq TAK-935/g) by dividing these dpm/mL or dpm/g concentrations by the specific activity of the administered radioactive dose (e.g., dpm/ng).

6.4 TAK-935 and Metabolite Concentrations

Concentration data determined at the collection times and per the bioanalytical methods described in Section 6.1 and Section 6.2, respectively, will be used for the calculation of plasma and urine TAK-935 and M-I; plasma, urine, and feces [^{14}C]TAK-935; and whole blood, plasma, urine, and feces total radioactivity PK parameters.

In order to plot M-I concentrations along with TAK-935 concentrations and total radioactivity TAK-935 concentration equivalents in the same figures, plasma M-I concentrations will also be presented in TAK-935 equivalents (i.e., ng TAK-935/mL) using the following formula:

$$\text{M-I concentration (ng TAK-935/mL)} = \text{M-I concentration (ng/mL)} \times MW_{\text{TAK-935}} / MW_{\text{M-I}}$$

In addition, the arithmetic mean plasma concentrations of other metabolites (i.e., not including M-I) combined in TAK-935 equivalents in Period 2 will be estimated and plotted along with plasma TAK-935 and M-I (in TAK-935 equivalent) concentrations, and whole blood and plasma total radioactivity concentration equivalents in the same in-text figures. The arithmetic mean plasma concentrations of other metabolites combined will be determined using the following formula:

$$\text{Mean}_{(\text{Other Metabolites})} = \text{Mean}_{(\text{Total Radioactivity})} - [\text{Mean}_{(\text{TAK-935})} + \text{Mean}_{(\text{M-I})}]$$

6.5 NonCompartmental Pharmacokinetic Analysis and Parameter Calculation

6.5.1 Whole Blood and Plasma Pharmacokinetic Parameters

The appropriate noncompartmental PK parameters will be calculated from the whole blood and plasma total radioactivity concentration equivalent (plasma in both Periods 1 and 2, whole blood in Period 2 only) and plasma TAK-935 and M-I concentration (Periods 1 and 2) versus time data using Phoenix® WinNonlin® Version 8.1 or higher. Actual sample times will be used in the calculations of the PK parameters. The calculation of the actual times for plasma TAK-935 and M-I PK samples in Period 1 will be in respect to the time of the single oral dose of 300 mg TAK-935 in Period 1. The calculation of the actual times for plasma [^{14}C]TAK-935 and total radioactivity PK samples in Period 1 will be in respect to the time of the start of the 15-minute IV infusion of 50 µg (~1 µCi) [^{14}C]TAK-935 in Period 1. The calculation of the actual times for plasma TAK-935 and M-I PK samples, and whole blood and plasma total radioactivity PK samples in Period 2 will be in respect to the time of the single oral dose of 300 mg (~100 µCi) [^{14}C]TAK-935 in Period 2. All PK parameters included in the protocol are listed in Table 6.5 below, and are defined as appropriate for study design.

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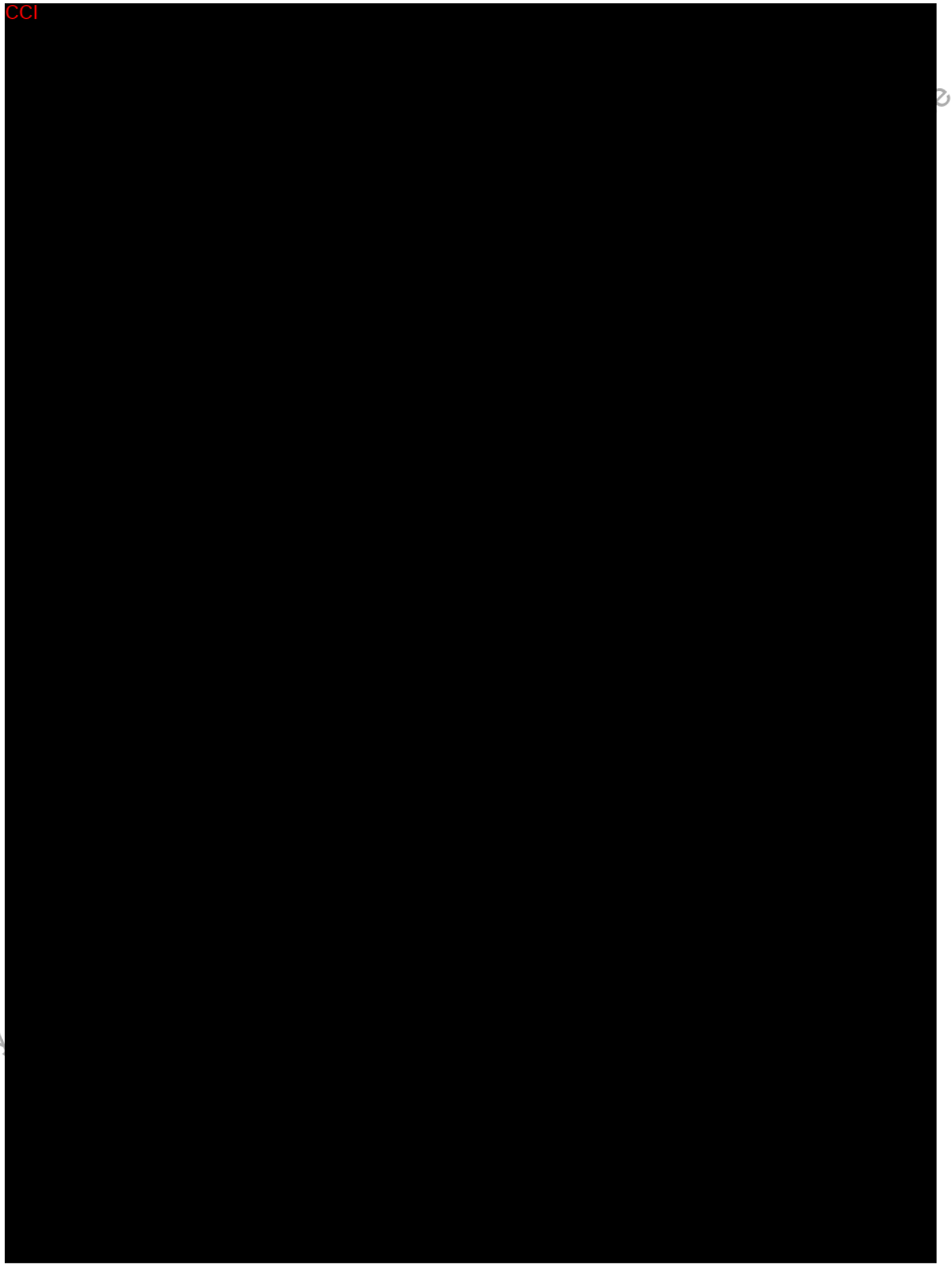

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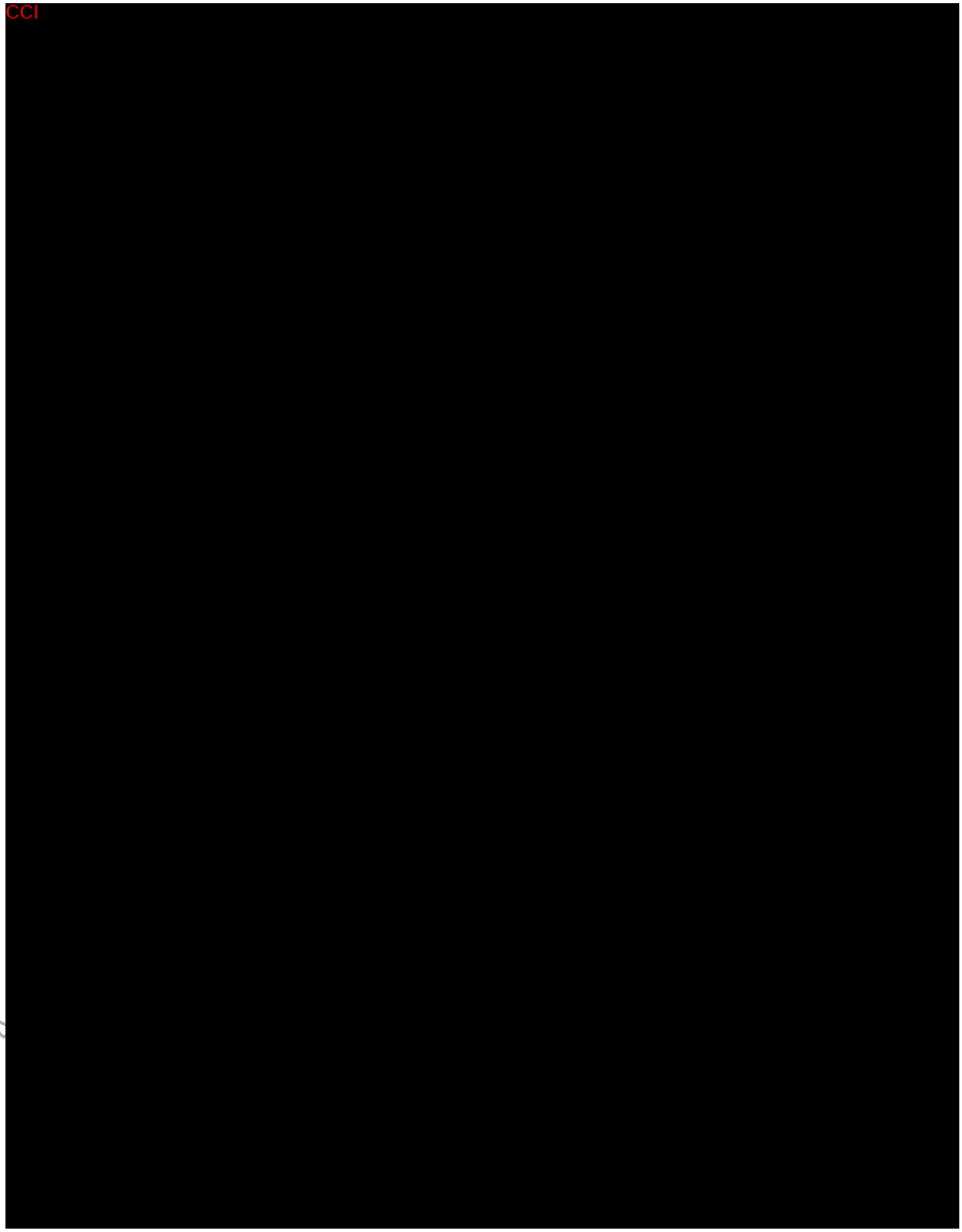

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The following noncompartmental PK parameters will be calculated for urine, feces, and urine and feces combined [^{14}C]TAK-935 concentrations (Period 1), urine TAK-935 and M-I concentrations (Period 2), and urine, feces, and urine and feces combined total radioactivity concentration equivalents (Periods 1 and 2), as appropriate, using SAS® Version 9.4 or higher. All PK parameters included in the protocol are listed in Table 6.7 below and are defined as appropriate for study design.

