COVANCE

Ipsen Innovation

Protocol No.: D-FR-52120-223

A PHASE III, MULTICENTER, RANDOMISED, DOUBLE-BLIND, PARALLEL GROUP, PLACEBO CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF ONE OR MORE INTRADETRUSOR TREATMENTS OF 600 OR 800 UNITS OF DYSPORT FOR THE TREATMENT OF URINARY INCONTINENCE IN SUBJECTS WITH NEUROGENIC DETRUSOR OVERACTIVITY DUE TO SPINAL CORD INJURY OR MULTIPLE SCLEROSIS

Covance Study ID: 000000146513

STATISTICAL ANALYSIS PLAN

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APPROVALS

The undersigned agree that all required reviews of this document are complete, and approve this Statistical Analysis Plan v1.0 as final. Programming of the tables, figures and listings based upon the specifications within this document can proceed.

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REVIEWERS

The following reviews of the SAP were conducted:

Name and Title	Role	Last Version Reviewed	Company/ Organisation
PPD	PPD	Pre-final 4	Covance
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Pre-Final	16-March-2018
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TABLE OF CONTENTS

GLOSSARY OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
AESI	Adverse events of special interest
ANCOVA	Analysis of Covariance
ASIA	American Spinal Injury Association
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
BTX	Botulinum Toxin
BTX-A	Botulinum Toxin Type A
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIC	Clean intermittent catheterisation
Cm	centimetre
CS	Compound symmetry
CSR	Clinical Study Report
DBPC	Double-blind placebo-controlled
DC	Detrusor compliance
ECG	Electrocardiogram
EFP	End fill pressure
EOS	End of study
EQ-5D-5L	EuroQol 5-dimension 5-level
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GLMM	Generalised Linear Mixed Model
Ho	Null hypothesis
Ha	Alternative hypothesis
ICH	International Conference on Harmonisation
IDC	Involuntary detrusor contraction
IMP	Investigational medicinal product
I-QoL	Incontinence quality of life
IVRS	Interactive Voice Response System
Kg	kilogram
LOCF	Last observation carried forward
LPLV	Last patient last visit
LSMEANS	Least square means
n	Number of subjects
NA	Not applicable
MAR	Missing at random
MCC	Maximum cystometric capacity
MDP	Maximum detrusor pressure
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed model repeated measures
mPGI-I	Modified patient global impression – improvement
mITT:	Modified Intention-To-Treat
MS	Multiple sclerosis
NDO	Neurogenic detrusor overactivity
PdetMax@1stIDC	Maximum detrusor pressure at first involuntary detrusor contraction
PP	Per-protocol
PT	Preferred Term

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System®
SCI	Spinal Cord Injury
SD	Standard Deviation
SMQ	Standardised MedDRA Query
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TFLs	Tables, Figures and Listings
U	Units
UTI	Urinary tract infection
UI	Urinary incontinence
VC	Variance components
vs	Versus
Vol@1stIDC	Volume at first involuntary detrusor contraction
WHO	World Health Organisation

1 SOURCE DOCUMENTS

This statistical analysis plan (SAP) Final v1.0 has been developed to supplement the statistical analysis described in the clinical trial protocol (D-FR-52120-223).

This SAP Final v1.0 describes the methodology and considerations of the planned analyses and a list of all the tables, figures and listings (TFLs) for this study. A detailed description of the planned TFLs will be provided in a separate TFLs shell document. Any minor changes to the TFL shells including but not limited to changes in TFL numbering, TFL footnotes or to the title of the TFLs will not require a revision to this SAP Final v1.0. Any major changes to the TFL shells or SAP Final v1.0 text may result in a revised amendment to this SAP.

This SAP and any amendments will be finalized prior to the lock of the clinical database. Any changes to the analyses described in this document or additional analyses performed to supplement the planned analyses will be described in the clinical study report (CSR).

The SAP was written based on the following documentation:

- International Council on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" (ICH Guideline E9 1998)
- ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports" (ICH Guideline E3 1996)

Document	Date	Version
Protocol	14 September 2015	Final 1.0
Protocol Amendment 1	20 April 2018	Final 2.0
CCI [redacted]	19 September 2017	
eCRF	18 October 2017	Final 3.0
Data Model Specification for CRF Health	17 February 2016	Version 2
Trial Manager Tailoring Specification for CRF Health	23 May 2016	Version 4
I-QOL User Manual	March 2013	US English
Bladder Diary Terminology Document	07 April 2017	Version 3
EQ-5D-5L User Guide	April 2015	Version 2.1
222 SAP	08 March 2018	Final

2 PROTOCOL DETAILS

2.1 Study Objectives

Primary Study Objective:

- To assess the efficacy of two Dysport doses (600 units [U] and 800 U), compared to placebo in reducing urinary incontinence (UI) from Baseline to Week 6 following the first investigational medicinal product (IMP) administration.

Secondary Study Objectives:

- To assess the efficacy of two Dysport doses (600 U and 800 U), compared to placebo in improving bladder diary measures, urodynamic and patient-reported efficacy endpoints following the first IMP administration, including assessing duration of effect.

- To assess the efficacy of two Dysport doses (600 U and 800 U) in improving bladder diary measures and patient-reported efficacy endpoints following retreatment IMP administrations, including assessing duration of effect.
- To assess the safety of two Dysport doses (600 U and 800 U) for the treatment of UI due to neurogenic detrusor overactivity (NDO).

2.2 Overall Study Design

This is a Phase III, multicenter, randomised, double-blind, parallel group, placebo controlled study to assess the efficacy and safety of two Dysport doses (600 U and 800 U) administered to the bladder of adult subjects with NDO due to spinal cord injury (SCI) or multiple sclerosis (MS).

The target population is subjects with UI caused by NDO due to either SCI or MS, who have not been adequately managed with oral medication and who routinely require clean intermittent catheterisation (CIC) to manage their bladder function.

The study will include two treatment periods.

- A double-blind placebo controlled (DBPC) treatment, i.e. following Treatment 1 on Day 1 during which subjects receive a single IMP treatment administration of either
  - Dysport 600 U
  - Dysport 800 U
  - Placebo.

  DBPC Cycle will run from randomisation and treatment on Day 1 to the administration of Treatment 2. The length of the DBPC period will depend on when the patient receives Treatment 2.
- A subsequent double-blind active treatment period, during which subjects can receive multiple active IMP retreatment administrations of either;
  - Dysport 600 U
  - Dysport 800 U.

  Subjects who were randomised to receive Dysport at Treatment 1 (600 U or 800 U) will continue to receive the same dose for all subsequent treatments and those who were initially randomised to placebo will receive either 600 U or 800 U, depending on their allocated randomisation sequence (see next section).

The study contains two subsets:

•Urodynamic subset (planned ≥ 200 subjects)

o All subjects in this subset must have standardised urodynamics (as described in the Study Specific Urodynamic Manual) during Screening and at Week 6 following each study treatment

o Screening standardised urodynamics must confirm the presence of NDO

•Non-Urodynamic subset

o All subjects in this subset must have documented urodynamic proven NDO in the 12 months prior to Screening. If not, then urodynamics must be performed per local practice during Screening to confirm the diagnosis of NDO

o Urodynamics will not be performed in the post-screening period in this subset

Screening

Screening period will last for up to 30 days, but can be extended in certain circumstances to obtain an appropriately and fully completed bladder diary or to obtain a valid bladder diary. Furthermore, where a urinary tract infection (UTI) occurs after completion of the bladder diary and impacts the ability to perform urodynamics, the time to Screening Visit 2 can be extended until the UTI is resolved. During the screening period, informed consent will be obtained and eligibility for study participation will be assessed. Subjects will complete a 7-day bladder diary, urodynamic assessment, patient-reported outcome questionnaires and have blood and urine samples taken.