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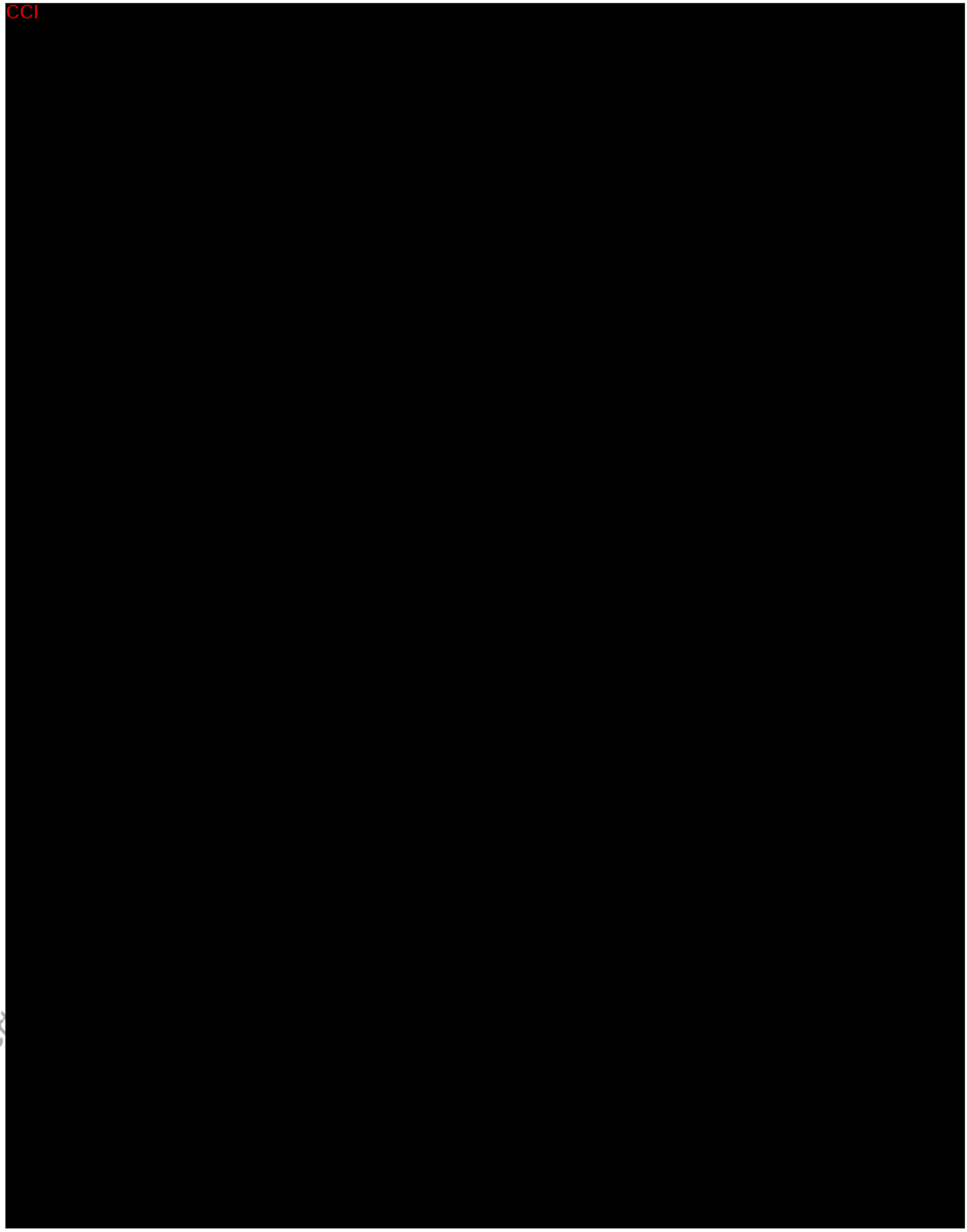

6.6 Data Summarization and Presentation

All statistics will be generated using SAS® Version 9.4 or higher.

Concentrations data will be listed and summarized by analyte, treatment, and time point for all subjects in the PK Population. Concentration data will be presented with the same level of precision as received from the bioanalytical laboratory. Descriptive statistics, including the number of observations (n), arithmetic mean (Mean), standard deviation (SD), arithmetic percent coefficient of variation (CV%), standard error of the mean (SEM), minimum, median, and maximum will be calculated for all nominal concentration time points. Excluded subjects will be included in the concentration listings, but will be excluded from the descriptive statistics and noted as such in the tables. All BLQ values will be presented as "BLQ" in the concentration listings and footnoted accordingly. Whole blood:plasma total radioactivity partitioning ratios will be listed and summarized by time point for all subjects in the PK Population using the same descriptive statistics as above, and also including Geom Mean and geometric percent coefficient of variation (Geom CV%).

Urine sample weight (including additive(s), if any) and fecal homogenate weight will be listed and summarized by collection interval for all subjects in the PK Population. Urine sample and fecal homogenate weight data will be presented with the same level of precision as received from the clinic. These data will be summarized using the same descriptive statistics as for the concentration data. Excluded subjects will be included in the listings, but will be excluded from the descriptive statistics and noted as such in the tables.

PK parameters will be listed and summarized by analyte and treatment for all subjects in the PK Population. Pharmacokinetic parameters will be reported to 3 significant figures for individual parameters, with the exception of t_{max}, which will be presented with 3 decimal places. Descriptive statistics (n, arithmetic mean, SD, CV%, SEM, minimum, median, maximum, Geom Mean, and Geom CV%) will be calculated for all PK parameters. Excluded subjects will be listed in the PK parameter tables, but will be excluded from the descriptive statistics and noted as such in the tables.

The level of precision for each descriptive statistic will be presented as follows: minimum/maximum with same precision as individual values, mean/median/Geom Mean with one more level of precision than minimum/maximum, SD/SEM with one more level of precision than mean/median/Geom Mean, n will be presented as an integer, and CV%/Geom CV% will be presented to the nearest tenth.

Mean and individual whole blood and plasma concentration-time profiles will be presented on linear and semi-log scales. Linear mean plots will be presented with and without SD. Mean and individual whole blood:plasma partitioning ratio-time profiles will be presented on linear scale with and without SD. Mean and individual urine, feces, and urine and feces combined cumulative excretion (recovery)-time profiles will be presented on linear scale with and without SD.

Arithmetic mean plasma TAK-935-equivalent concentrations of other metabolites combined in Period 2 will be plotted along with TAK-935 and M-I (as TAK-935 equivalent) concentrations, and whole blood and plasma total radioactivity concentration equivalents in the same in-text figures on linear and semi-log scales without SD bars.

Arithmetic mean Cum%Dose for other metabolites combined in urine in Period 2 will be presented in the text of the CSR but not in any tables or figures.

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7. SAFETY

All case report form (CRF) data will be listed by subject and chronologically by assessment time points. This will include rechecks, unscheduled assessments, and early termination.

Applicable continuous variables will be summarized using n, arithmetic mean, SD, minimum, median, and maximum.

The level of precision will be presented as follows: minimum/maximum in the same precision as in the database, mean/median in one more precision level than

minimum/maximum, SD in one more precision level than mean/median, and n and % will be presented as an integer.

Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators.

7.1 Subject Discontinuation

Subjects will be summarized by the number of subjects dosed, completed, and discontinued the study with discontinuation reasons.

7.2 Demographics

Descriptive statistics will be calculated for continuous variables (age, weight, height, and body mass index). Age will be derived from date of birth to date of first dosing. Frequency counts will also be provided for categorical variables (race, ethnicity, and sex).

7.3 Adverse Events

All adverse events (AEs) occurring during this clinical trial will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 23.0.

All AEs captured in the database will be listed in by-subject data listings including verbatim term, coded term, treatment, severity, relationship to study drug, and action; however, only treatment-emergent AEs (TEAEs) will be summarized.

A TEAE is defined as an AE that is starting or worsening at the time of or after study drug administration. Each TEAE will be attributed to a treatment based on the onset date and time of the AE.

If an AE increases in severity, that AE will be given a resolution date and time and a new record will be initiated with the new severity. If the severity of an AE remains the same or decreases, the AE will be kept open through to resolution.

If the onset time of an AE is missing and the onset date is the same as or occurs after the treatment dosing date, then the AE will be considered treatment emergent. If the onset date of an AE is missing, then the AE will be considered treatment emergent.

TEAEs will be tabulated by System Organ Class (SOC) and Preferred Term (PT). Summary tables will include the number of subjects reporting the AE and as a percent of the number of subjects dosed by treatment and overall. The number of AEs will be tabulated in a similar manner. A table summarizing the number of TEAEs by severity and relationship to study drug will also be included.

Serious adverse events (SAEs) and AEs leading to discontinuation, if present, will also be listed. Applicable narratives will be included in the CSR.

7.4 Clinical Laboratory Tests (Serum Chemistry, Hematology, Coagulation, Urinalysis)

Clinical laboratory tests for serum chemistry, hematology, coagulation, and urinalysis will be performed at Screening, Day -1 and Day 3 of each period, and Discharge or Early Termination.

All clinical laboratory data will be listed by subject and presented using conventional units to align with the CRF.

Out-of-normal range flags will be recorded as follows: high (H) and low (L) for numerical results and did-not-match (*) for categorical results. If a value fails the reference range, it will automatically be compared to a computer clinically significant (CS) range. If the value falls within the computer CS range, it will be noted as "N" for not clinically significant (NCS). If the value fails (i.e., falls outside of the CS range) the computer CS range, it will be flagged with a "Y" which prompts the Principal Investigator (PI) to determine how the out-of-range value should be followed using 4 Investigator flags: "N", not clinically significant, "R", requesting a recheck, "^", checking at the next scheduled visit, or "Y", clinically significant. To distinguish the PI flag from the computer CS range flags, the PI flags of "N" and "Y" will be presented as "-" and "+", respectively, in the data listing. Additionally, the PI will provide a fourth flag when the third flag indicates "R" or "^". This fourth flag is intended to capture final CS (+)/NCS (-) when the third flag does not document significance.

Out-of-range values and corresponding recheck results will be listed. Results that are indicated as CS by the PI will be listed by subject in a table. This table will also list the results at all other time points for the laboratory test and subject with at least one value deemed as CS by the PI.

For all numeric laboratory values, descriptive statistics will be presented for each laboratory test by assessment time point (and by treatment for baseline and Day 3 time points). Change from baseline will be summarized in a similar manner. Baseline is defined as the result closest and prior to dose which may include unscheduled or recheck results. This will typically be the result collected on Day -1 of each period. Postdose unscheduled events or rechecks will not be included in summaries. Similarly, early termination results will not be included in summaries.

For each laboratory test, a shift table will be developed to compare the frequency of the results at baseline (above normal, normal, or below normal) with the respective Day 3 postdose results. For urinalysis tests, the categories are normal and outside normal.

7.5 Vital Signs

Blood pressure (systolic and diastolic), heart rate, respiratory rate, and temperature will be measured at Screening, Day -1 (within 24 hours prior to oral dosing) and Day 1 Hour 0.5 of each period, Day 1 Hour 2 of Period 2, and Discharge or Early Termination (respiratory rate and temperature will not be measured at Discharge or Early Termination).

Descriptive statistics will be presented for each vital sign parameter by assessment time point (and by treatment for baseline and Day 1 Hour 0.5 and Hour 2 [Period 2 only] time points). Change from baseline will be summarized in a similar manner. Baseline is defined as the result closest and prior to dose which may include unscheduled or recheck results. This will typically be the result obtained on Day -1 of each period. Postdose unscheduled events or rechecks will not be included in summaries. Similarly, early termination results will not be included in summaries.

7.6 Electrocardiogram

12-lead ECGs [heart rate (HR), PR, QRS, QT, and corrected QT (QTc) interval using Fridericia's correction (QTcF)] will be performed at Screening, Day -1 (within 24 hours prior to oral dosing) of each period, Day 1 Hour 0.5 of Period 2, and Discharge or Early Termination.

Descriptive statistics will be presented for each ECG parameter by assessment time point (and by treatment for baseline and Day 1 Hour 0.5 [Period 2 only] time points). Change from baseline will be summarized in a similar manner. Baseline is defined as the result closest and prior to dose which may include unscheduled or recheck results. This will typically be the result obtained on Day -1 of each period. Postdose unscheduled events or rechecks will not be included in summaries. Similarly, early termination results will not be included in summaries.

All ECG data will be listed by subject and QTcF values that are > 450 msec and increase from baseline > 30 msec will be flagged.

7.7 Concomitant Medications

All concomitant medications recorded during the study will be coded with the World Health Organization (WHO) Dictionary Version 01-Mar-2020 b3 and listed.

7.8 Physical Examination

Physical examinations will be performed at Screening Day -1 of each period, and Discharge or Early Termination. Symptom-driven physical examinations may be performed any time, at the Investigator's discretion. Abnormal findings will be reported as medical history or adverse events. All data found in the CRF will be listed.

7.9 Neurological Examination

Neurological examinations will be performed at Screening Day -1 of each period, and Discharge or Early Termination. Results of neurological examinations will be listed by subject.

7.10 Columbia Suicide Severity Rating Scale (C-SSRS)

Assessments of C-SSRS questionnaires will be performed using Baseline/Screening Version at screening and Since Last Visit Version at Day -1 of each period, Day 3 of Period 1, and Discharge or Early Termination. The C-SSRS results will be listed by subject.

8. SUMMARY OF CHANGES FROM PROTOCOL-PLANNED ANALYSIS

The analyses described in this SAP are aligned with those analyses described in the protocol.

9. SUMMARY TABLES AND FIGURES

Summary tables and figures are numbered following the International Council for Harmonisation (ICH) structure but may be renumbered as appropriate during the compilation of the tables and figures for the CSR. Note that all summary tables and figures will be generated using SAS® Version 9.4 or higher.

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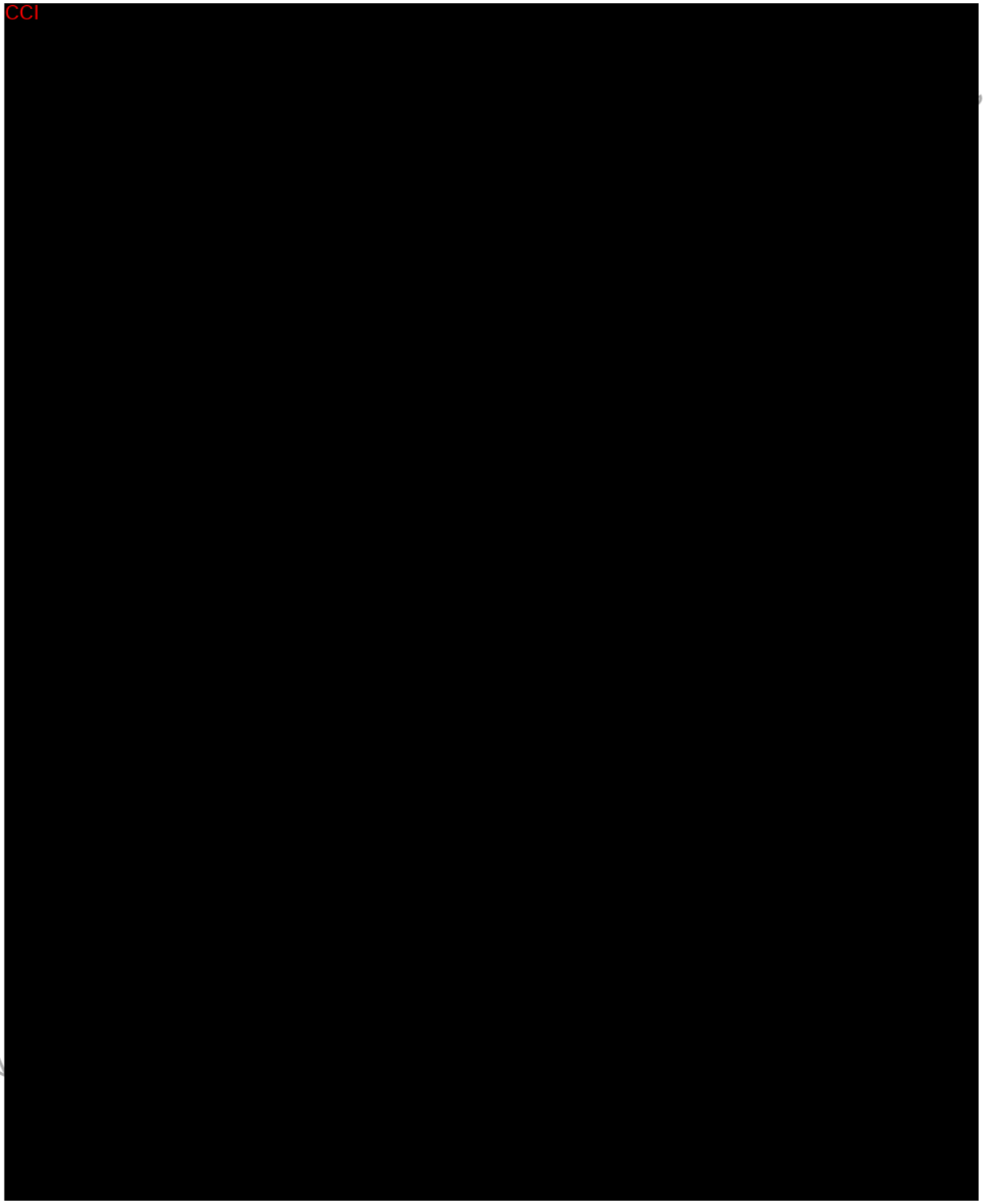