Randomisation/treatment

The Treatment Visit (Day 1) should occur up to 14 days after the screening period, but can be extended until the UTI is resolved (where a UTI has occurred and impacts the ability to perform IMP administration). At the Treatment 1 visit on Day 1, subjects who meet all the eligibility criteria will be randomised (in a 2:2:1:1 ratio) to one of four treatment sequences:

Sequence	Subjects	1st Treatment in DBPC Cycle	Subsequent retreatment(s) in Dysport Cycles (Dysport Cycle 1, Dysport Cycle 2, etc)
1	110 subjects	Dysport 600 U	Dysport 600 U
2	110 subjects	Dysport 800 U	Dysport 800 U
3	55 subjects	Placebo	Dysport 600 U
4	55 subjects	Placebo	Dysport 800 U

During the analysis of DBPC cycle, the two placebo containing sequences will be pooled into a single arm.

Randomisation will be stratified by;

- Aetiology of NDO (SCI or MS)
- Previous intradetrusor botulinum toxin type A (BTX-A) usage (BTX-A naïve vs. BTX-A non-naïve).

Follow-up (after IMP administration in DBPC cycle):

- Week 1 (Day 8) (telephone)
- Week 2 (Day 15) (clinic visit)
- Week 4 (Day 29) (telephone)
- Week 6 (Day 43) (clinic visit; primary timepoint)
- Week 12 (Day 85) (clinic visit; the retreatment could be requested by subject from this visit)
- Every 12 weeks (telephone visits; until retreatment received or end of study (EOS) at Weeks 104 to 116).

Details of the procedures performed at each visit following the first treatment are shown in the schedule of assessments, Appendix V.

Retreatment assessment

A subject may request retreatment with IMP at any time ≥12 weeks after their most recent study treatment.

The retreatment criteria are as follows:

1) Retreatment requested by subject;
2) More than 12 weeks (84 days) since the previous IMP administration;
3) CCI [redacted];
5) In the investigator's opinion it is safe and appropriate to provide retreatment.

A patient may only be retreated if eligible based on the study retreatment criteria. The bladder diary device/portal may provide an indication that the patient is within 30% of their Baseline (Screening) UI level, however to confirm eligibility a manual calculation can be performed by multiplying the weekly number of UI episodes on the screening bladder diary by 0.7. If the subject has a current number of weekly UI episodes greater than this calculated number then the subject is within 30% of their Baseline UI level and meets the retreatment criterion #3.

Example calculation:

- Study Baseline (Screening) number of weekly UI episodes = 28 episodes
  28 episodes x 0.7 = 19.6 (rounded up to 20)
- Subject is therefore eligible for retreatment if current weekly UI episodes are 20 or more.

Retreatment should ideally occur within 14 days of confirmation of eligibility for retreatment and can occur up to and including Week 104 following the first IMP administration of the first period.

Retreatment follow-up

Follow-up after each retreatment follows the same schedule as the first IMP administration (Treatment 1).

- Week 1 (Day 8) (telephone)
- Week 2 (Day 15) (clinic visit)
- Week 4 (Day 29) (telephone)
- Week 6 (Day 43) (clinic visit)
- Week 12 (Day 85) (clinic visit; the retreatment could be requested by subject from this visit)
- Every 12 weeks (telephone visits; until retreatment received or EOS at Weeks 104 to 116).

Details of the procedures performed at each Retreatment Follow-up Visit in the Dysport cycle are contained in Appendix V.

End of Study Visit

The EOS Visit will take place between 104 and 116 weeks after the first IMP administration on Day 1. Subjects may receive study retreatment up to and including Week 104 and a minimum of 12 weeks of follow-up is required after each IMP administration. For those subjects completing the study, the EOS Visit will occur:

- At Week 104 after the first IMP administration, if it has been more than 12 weeks since the previous IMP administration.
- At Week 12 Retreatment Follow-up Visit, if the subject received their most recent IMP administration between Week 92 and Week 104 following their first IMP administration.

Early discontinuation

A subject who discontinues the study early should, if at all possible, be followed-up for at least 12 weeks following their most recent IMP administration and should attend the EOS Visit.

Duration of subject participation

104 weeks (24 months) to 116 weeks depending on the timing of final IMP administration.

2.3 Sample Size and Power

The sample size is based on the ability to detect a statistically significant treatment difference in the weekly number of UI episodes at Week 6 following the first IMP administration in the two Dysport arms (600 U and 800 U) compared to the placebo arm.

Assuming a weekly decrease of 21 UI episodes in each Dysport arm and a weekly decrease of 12 UI episodes in the placebo arm, with a common standard deviation of 20 UI episodes, 80% power, and an alpha of 0.025 (as testing of both the 600 U and 800 U doses vs. the placebo dose will be performed simultaneously), a sample size of 96 subjects per dose group (a total of 288 subjects) is needed. Dropout between randomisation and Week 6 (primary efficacy timepoint) is expected to be 10%, and thus a total of 318 subjects would be needed to be enrolled. However, in order to ensure that the development program will deliver adequate Dysport exposure data to meet ICH E1 guideline recommendations, a total of 330 subjects are planned to be randomised. Subjects who leave the study early will not be replaced.

Sample size calculations were performed in SAS Studio 3.6.

3 EFFICACY AND SAFETY VARIABLES

For the purpose of all analysis, the study baseline is defined as the last value available during screening or day of treatment visit prior to the first study IMP treatment administration (Treatment 1) i.e. prior to the DBPC Cycle. This study baseline will be used in analysis of the efficacy endpoints and the safety endpoints for all treatment cycles.

3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the mean change from study baseline in weekly number of UI episodes at Week 6 after the first IMP administration (Treatment 1).

3.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are divided into those that relate to parameters measured in the bladder diary, those measured by urodynamic filling cystometry and those that are quality of life measures. From these secondary measures, there are two that have been selected to be analysed as part of a hierarchal testing scheme see Section 3.2.1.

Bladder diary measures:

Mean change from study baseline to post-treatment timepoints in the following variables:

- weekly number of UI episodes (except for week 6 after Treatment 1 which is the primary efficacy endpoint)
- total daily urinary frequency (spontaneous void and CIC)
- daily spontaneous voiding frequency
- daily CIC frequency
- total 24-hour voided volume (spontaneous void and CIC)
- 24-hour voided volume (spontaneous void only)
- 24-hour voided volume (CIC only)
- total volume per void (spontaneous void and CIC)
- volume per void (spontaneous void only)
- volume per void (CIC only)

Proportion of subjects with:

- no episodes of UI (i.e. 100% improvement where continence is achieved)
- UI response at several levels (i.e. ≥30% improvement, ≥50% improvement, ≥75% improvement)

Urodynamic filling cystometry measures (urodynamic subset only):

Mean change from study baseline to week 6 after Treatment 1 in the following variables:

- MCC
- MDP during storage
- Vol@1stIDC (subjects without a post-treatment IDC will have their Vol@1stIDC imputed from their MCC)
- maximum detrusor pressure at first involuntary detrusor contraction (PdetMax@1stIDC)

- end fill pressure (EFP)
- detrusor compliance (DC)

Proportion of subjects with:

- No IDCs (i.e. urodynamic cure is achieved)

Patient-reported outcome questionnaires:

Mean change from study baseline to post-treatment timepoints in the following variables:

- I-QoL total summary score
- I-QoL Score of domain: Avoidance and limiting behaviour
- I-QoL Score of domain: Psychosocial impact
- I-QoL Score of domain: Social embarrassment
- EuroQol 5-dimension 5-level (EQ-5D-5L): Total descriptive score
- EQ-5D-5L: self-rated health (VAS)
- modified patient global impression - improvement (mPGI-I) score (to be assessed at each timepoint without comparison to baseline)

Duration of effect following the first and subsequent treatments

- time to request retreatment
- time to eligibility for retreatment
- time between treatments.