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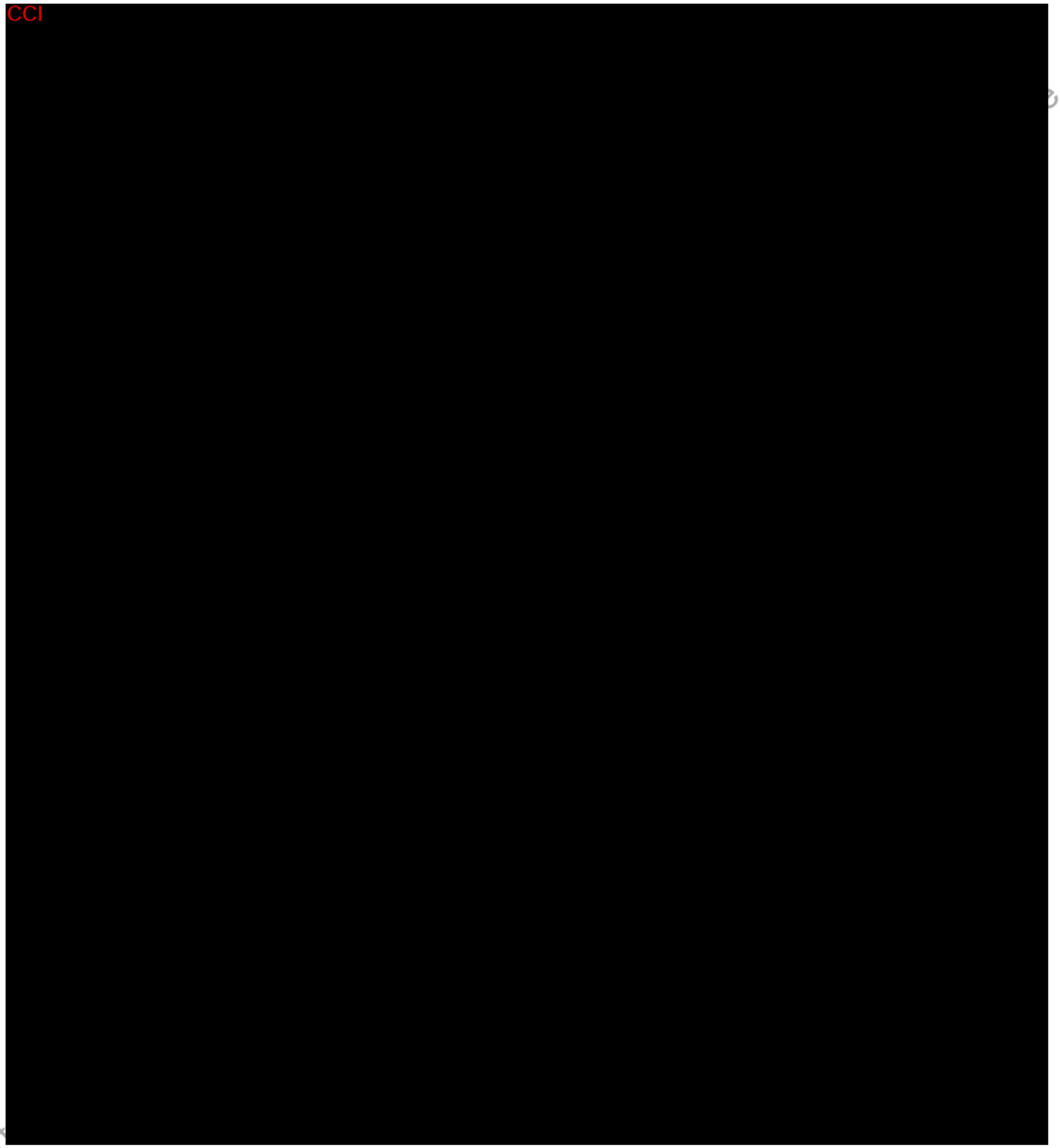

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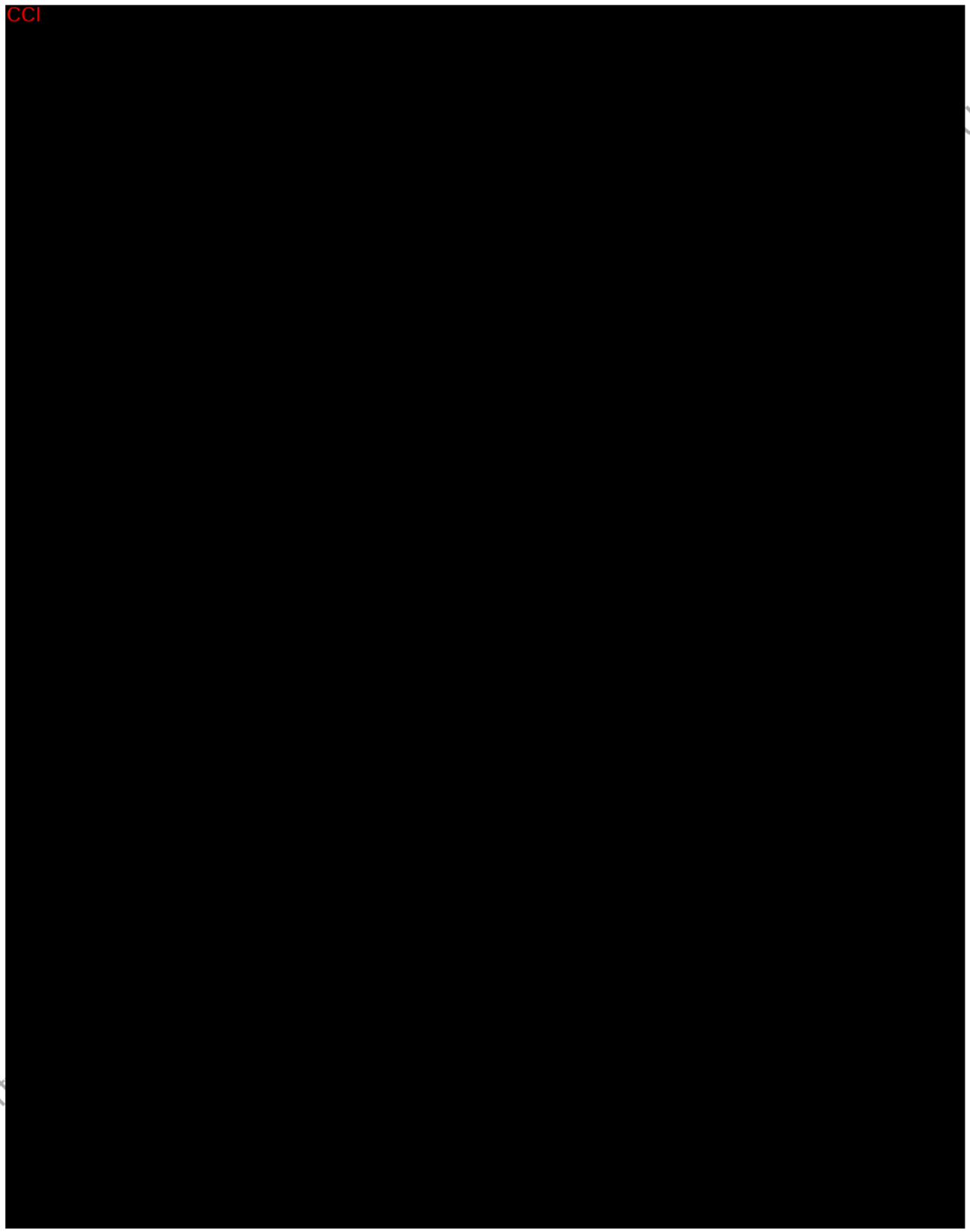

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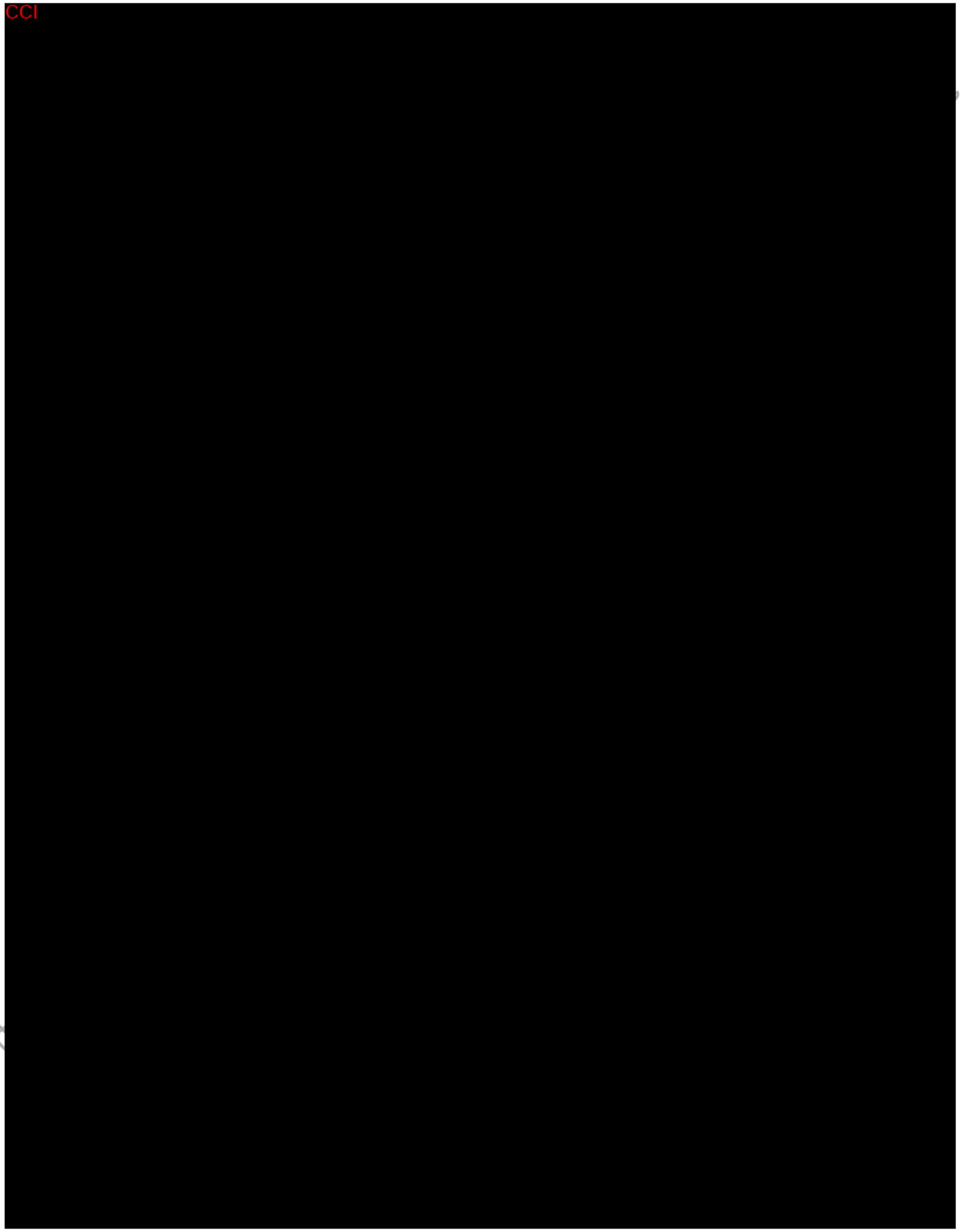