Detailed definitions of all efficacy endpoints are presented in Appendix II.

3.2.1 Hierarchical Analysis of Selected Secondary Endpoints

A hierarchical analysis will be performed in the order listed for the following secondary efficacy endpoints at Week 6 after Treatment 1:

1) Proportion of subjects with no episodes of UI (i.e. continence is achieved):
   - measured by 7-day bladder diary.
2) Mean change from study Baseline (assessed at Screening) in the I-QoL total summary score:
   - measured by patient-reported questionnaire.

3.3 Safety Variables

Safety will be assessed throughout the study by evaluating:

- Treatment Emergent Adverse Events (TEAEs)
- Adverse events of special interest (AESI)

  - Adverse events (AEs) related to toxin spread
  - AEs related to hypersensitivity
- Other protocol defined TEAEs
  - Urinary Tract Infections (UTI)
- Vital signs (heart rate, respiratory rate, blood pressure and body temperature)
- Laboratory blood parameters (haematology and serum chemistry)
- Laboratory urine parameters (laboratory urinalysis/microscopy, culture and sensitivity)
- Development of BTX-A antibodies (neutralizing)
- Usage of concomitant medications and therapies.

Timepoints for safety evaluations are detailed in Appendix V.

4 PHARMACOKINETIC/PHARMACODYNAMIC VARIABLES

Not applicable.

5 ANALYSIS POPULATIONS

5.1 Screened Population

Screened population includes all subjects screened (enrolled); these are subjects who have signed the informed consent.

5.2 Randomised Population

All subjects assigned a randomisation number. Randomised subjects will be analysed according to their randomised treatment.

5.3 Safety Population

All subjects who received at least one IMP administration (including only partial administration) of the IMP. Safety subjects will be analysed according to their actual treatment received.

5.4 Modified Intention-to-Treat Population

All randomised subjects who received at least one IMP administration. Modified intention-to-treat (mITT) subjects will be analysed according to randomised treatment.

5.5 Per Protocol Population

All subjects in the mITT population who have no important protocol deviations that could potentially affect the primary efficacy endpoint outcome for the subject. Per Protocol (PP) subjects will be analysed according to the randomised treatment.

5.5.1 Protocol Deviations

Protocol deviations are defined as any change, divergence, or departure from the study design or procedures defined in the study protocol. Important protocol deviations are a subset of protocol deviations that may significantly impact the correctness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. A detailed list of protocol deviations that will be mapped to protocol deviation coded term based

on Ipsen SDTM+ User Guide are contained in the separate document titled "Ipsen 222 and 223: Protocol Deviations"; this will be standalone working document which will be finalised prior to database lock.

5.5.1.1 Important Protocol Deviations Leading to Exclusion from the PP Analysis

Only those important protocol deviations considered to have a major effect on primary efficacy analysis will lead to complete exclusion of the patient from the PP population. The majority of the important protocol deviations leading to exclusion from the PP population will be determined programmatically from the data. Those criteria which require clinical or medical monitoring interpretation will be reviewed prior to database lock these will be outlined in the "Ipsen 222 and 223: Protocol Deviations" document.

5.5.1.2 Handling of Stratification Factors

Stratification errors (e.g. previous intradetrusor BTX-A usage) discovered after randomisation cannot be changed in the IVRS system and subjects will be analysed according to their eCRF recorded strata (i.e. correct strata) for the primary analysis of efficacy.

Mis-stratifications will be documented as a protocol deviation, and the incorrect stratification recorded in Interactive Voice Response System (IVRS) (NDO medical history for aetiology of NDO [SCI or MS], and prior medications for previous intradetrusor BTX-A usage for UI [BTX-A naïve or BTX-A non-naïve] in the bladder) will be used to perform a sensitivity analysis on the primary endpoint. A listing with the eCRF versus IVRS recorded stratifications will be displayed for the randomised subjects.

5.6 Urodynamic Population

All subjects in the mITT population included in the urodynamic subset at randomisation.

6 DATA HANDLING

6.1 Time points and Visit Windows

Day 1 is defined as the day of the first IMP administration. Relative days after Day 1 are calculated as (assessment date Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date Day 1 date). The day prior to Day 1 is Day -1.

Generally, all analysis will be performed using data at nominal visits (see Table 1). Only if the data is missing, the unscheduled visits (or early withdrawal visit) within the visit window will be used in analysis of efficacy endpoints. For the 7-day bladder diary, the entire 7-day duration need not be included in the entire visit window for it to be assigned to that visit e.g. if a patient has start date of the 7-day bladder diary on Day 61, then the 7th day would fall on Day 67, and would be assigned to Week 6 diary data.

If multiple unscheduled visits occur within a single visit, then the unscheduled visit closest to the target day of the visit window will be used in the analysis. If there is a tie, the later unscheduled visit will be used in the analysis. Similarly, if there are both scheduled and unscheduled visits prior to Treatment 1 then the last assessment prior to the Treatment 1 will be used as baseline in analysis of efficacy endpoints.

Table 1 Definition of Visit Windows

Visit	Target Day of Visit[a]	Acceptable visit window mITT/PP/urodynamic analyses
Screening	Day –30	NA
Treatment visit of DBPC cycle	Day 1	NA
Week 2	Day 15	Days 8 to 22 (Day 15±7 days)
Week 6	Day 43	Days 23 to 63 (Day 43±20 days)
Week 12	Day 85	Days 64 to 106 (Day 85±21 days)
Week 24	Day 169	Days 107 to 211 (Day 169-62 days and +42 days)
Week 36	Day 253	Days 212 to 295 (Day 253-41 days and +42days)
Routine visit every 12 weeks until retreatment occurs or EOS	Day x + 84	Day x-41 days and Day x +42days)
End of Study[b] (Week 104)	Day X	Day X±14 days
Retreatment Assessment Visit		Within 14 days of request
Retreatment Visit of treatment cycle 2[c]	Day 1	Within 14 days of confirmed eligibility.
Week 2	Day 15	Days 8 to 22 (Day 15±7 days)
Week 6	Day 43	Days 23 to 63 (Day 43±20 days)
Week 12	Day 85	Days 64 to 106 (Day 85±21 days)
Week 24	Day 169	Days 107 to 211 (Day 169-62 days and +42 days)
Week 36	Day 253	Days 212 to 295 (Day 253-41 days and +42days)
Routine visit every 12 weeks until retreatment occurs or EOS	Day x + 84	Day x-41 days and Day x +42days)
End of Study[b] (Week 104 to Week 116)	Day X	Day X ±14 days

[a] Relative to the date of the first IMP administration (Day 1) of DBPC Cycle
[b] The EOS visit will occur at Week 104 for subjects who had their most recent IMP administration at Week 92 or earlier.
[c] The visit window from treatment cycle 3, 4, 5, etc. is the same as treatment cycle 2.

6.2 Handling of Dropouts or Missing Data

6.2.1 Analysis Endpoints

6.2.1.1 Efficacy Endpoints

Refer to Section 3.1 and 3.2 for the list of primary and secondary efficacy endpoints and Section 3.2.1 for the list of secondary endpoints used in the hierarchal analysis.

Bladder diary: For data collected from the 7-day bladder diary, if there is 1 or 2 days with no data, the arithmetic means recorded (on the 5 or 6 days that do have events recorded) from the bladder diary parameters will be used for the days with no recorded bladder diary data. If there are more than 2 days of missing data, then the 7-day bladder diary data will be considered invalid.

Primary efficacy endpoint: No imputation is planned for the primary analysis of the primary endpoint. A sensitivity analysis of the primary efficacy endpoint will be performed using multiple imputations (MI) for missing or invalid data (see Section 7.6.4.3).