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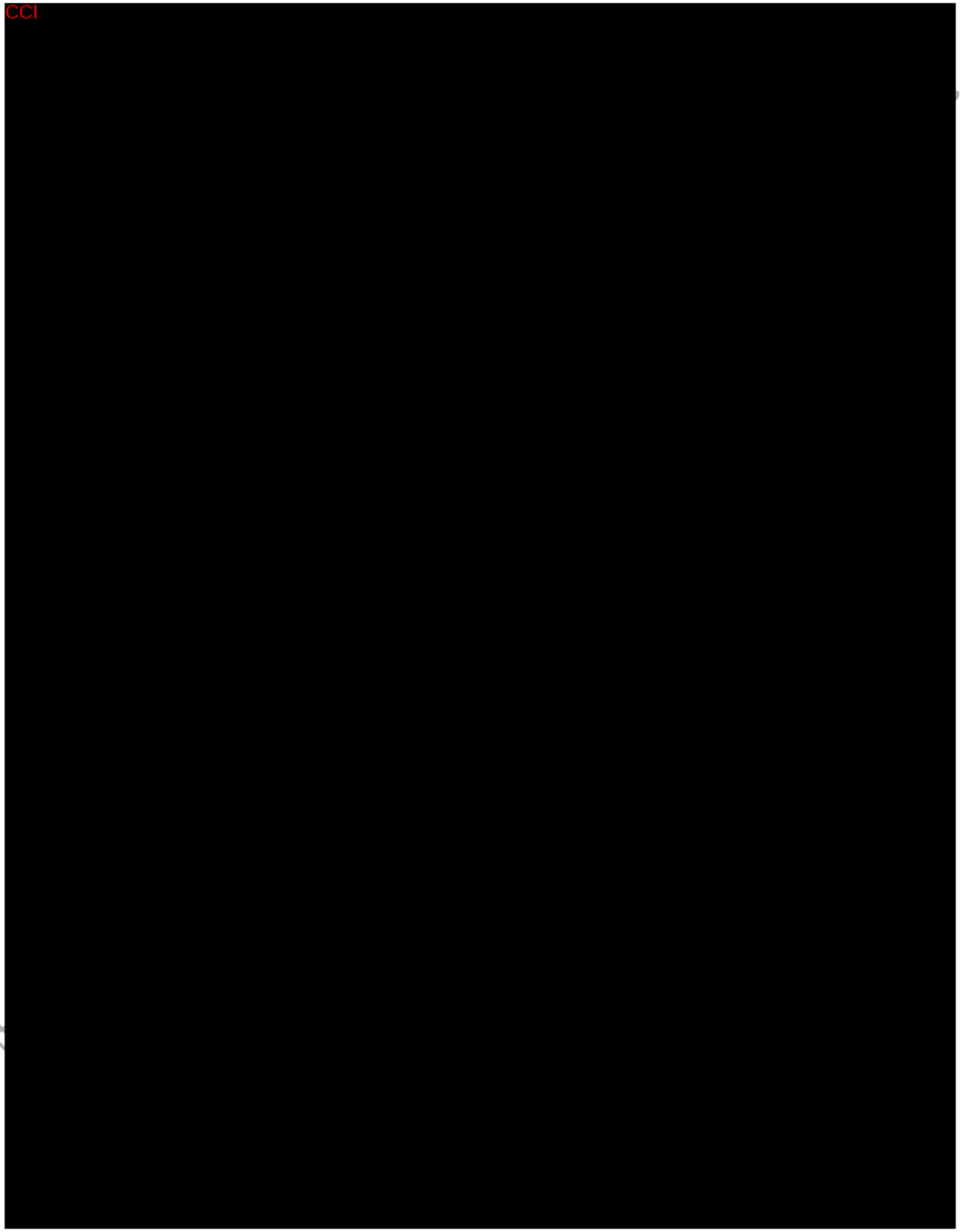

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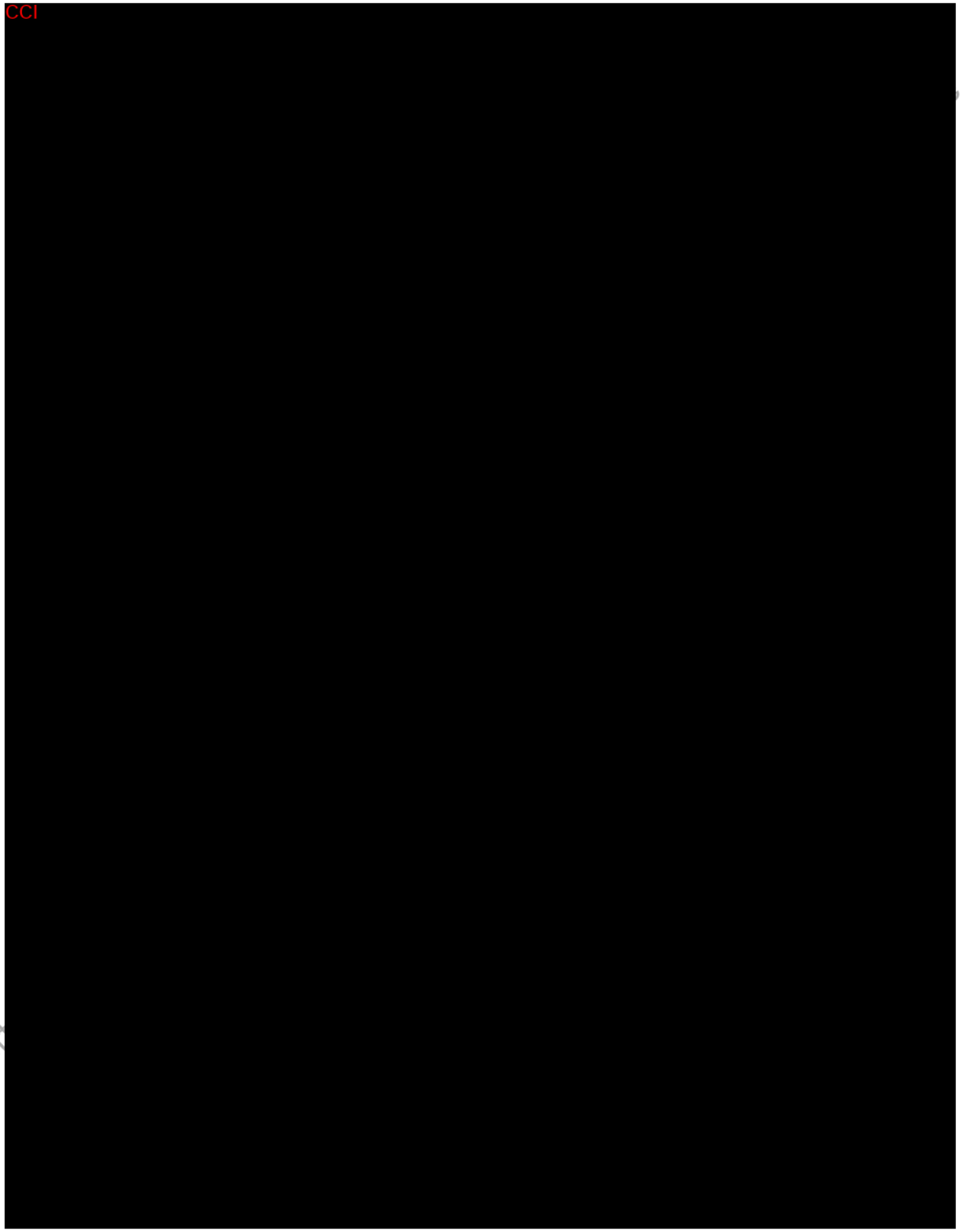