Urodynamic secondary efficacy endpoints: All urodynamic data will be reviewed by independent central reviewers to determine the final values for the urodynamic parameters. Only the central reader urodynamic values will be used for analysis purposes. For the secondary efficacy endpoint of Vol@1stIDC, subjects who do not exhibit a post-treatment IDC after the first IMP administration will have Vol@1stIDC imputed using the recorded corrected MCC volume at that post-treatment visit.

Quality of life secondary endpoints: For I-QoL total summary score, in accordance with the I-QoL User's Manual (US English version, March 2013), if no more than three items are omitted, a normal arithmetic mean substitution will be computed for these omitted items and imputed to calculate the total summary score. If more than three items are omitted, then there will be no more imputation for those omitted items, and the total summary score will be missing. Similarly, this rule will be applied for each of the domain scores (avoiding and limiting behavior, psychosocial impact, and social embarrassment). These derived scores will be used for analysis, and the investigator recorded eCRF I-QoL total summary score, and each recorded domain score will only be listed.

The formula for the derived scale scores is as follows:

Scale Score = {(the sum of the items lowest possible score) / possible raw score range} * 100

For continuous endpoints analysed by mean or mean change values, inference will be done using mixed-models repeated measures, which assumes that missing outcomes are missing at random (MAR).

6.2.1.2 Safety Endpoints

In general, all available data from subjects who have prematurely discontinued from the study will be used for analysis. For AEs with missing information for the intensity and causality, it will be represented as a missing category.

6.2.2 Missing or Partial Date

In all listings, missing or incomplete dates will be left as they have been recorded. However, for calculation / sorting / assignation based on dates, the following methods will be used:

(1) If the onset date of an AE/concomitant medication is missing / incomplete, it is assumed to have occurred during the study treatment phase (i.e. a treatment-emergent adverse event (TEAE) for AEs) except if the partial onset date or stop date indicates differently.

(2) A missing / incomplete date of medical history or disease diagnosis will be assumed to have occurred before any study treatment. For calculation purposes, if only the year is available, then the first day of January will be used to impute, if only the day is missing then the first day of the month will be used to impute.

(3) An AE could be assigned to several possible treatment cycles according to its partial onset date and stop date. If only the AE start day is missing, then the AE will be assigned to that treatment cycle that includes the first day of that month. If the AE start date has a

missing month, then January will be used. An AE with missing start date will be assigned to each treatment cycle before its end date. The Analysis Data Model programming specifications will outline the rules in more detail. During the study, examples of date imputations will be shared with the team to ensure AE assignment to treatment cycles are in agreement with the team.

(4) In calculations with date of the first IMP administration, if missing, the date of randomisation will be used.

7 STATISTICAL METHODS

7.1 General Principles

All data processing, summarisation and analyses will be performed using the SAS Environment / Version 9.4 (or later) of the SAS® statistical software package.

All data collected during the study will be presented in listings without any imputation by treatment group, subject, assessment and visit (where applicable), unless otherwise specified.

Data will be presented in summary tables by treatment group (as described below), assessment and visit (where applicable).

Overall, the analysis strategy is to evaluate efficacy and safety data from the initial DBPC Cycle and to evaluate efficacy and safety over repeated Dysport treatments, using analyses by Dysport Cycle (Dysport Cycle 1, 2…etc.), as illustrated in schematic diagram later in this section. In general, tables associated with the DBPC Cycle will be separate from the tables assessing repeat treatment with Dysport which are presented by Dysport Cycle:

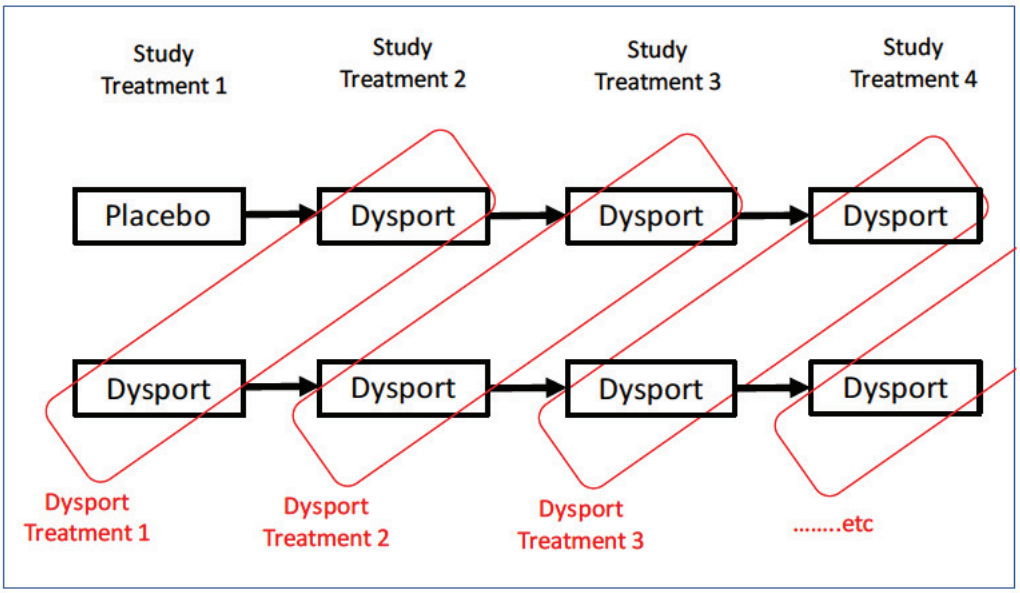
- During analysis of the DBPC (DBPC cycle), data will be displayed using the following treatment group labels, in the order presented:
    - Placebo
    - Dysport 600 U
    - Dysport 800 U
    - All Dysport
- During analysis by Dysport Cycle, data will be displayed by number of Dysport treatments (see diagram below) using the following treatment group labels:
    - Dysport Cycle 1
        - Dysport 600U
        - Dysport 800U
        - All Dysport
    - Dysport Cycle 2
        - Dysport 600U
        - Dysport 800U
        - All Dysport
    - Dysport Cycle X

- Dysport 600U
- Dysport 800U
- All Dysport

Analysis of Dysport Cycle 1 will therefore include (see diagram below):

- Data from subjects who received a Dysport treatment after having initially received placebo as their first study treatment on Day 1 i.e. will only use data from their first Dysport treatment,
- Data from subjects who received Dysport as their first study treatment on Day 1

Schematic diagram summarising concept of Dysport Cycles:



Descriptive summary statistics for continuous variables will include the number of subjects (n), mean, standard deviation (SD), median, minimum and maximum.

Descriptive summary statistics for categorical variables will include frequency counts and percentages [n (%)]. The denominator for percentage calculations will be the number of subjects in the analysis population for the designated treatment cycles. Unless stated otherwise in the table shells (e.g. for the TEAE of MS relapse, the denominator only relates to the number of MS subjects),

Dates will be displayed as DDMMMYYYY.

Overall, in the statistical tables the category "Missing" will be presented if the number missing is > zero for at least one treatment group.

Unless otherwise specified, the eCRF recorded strata (i.e. the correct strata) will be analysed for all used in all the data displays.

7.2 Subject Disposition and Data Sets Analysed

Subjects randomised will be summarised by country and site, and also summarised by aetiology of NDO (SCI or MS), and previous BTX-A usage (BTX-A naïve vs. BTX-A non-naïve in the bladder) for the Randomised population.

The number of subjects screened but not randomised (screen failures) will be tabulated by country. The reasons for screen failures will be listed.

The randomisation details will be displayed in a listing for the Randomised population.

The number and percentages of enrolled subjects included in analysis populations (Randomised, Safety, mITT, PP and urodynamic) will be summarised by treatment group and overall. The reason for subject exclusion from each of the populations will be tabulated and listed.