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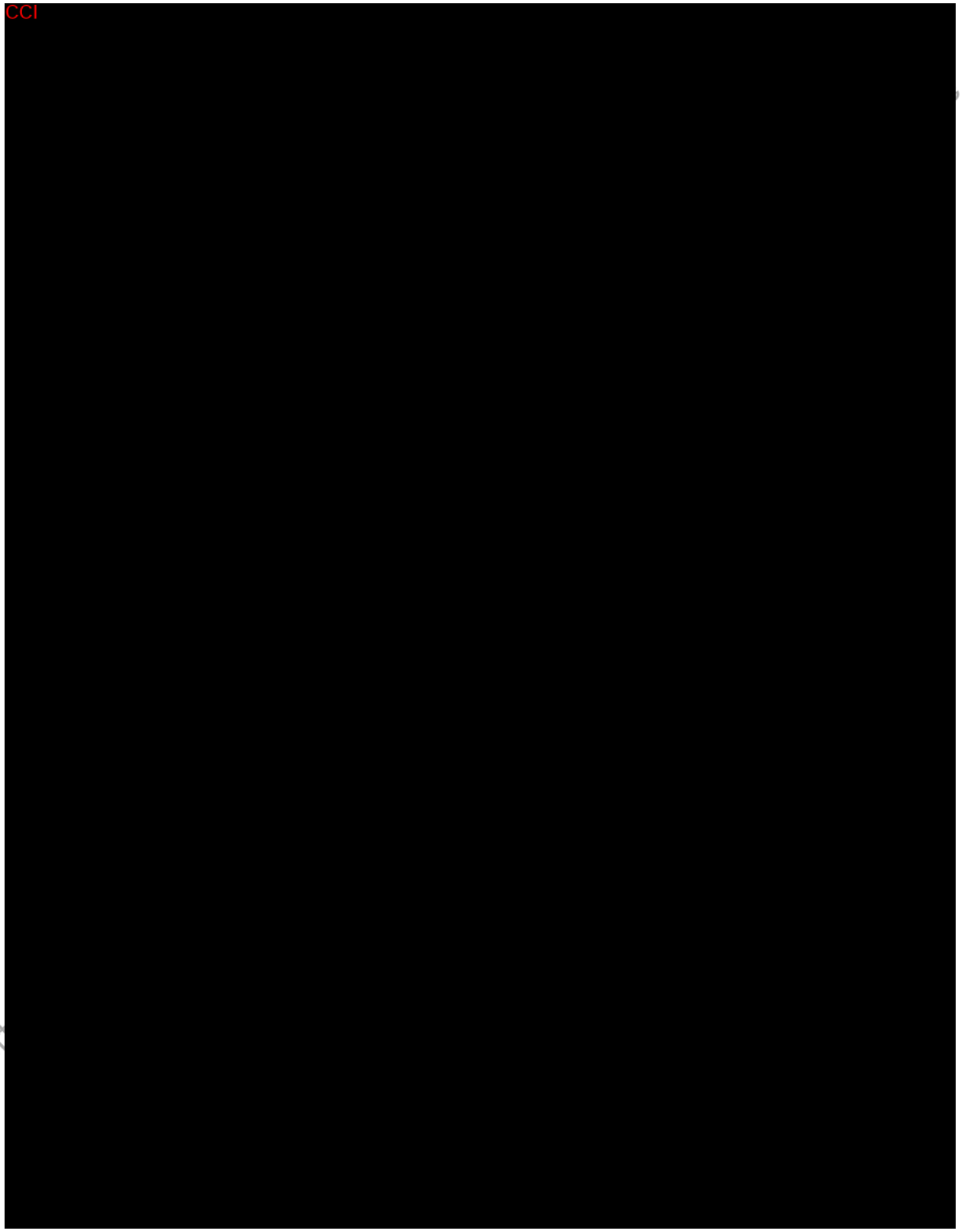

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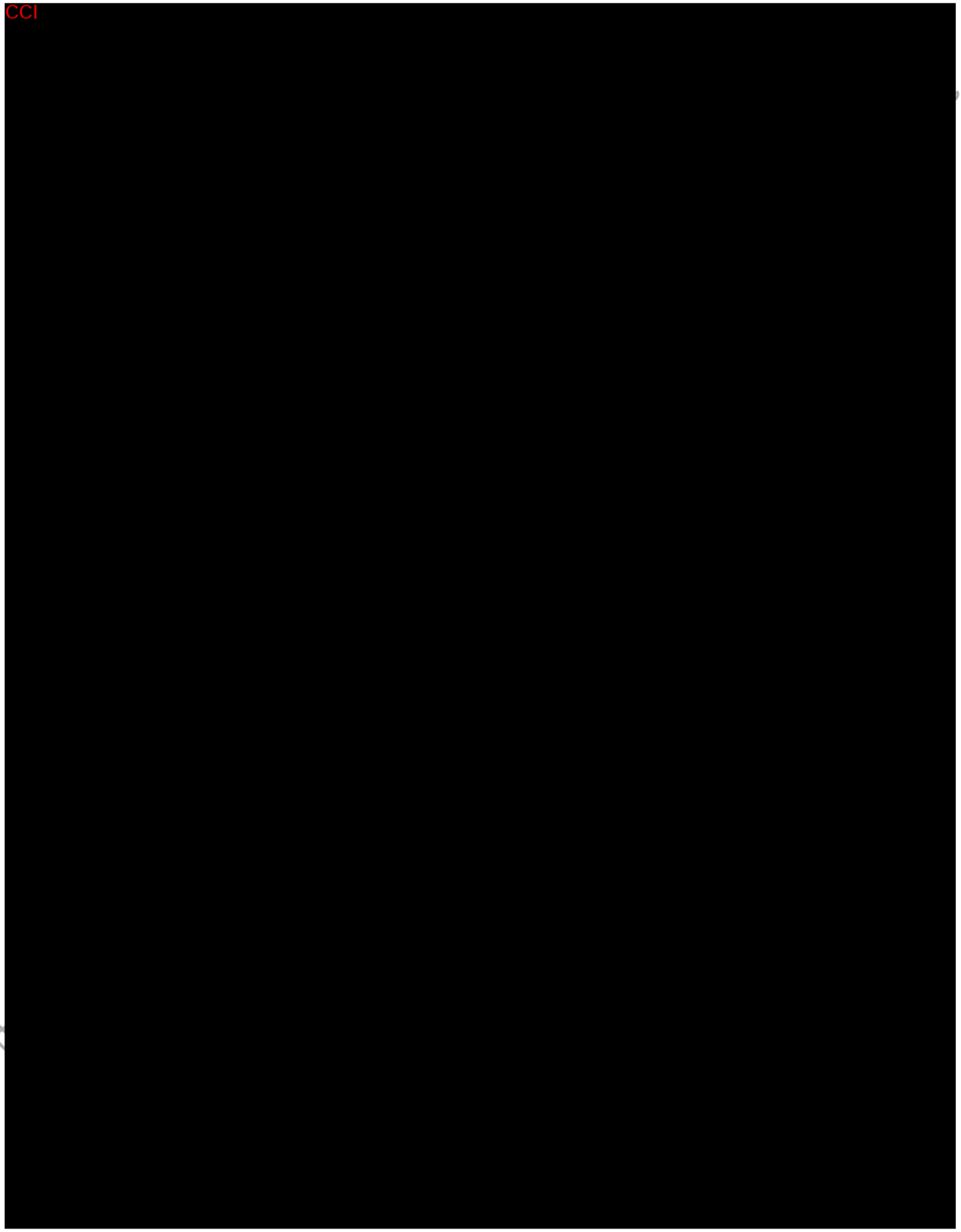

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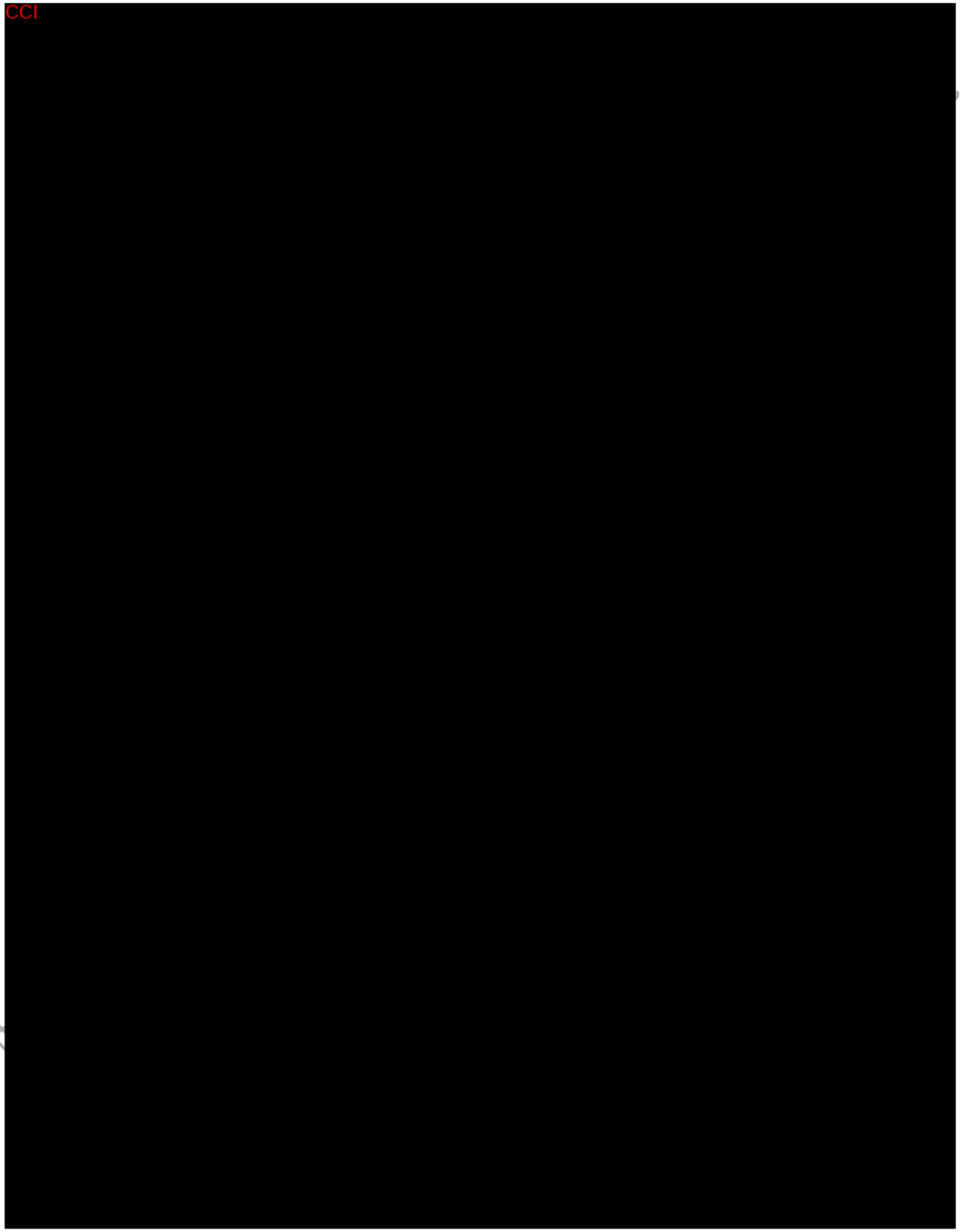