In addition, the number and percentage of subjects who completed the study, prematurely discontinued the study with primary reasons will be tabulated by treatment group in the Randomised population. The number of subjects entering, prematurely withdrawing with primary reasons will be tabulated by treatment group in the Randomised population for the DBPC Cycle and by Dysport Cycle. Subject disposition data, including retreatments after the first IMP administration, and study discontinuation will be listed.

7.3 Protocol Deviations

All protocol deviations will be listed for the Randomised population.

The protocol deviations, including defining those leading to exclusion from the PP population, will be identified before data are unblinded.

7.4 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be listed and summarised for the mITT population.

Standard descriptive statistics including 95% confidence interval (CI) will be presented for the continuous variables of:

- Age (years)
- Weight (kg);
- Height (cm);
- Body mass index (BMI) (kg/m^2) calculated as [weight(kg)/(height(cm)/100)^2]

The total counts and percentages of subjects will be presented for the categorical variables of:

- Age groups [≥18 and ≤ 40, >40 and ≤ 65, > 65 years (further categorising to >65 and ≤ 75, and >75 years))
- Sex (Male, Female);
- Race (Asian, Black or African American, White, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native and Other);
- Ethnicity (Hispanic/Latino, Not Hispanic/Latino);
- Stratification variables:

- aetiology of NDO (SCI, MS)
- previous intradetrusor BTX-A usage (BTX-A bladder naïve, BTX-A bladder non-naïve).

- Other baseline characteristics:
  - prior NDO oral medications (Yes, No)
  - concomitant NDO oral medications at time of first IMP administration (Yes, No)
  - prior treatment of anticholinergics (Yes, No)
  - concomitant treatment of anticholinergics at time of first IMP administration (Yes, No)
  - prior beta-3 agonists (Yes, No)
  - concomitant beta-3 agonists at time of first IMP administration (Yes, No)
  - daily CIC frequency at baseline
  - history of UTI in the 6 months prior to study (Yes, No)
  - using a wheelchair regularly in subjects with MS (Yes, No)

No formal tests of statistical significance will be performed on the demographic and baseline data. Other baseline data not only measured at screening will be summarised by treatment group with the post-baseline measurements.

The demographics and baseline characteristics data will also be summarised by aetiology of NDO (SCI, MS) for the mITT population.

Pregnancy test will be listed only.

7.4.1 UTI Prior to First IMP Administration

The counts and percentages of the following categories will be summarised for the mITT population:

- Overall subjects with UTI prior to first IMP administration
- Subjects with a medical history of UTI
- Subjects with a medical history of UTI within 6 months prior to screening
- Subjects with a recorded AE of UTI between informed consent and first IMP administration

7.4.2 Medical History

Medical History (significant medical or surgical history, NDO medical history for SCI and MS subjects) will be coded by Sponsor using the Medical Dictionary for Regulatory Activities [MedDRA v21.0 (March 2018); latest version if updated during the study). All medical history will be listed, and the number and percentage of subjects with any medical history will be summarised for the mITT population by system organ class (SOC) and preferred term (PT) for each treatment group and overall.

NDO Medical History will be summarised by aetiology of NDO (SCI, MS). Duration of NDO will be calculated as (informed consent date date of development of NDO symptoms)*12/365.25 and reported as whole months, and presented using standard descriptive statistics.
For SCI history, percentage of neurological level of stable SCI, cause of stable SCI, American Spinal Injury Association (ASIA) Grade and neurological syndrome will be summarised. Duration of SCI will be calculated as (date of the first IMP administration date of stable SCI)*12/365.25 and reported as whole months, and presented using standard descriptive statistics.
For MS history, the percentage of level of mobility, classification of MS will be summarised. Duration of MS will be calculated as (date of the first IMP administration date of initial diagnosis)*12/365.25 and reported as whole months, and presented using standard descriptive statistics. Duration of onset of symptoms will be calculated as (date of the first IMP administration date of onset of symptoms)*12/365.25 and reported as whole months, and presented using standard descriptive statistics.

7.4.3 Prior and Concomitant Medications

Medications received prior to or concomitantly with treatment will be coded by Sponsor using World Health Organisation Drug Dictionary (WHO Drug Dictionary; Version B2-BDE March 2016 or a later version if updated during the study), and will be summarised by treatment group and overall with the number and percentage of subjects, by therapeutic class (the Anatomic Therapeutic Chemical [ATC] Classification codes) and preferred term. The concomitant medications and therapies will be summarised separately for the DBPC Cycle and by Dysport Cycle (Dysport Cycle 1, 2, etc).

Prior medications and concomitant medications are defined as follows:

Prior medications/non-drug therapies are those taken within 30 days prior to screening with a stop date prior to the date of the first IMP administration. Prior medications or therapies for NDO are those with both start date and stop date prior to the date of the first IMP administration.

Concomitant medications are those with a start date on or after the date of the first IMP administration, or those with a start date before the date of the first IMP administration and a stop date on or after the date of the first IMP administration (or ongoing).

Prior medications and concomitant medications will be listed together and summarised separately for the mITT population. Similarly, this will be listed and summarised for the prior and concomitant medications for NDO, and for prophylactic antibiotic for initial treatment, retreatments and urodynamic assessments.

Concomitant Surgical Procedures will be summarised by SOC and PT for the mITT population.

7.5 Treatment Exposure

Treatment exposure will be summarised descriptively by treatment group (placebo, Dysport 600 U, Dysport 800 U, All Dysport) in the Safety population. IMP administration data will be listed for the Safety population.

The treatment exposure will be summarised by number and percentage of subjects treated in each treatment cycle (DBPC cycle, Dysport Cycle 1, Dysport Cycle 2, etc), the number of

Dysport Cycles will be displayed descriptively using summary statistics for the Safety population.

The treatment exposure in weeks will be summarised by treatment group as below:

For overall study (irrespective of number of treatments)

- Total IMP exposure across the study will be calculated as (Last attended visit date in the study first IMP administration date + 1) / 7. Data will be presented in weeks for placebo, 600 U Dysport, 800 U Dysport, All Dysport groups.
- The number of subjects cumulatively exposed to IMP for at least 12 weeks, 24 weeks, 52 weeks, 78 weeks and 104 weeks will be summarised for placebo, 600 U Dysport, 800 U Dysport and All Dysport groups.
- Total Dysport exposure across the study will be calculated as (Last attended visit date in the study first Dysport injection date + 1) / 7. Data will be presented in weeks for 600 U, 800 U and All Dysport groups.
- The number of subjects cumulatively exposed to Dysport at least 12 weeks, 24 weeks, 52 weeks, 78 weeks and 104 weeks will be summarised. Data will be presented in weeks for 600 U, 800 U and All Dysport groups

For Dysport Cycles

- The total number of subjects who received 1, 2, 3, …etc and at least 1, 2, 3…etc Dysport treatments at 600 U, 800 U and All Dysport will be summarised .

7.6 Efficacy

The primary analysis based on the primary efficacy endpoint (mean change from study baseline in weekly number of UI episodes at Week 6 after the first IMP administration) will be performed on the mITT population.

The analysis for urodynamic parameters will be performed on the urodynamic population.

7.6.1 Significance Testing and Estimations

The primary efficacy hypotheses are as follows:

1) Ho: There is **no** difference between treatment with Dysport 600 U or Dysport 800 U and treatment with placebo with respect to the change from baseline to Week 6 after the first study treatment in the number of UI episodes per week.
2) Ha: There **is** a difference between treatment with Dysport 600 U or Dysport 800 U and treatment with placebo with respect to the change from baseline to Week 6 after the first study treatment in the number of UI episodes per week.

7.6.2 Multiplicity Adjustment

For the primary endpoint, due to multiple pairwise comparisons of each Dysport dose group versus placebo, a Hochberg correction will be applied to control the type one error at 5% significance level. The p-values from the two pairwise tests are ordered in magnitude from largest to smallest.