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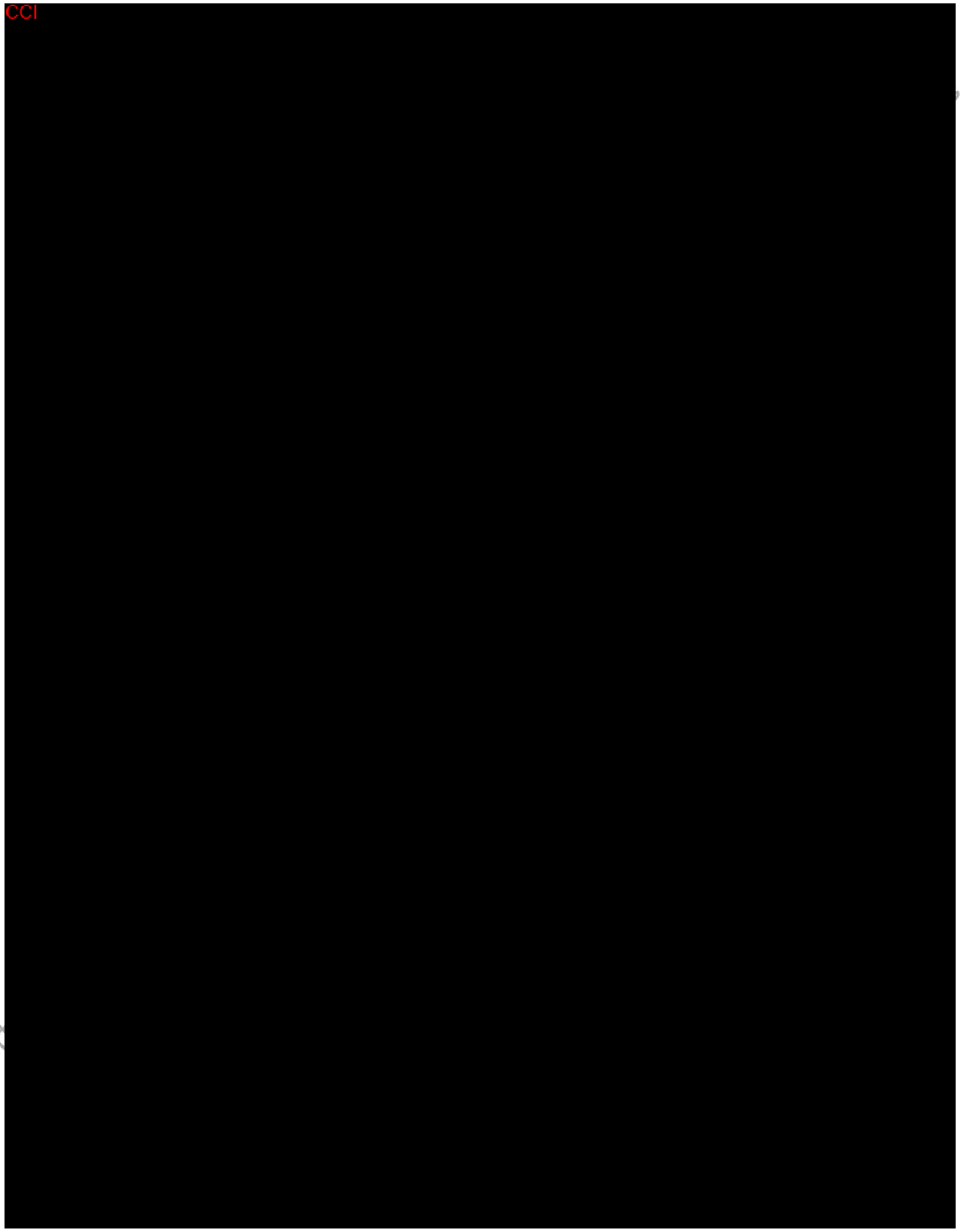

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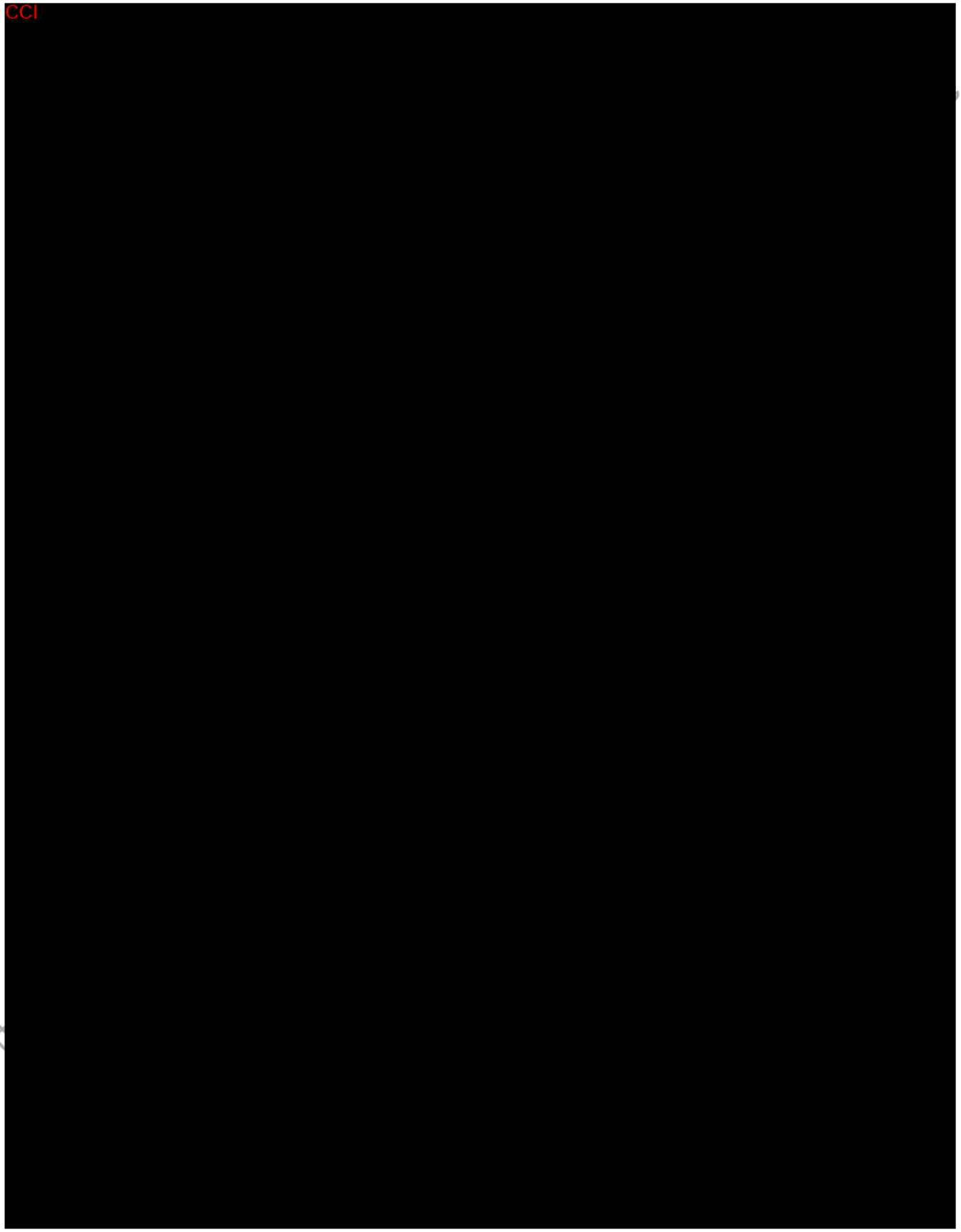