If both p-values for the two primary tests (the test of 600 U vs. placebo and the test of 800 U vs. placebo) are lower than 0.05, both will be declared statistically significant. If one of the primary tests has a p-value greater or equal to 0.05, then the other test will be declared

statistically significant if its p-value is lower than 0.025 (and thus half of the overall experiment wise alpha of 0.05).

The two ordered secondary endpoints will be tested for both doses at the 0.05 level (using a hierarchical methodology) if, for both doses, the two primary tests achieve a p-value lower than 0.05. If one of the primary tests has a p-value greater or equal to 0.05, and the other has a p-value lower than 0.025, secondary endpoints will be assessed (using hierarchical methodology) for the dose group with p-value lower than 0.025, at the 0.025 significance level.

In order to control the family-wise type one error, the following hierarchical testing procedure will be applied for the testing of the superiority of both Dysport doses to placebo for the primary and selected secondary endpoints (ordered as described in Section 7.6.5):

- Step 1: The Dysport 600 U and Dysport 800 U will be compared to placebo on the primary endpoint. If the p-values associated with both doses are <0.05 then both doses will be declared statistically significant and the testing will proceed at the 0.05 level from step 2 onwards. If one dose has p≥0.05 but the other has p<0.025 (significant dose) then testing will proceed at the 0.025 level from step 2 onwards on the significant dose only. If both dose groups have p≥0.05 or one dose group has p≥0.05 and the other dose group has p≥0.025, the testing procedure will be stopped.
- Step 2: The Dysport 600 U and Dysport 800 U will be compared to placebo for the first hierarchical secondary endpoint. Testing will be at the significance level defined in step 1 (0.05 or 0.025). If the p-value associated with this test is lower than the significance level defined in step 1 then it will be considered significant and testing will proceed to step 3. Otherwise the testing procedure will be stopped.
- Step 3: The Dysport 600 U and Dysport 800 U will be compared to placebo for the second hierarchical secondary endpoint. Testing will be at the significance level defined in step 2 (0.05 or 0.025). If the p-value associated with this test is lower than the significance level defined in step 2 then it will be considered significant.

The above testing rules ensure that the hierarchical procedure controls the experiment-wise type one error (i.e. over the three tests) at the 0.05 level for relevant secondary endpoints.

In the event the hierarchical testing procedure is stopped at the end of any particular step, the testing of the following steps will be considered descriptive only and no formal statistical conclusion will be drawn.

Each other secondary endpoint not included within the hierarchical testing procedure will be analysed for exploratory purposes only to compare each Dysport dose to placebo at a 0.05 type one error rate.

7.6.3 Primary Efficacy Analysis

The primary efficacy endpoint is mean change in the weekly number of UI episodes from study baseline to Week 6 after the first treatment. Seven-day bladder diaries that contain data recorded on at least 5 days will be included in the analysis.

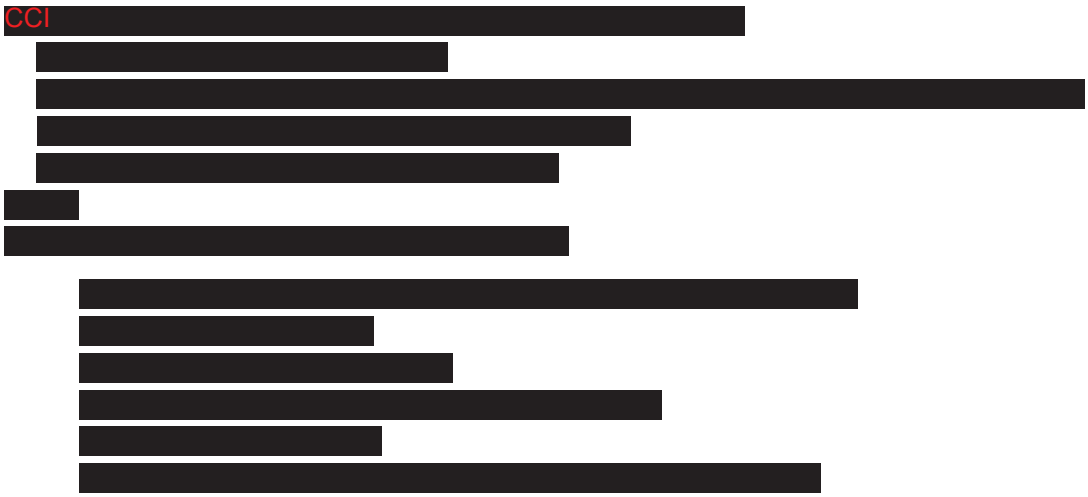
As all subjects should have visits up to and including week 12, but thereafter visits are dependent on whether the subject receives retreatment, statistical testing between treatment

groups will be performed only up to Week 12, inclusive. Descriptive statistics table will present any timepoint.

Weekly number of UI episodes and the mean change from study baseline will be presented for the DBPC Cycle. The mixed model repeated measures (MMRM) analysis will be conducted with the change of the weekly number of UI episodes from study baseline as response variable. Fixed effect variables include treatment group, visit (Week 2, Week 6 and Week 12), treatment-by-visit interaction, stratification variables [the aetiology of NDO and prior intradetrusor BTX-A usage for UI] and study baseline value of weekly number of UI episodes. Random effect will include the subject effect. An unstructured covariance matrix will be specified in the mixed model to account for within subject correlation. If model fails to converge, the structure of first order autoregressive AR (1), compound symmetry (CS) or variance components (VC) will be used.

The least square means (LSMEANS) of the change of weekly number of UI at each visit in each group with standard error, the difference of mean between the two treatment groups at each visit, the 95% CI of the difference and the p-value for treatment group will be presented. The comparison of main interest will be treatment difference at Week 6.

The SAS codes of MMRM for reference are below.



The validity of the model assumptions of normality will be investigated using residual plots. The LS means of change from study baseline for weekly UI in the DBPC and Dysport Cycles will be presented in line plots by treatment groups.

7.6.4 Sensitivity Analyses for the Primary Efficacy Endpoint

7.6.4.1 Using PP Population

Primary efficacy analysis will be conducted on the PP population as a supportive analysis.

7.6.4.2 Using ANCOVA

The analysis of covariance (ANCOVA) will be conducted for the two primary tests (Dysport 600 U vs. placebo, and Dysport 800 U vs. placebo), with the change of the weekly number of UI episodes from study baseline as response variable, including treatment group, stratification variables [the aetiology of NDO (SCI or MS) and prior intradetrusor BTX-A usage for UI

(BTX-naïve or BTX-non-naïve)] and study baseline value of weekly number of UI episodes as covariates.

The least square means (LSMEANS) of the change of weekly number of UI at Week 6 in each group with standard error, the difference of mean between the treatment groups, the 95% CI of the difference and the p-value for treatment group will be presented.

The SAS codes of ANCOVA for reference are below.

CCI [redacted]

7.6.4.3 Using MI

In presence of missing data in the primary efficacy endpoint, a multiple imputation approach for handling missing data will be undertaken on the mITT population. CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

In above codes, the variables are defined as:

CCI [redacted]

7.6.4.4 Using Mis-Stratification Factors

As discussed in Section 5.6.2, the primary endpoint will be analysed with the MMRM using the incorrect stratification factors as recorded in IVRS for the mITT population.

7.6.5 Hierarchical Analysis of Secondary Efficacy Endpoints

As specified in Section 7.6.12, a hierarchical analysis will be performed in the order listed for the following two secondary efficacy endpoints at Week 6 after the first IMP administration:

1) Proportion of subjects with no episodes of UI (i.e. continence is achieved)

2) Mean change from study Baseline in the I-QoL total summary score

The Derivation rules are specified in Section 3.2 and Appendix II.

For 1), a logistic generalised linear mixed model (GLMM) for repeated measures will be fitted for UI responses using repeated measurements at Week 2, Week 6, and Week 12. The "proportion of subjects with no episodes of UI" will be analysed as a response variable, the model will include treatment group, stratification variables, study baseline value, visit (week 2, week 6 and week 12), study baseline*visit and treatment*visit interactions as fixed effect. The study baseline value will be weekly number of UI episodes. The logistic GLMM is fitted using the logit link and the binomial distribution. Odds ratios, 95% CIs of odds ratio, and p-values for treatment group comparisons at each visit (week 2, week 6 and week 12) will be presented.

The SAS codes of GLMM for reference are below.

CCI [redacted]

In above codes, the variables are defined as:

CCI [redacted]

CCI [redacted]

For 2), MMRM model will be fitted using the "mean change" endpoint, as the response variable to obtain the p-value of treatment groups. The model will be the same as primary analysis model in section 7.6.3. The least square means of change at Week 6 in each group with standard error, the mean difference of pairwise comparison, the 95% CI of the difference and the p-value for the treatment groups will be presented for each model.

If the testing procedure is stopped at the end of any particular step, the outcomes of the following steps will be presented and used for description only and no formal statistical conclusion will be drawn.

7.6.6 Other Analysis of Secondary Efficacy Endpoints

The analysis of efficacy of the above-mentioned endpoints (primary endpoint and secondary endpoints included in the hierarchical analysis) will be conducted at timepoints other than Week 6 in the DBPC Cycle and is described below (except urodynamic endpoints as only performed at Week 6). The analysis of other secondary endpoints (see Section 3.2) is also described below.

Descriptive summaries will be performed for the DBPC Cycle and by Dysport Cycles (i.e. Dysport Cycle 1, Dysport cycle 2 …), see the schematic diagram in Section 7.1.

Statistical comparison analyses are only applicable for the DBPC treatment cycle. Analyses between treatment groups, Dysport 600 U vs. Placebo, and Dysport 800 U vs. Placebo will be performed accordingly using GLMM and MMRM as mentioned below for each endpoint. As all subjects should have visits up to and including week 12, but thereafter visits are dependent on whether the subject receives retreatment, statistical testing between treatment groups will be performed only up to Week 12, inclusive. All secondary endpoints not included in the hierarchical analysis are considered as exploratory endpoints and will therefore be analysed for exploratory purposes only to compare each Dysport dose to placebo, alpha at 0.05 level.

7.6.6.1 Diary Parameters

Refer to Section 3.2 for details of diary parameter endpoints.

7.6.6.1.1 Weekly Number of UI Episodes

Mean change from study baseline

For both the DBPC Cycle and the Dysport Cycles, summary tables for mean values in each assessment visit and the mean change from study baseline will be presented using descriptive statistics

For the DBPC treatment cycle, mean change from study baseline to Week 2, and Week 12, will also be analysed using MMRM, using data from Week 2, 6 and 12, as in the primary efficacy analysis in section 7.6.3.

Thresholds of reduction

For both the DBPC Cycle and the Dysport Cycles, the number and percentage of subjects with UI will be summarised by improvement levels from study baseline (≥30% improvement, ≥50% improvement, ≥75% improvement, 100% improvement (no episodes of UI)) for each assessment visit.

Bar charts will also be plotted. For the DBPC treatment cycle, the GLMM for repeated measures will be fitted for UI responses using repeated measurements at Week 2, Week 6, Week 12. Each UI response level compared to study baseline (≥30% improvement, ≥50% improvement, ≥75% improvement or 100%) will be analysed as a response variable in each model, as described for the proportion of subjects with no UI episodes in section 7.6.5.

7.6.6.1.2 Daily Urinary Frequency and Voided Volume

For both the DBPC Cycle and by Dysport Cycles, the summary tables for mean values in each assessment visit and the mean change from study baseline will be presented using descriptive statistics.

For the DBPC treatment cycle, mean change from study baseline to Week 2, Week 6, and Week 12 will be analysed using MMRM, as in the primary efficacy analysis presented in Section 7.6.4.2.

7.6.6.2 Urodynamic Filling Cystometry Parameters

See Section 3.2 for list of urodynamic endpoints.

The summary tables for mean values at Week 6 and the mean change from study baseline for the DBPC cycle, and for the Dysport Cycles (i.e. Dysport Cycle 1, Dysport cycle 2 …) will be presented using descriptive statistics for continuous endpoints. For each of the "mean change" at Week 6 urodynamic parameters, an ANCOVA model will be fitted using the "mean change" endpoint, as the response variable to obtain the p-value of treatment groups. The model will be the same as the sensitivity analyses for the primary efficacy endpoint in 7.6.4.2. The LSMEANS of the mean change from study baseline at Week 6 in each group with standard error, the difference of mean between the two treatment groups, the 95% CI of the difference and the p-value for treatment group will be presented.

Number and percentage of subjects with no IDC will be also summarised. A logistic regression model will be performed with "proportion of subjects" as the response variable. The model will include treatment group, and stratification variables.

Odds ratio, 95% CI of odds ratio, and p-value will be presented.

The SAS codes of logistic regression for reference are below.

CCI

In above codes, the variables are defined as:

CCI [redacted]

Line plots of the LS means of changes will be plotted for MCC, MDP, Vol@1stIDC. In addition, a bar chart for the proportion of subjects with no IDC at Week 6 will be plotted.

7.6.6.3 Patient Reported Outcome Questionnaires

This includes the I-QOL, EQ-5D-5L and mPGI-I endpoints (see Section 3.2).

EQ-5D-5L comprises of the descriptive system for 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, where each dimension has 5 levels (1=indicating no problem, 2=indicating slight problems, 3=indicating moderate problems, 4=indicating severe problems, 5=indicating extreme problems). It also includes a self-rated health which is numbered from 0 (worst health you can imagine) to 100 (best health you can imagine):

Level	Mobility	Self-care	Usual Activities	Pain/Discomfort	Anxiety/Depression
1	I have no problems walking,	I have no problems washing or dressing myself	I have no problems doing my usual activities	I have no pain or discomfort	I am not anxious or depressed
2	I have slight problems walking,	I have slight problems washing or dressing myself	I have slight problems doing my usual activities	I have slight pain or discomfort	I am slightly anxious or depressed
3	I have moderate problems walking,	I have moderate problems washing or dressing myself	I have moderate problems doing my usual activities	I have moderate pain or discomfort	I am moderately anxious or depressed
4	I have severe problems walking,	I have severe problems washing or dressing myself	I have severe problems doing my usual activities	I have severe pain or discomfort	I am severely anxious or depressed
5	I am unable to walk	I am unable to wash or dress myself	I am unable to do my usual activities	I have extreme pain or discomfort	I am extremely anxious or depressed

The EQ-5D-5L descriptive system will be added numerically e.g. mobility=2, self-care=3, usual activities=2, pain/discomfort=3, anxiety/depression=2 gives a state=23232 i.e. slight problems with mobility, moderate problems with washing or dressing, slight problems with doing usual activities, moderate pain or discomfort, and slightly anxious or depressed. Missing values will be coded as a 9. The arithmetic score for the EQ-5D-5L score will be taken as 2+3+2+3+2=12.

For both the DBPC Cycle and by the Dysport Cycles, the summary tables for mean values in each assessment visit and the mean change from study baseline will be presented using descriptive statistics.

For the DBPC Cycle for I-QOL and EQ-5D-5L, mean change from study baseline to Week 6 and Week 12, will be analysed using MMRM, similar to the primary efficacy analysis. Mean mPGI-I score at Week 2, Week 6, Week 12 will be analysed as a response variable, using MMRM as in the supportive primary analysis, without baseline factor for mPGI-I.

The LS means of change from study baseline in DBPC cycle for I-QoL total summary score at all timepoints will be presented in a line plot by treatment groups up to Week 12.