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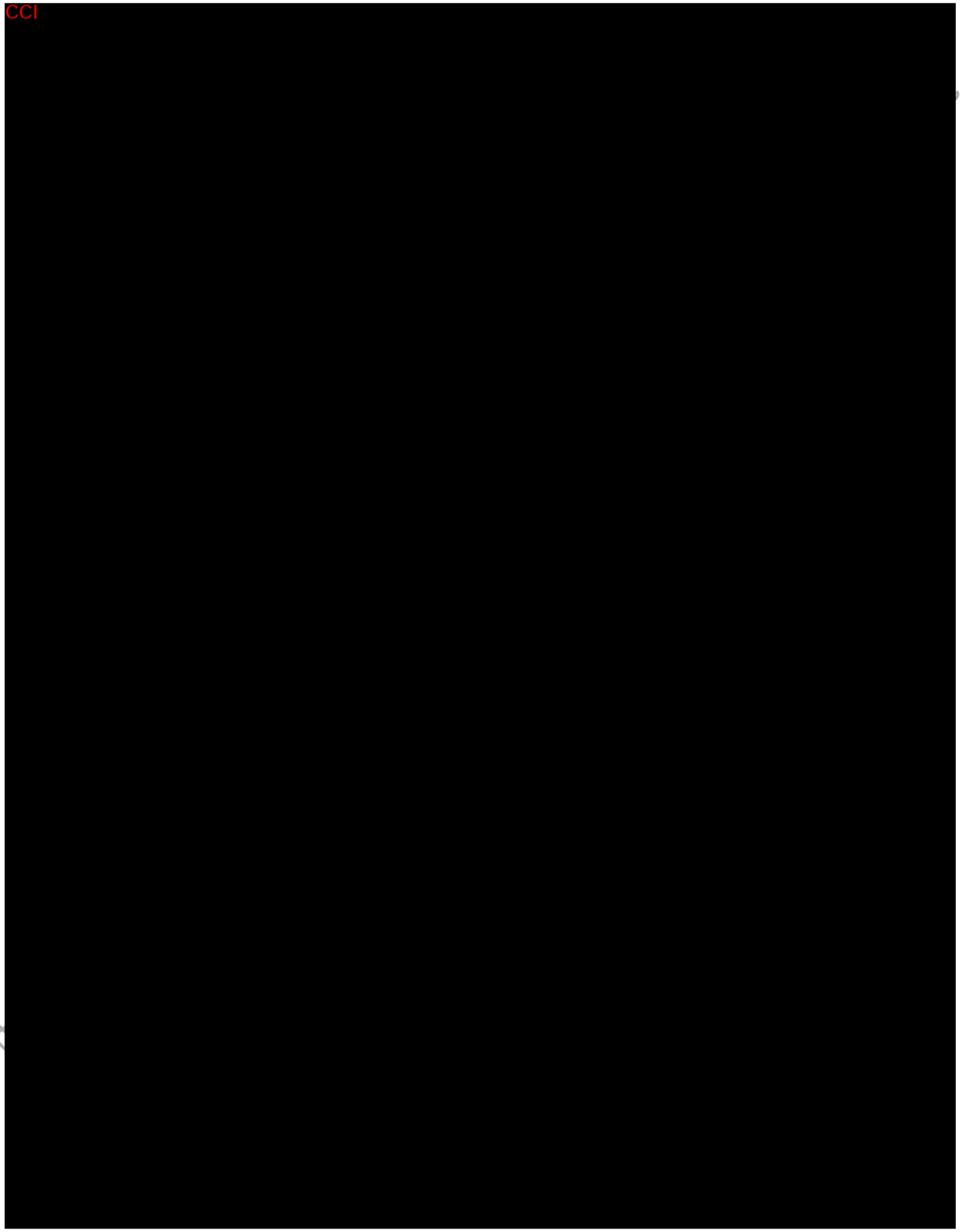

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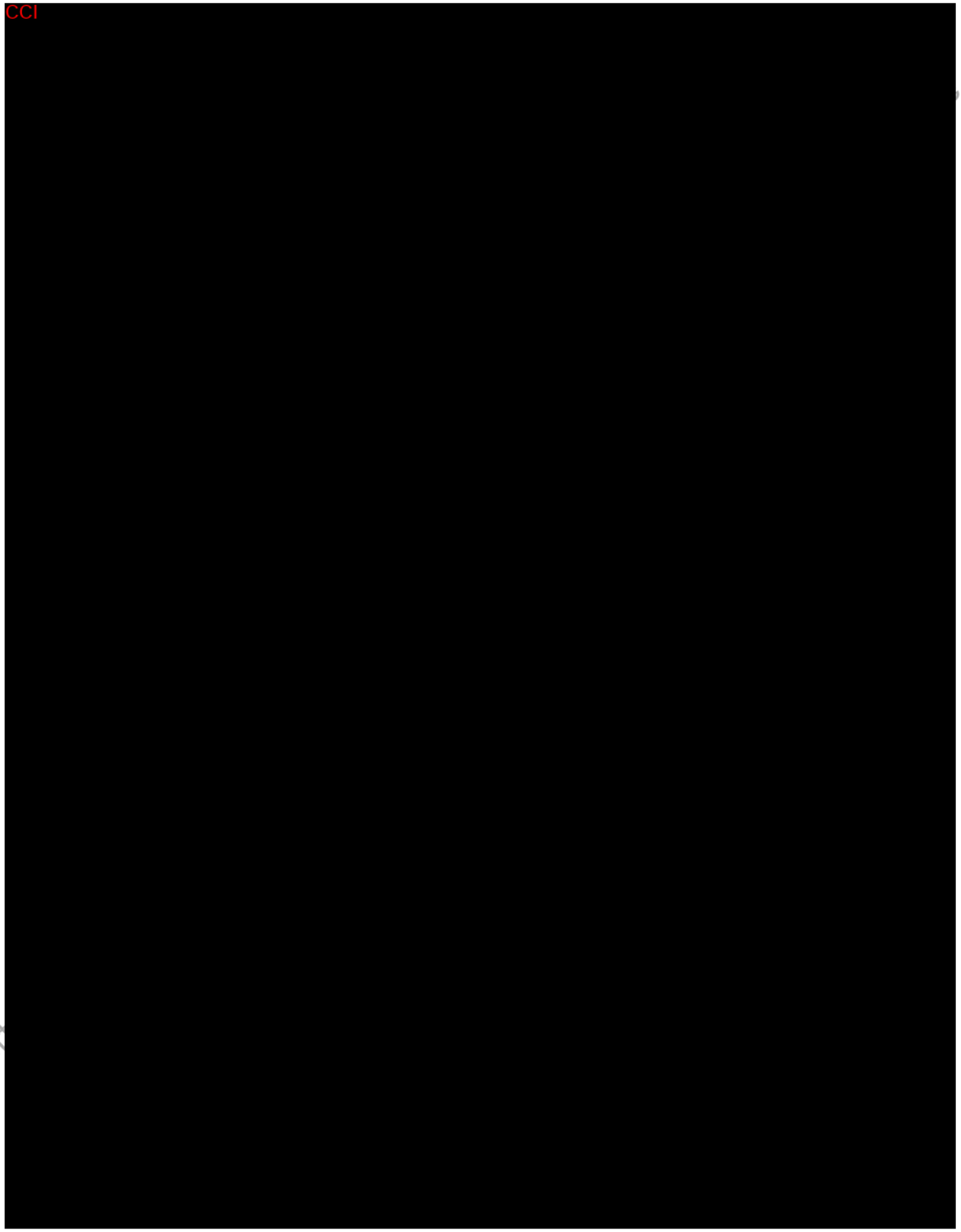

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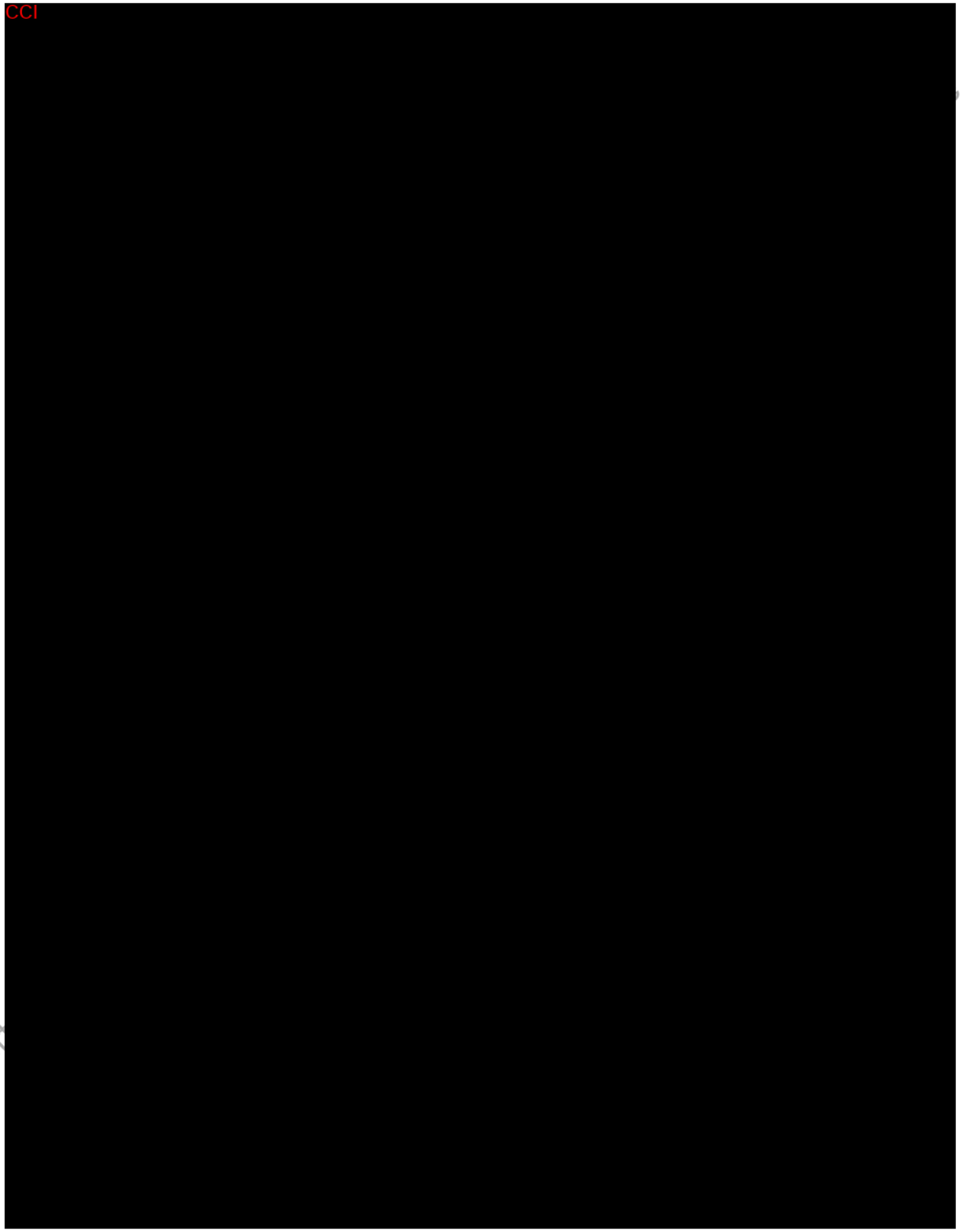

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