7.6.6.4 Retreatment intervals

For both the DBPC Cycle and by the Dysport Cycles, summary statistics will be displayed for time between treatments received, time to request and time to eligibility for retreatment. For the DBPC Cycle the number and percentage of patients receiving retreatment: ≥ Week 12 to < Week 16, ≥ Week 16 to < Week 20 weeks and then every 4 weeks will be presented.

The following formal statistics will be performed only for the time between treatments received endpoint. For both the DBPC Cycle and by the Dysport Cycles, median number of days together with the 25th and 75th percentiles and their 95% CI will be determined based on the Kaplan-Meier method. Patients with no retreatment will be censored at the last visit. The survival curves will be presented by treatment group as well.

For the DBPC and Dysport treatment cycles, the log-rank tests will be performed to compare survival curves between treatment groups, by providing p-values.

The SAS codes of survival analysis for reference are below.

CCI

7.6.7 Subgroup Analysis

1) For the primary endpoint (DBPC Cycle at Week 6), the following baseline subgroups will be assessed for the mITT population:
   - Aetiology of NDO (SCI or MS)
   - Prior intradetrusor BTX-A usage (BTX-A bladder naïve or BTX-A bladder non-naïve)
   - Age groups (≥18 to ≤ 40, >40 to ≤ 65, > 65 years)
   - Sex (Male or Female)
   - Concomitant use of anticholinergics and/or beta-3 agonists (Yes or No)

2) For the secondary efficacy endpoints included in the hierarchical analysis (DBPC Cycle at Week 6), the following baseline subgroup will be assessed for the mITT population:
   - Aetiology of NDO (SCI or MS)

For 1) and 2) descriptive statistics and statistical analysis will be performed for each subgroup as detailed in section 7.6.3 and 7.6.5, with subgroup*treat interaction included in the analysis model. The subgroup analysis will be omitted if the subcategories have fewer than 30 subjects counts.

For 1), the treatment differences and 95% CI will be presented for each subgroup (e.g. Aetiology of NDO: SCI and MS) on a forest plot.

7.7 Safety

All safety data will be included in the subject data listings. Summary tables will be based upon the safety population.

7.7.1 Adverse Events

All AEs will be coded by Sponsor using MedDRA v21.0 (March 2018); (the latest version if updated during the study), and will be classified by MedDRA preferred term and system organ class.

A TEAE is defined as any AE with start date/and time at or after the date/and time of the first dose of IMP, or any AE with start date/and time prior to the date/and time of the first dose of IMP whose intensity worsens at or after the date/time of the first dose of IMP. The Pre-treatment AE is defined as any AE with start date/and time prior to the first dose of IMP administration in DBPC Cycle, and after the date of informed consent.

All TEAEs will be assigned to either DBPC Cycle and/or Dysport Cycle X based on the start date and time, or intensity increase date. For example, for presentation of TEAEs by Dysport Cycle, if the start time/intensity increase time of TEAE is at or after the time of treatment administration of Dysport Cycle X, Day 1 and prior to the time of treatment administration of Dysport Cycle X+1, Day 1, the TEAEs will be assigned to Dysport Cycle X.

In this study, an AESIs for Dysport is TEAEs that suggest a possible remote spread of effect of the toxin or events suggestive of hypersensitivity like reactions. TEAEs due to possible remote spread of the effects of Dysport will be identified using the list of MedDRA PTs compatible with the mechanism of action of BTX-A and based on the recommendations from

the Committee for Medicinal Products for Human Use (CHMP) and the Food and Drug Administration (FDA). TEAEs potentially representing hypersensitivity reactions will be identified using the Standardised MedDRA Query (SMQ) (narrow search query) for hypersensitivity reactions. A list of MedDRA preferred terms, used to identify any potential AESI, is provided in Appendix IV.

All TEAEs identified using the search strategy described above will be medically evaluated during the study, before the database lock and unblinding, by the sponsor to identify events which could possibly represent 'remote spread of effect of toxin', or which are suggestive of 'hypersensitivity reactions' due to study treatment administration. Cases will be excluded if they are confounded by presence of alternative clinical etiologies (medical history, concomitant medication or diagnosis which could account for the symptoms); if they are considered to be local effects instead of distant spread as judged by the site of injection; the time period between the last study treatment administration and event onset is not in accordance with the expected mechanism of action; or due to insufficient information/evidence to make an assessment.

In the TFLs, only the final list of AESIs confirmed by the sponsor as "a possible remote spread event" or "hypersensitivity reactions" will be taken into account.

All AEs (with TEAEs flagged) reported during the study will be presented in a listing which will be sorted by treatment group in the respective assigned treatment cycle for that AE, subject ID, AE start date and time, primary system organ class (SOC), preferred term (PT), and verbatim text. The treatment cycle where the TEAE onset or intensity increased will be presented in the listing as well. Separate listings of all TEAEs, serious TEAEs, IMP-related TEAEs, TEAE of special interest, other protocol defined TEAEs, TEAEs leading to early withdrawal and TEAEs leading to death reported during the study will also be presented.

Overview tables will be produced for DBPC Cycle, Dysport Cycles and overall for the number and percentage of subjects with at least one of the following TEAEs, where subjects with more than one TEAE in a particular category are counted only once in that category. The number of TEAE occurrences will be provided as well. Note that for TEAEs that could only occur in the MS population (e.g. MS exacerbation), the denominator for the percentage calculation will relate to the number of MS patients; these TEAEs will be identified in the tables.

- any TEAE
    - intensity of TEAE (mild, moderate, severe)
    - Any IMP related TEAE
    - Any TEAE leading to withdrawal
- any serious TEAE
    - any IMP related serious TEAE
    - any serious TEAE leading to withdrawal
- any TEAE of special interest by type of AESI
    - any AESI leading to withdrawal
    - any serious AESI

- any UTI TEAEs
    - UTI TEAEs leading to withdrawal
    - serious UTI TEAEs
- TEAE leading to death

In view of the anticipated difference in duration of the Dysport and placebo treatment cycles, this overview table will also be provided including only TEAEs occurring up to 12 weeks after first IMP treatment administration.

A similar overview table will be produced for the number and percentage of subjects with at least one of the following events occurred pre-treatment for randomised subjects. The number of occurrences of the following events will be presented as well.

- any AE
    - Intensity of AE (mild, moderate, severe)
- any SAE
    - any SAEs leading to withdrawal
- AE leading to death

TEAEs will be summarised overall, for DPBC cycle, and Dysport Cycles with the number and percentage of subjects with TEAEs presented by primary SOC and PT. In addition, this table will be provided including only TEAEs occurring any time after first dose of IMP until up to 12 weeks after first IMP treatment administration. This will also be summarised by aetiology of NDO.

For AESIs, summary tables may also be produced following medical review of available information.

The same summaries for overall, for DBPC Cycle, and Dysport Cycles with the number and percentage of subjects with TEAEs presented by primary SOC and PT will be presented for serious TEAEs, IMP-related TEAEs, TEAEs leading to withdrawal, TEAEs of special interest, and other protocol defined TEAEs. TEAEs with PTs observed in ≥1%, ≥2%, and ≥5% of subjects and IMP-related TEAEs with PTs observed in ≥1%, ≥2%, and ≥5% of subjects will be summarised as well.

Additionally, TEAEs will be tabulated by decreasing overall PT frequency and intensity in each SOC and PT category.

The above will also be presented for SAEs.

7.7.2 Laboratory Evaluations

Clinical laboratory data from the central laboratory (haematology, biochemistry and urinalysis, and urine culture and sensitivity) will be listed in Standard International (SI) units. Any unscheduled laboratory assessments will be included in the listings. For post-baseline, only data from scheduled visits will be included in the summary tables.

Haematology parameters:

- Red blood cell count
- Haemoglobin

- Haematocrit
- Mean corpuscular volume
- Mean corpuscular hemoglobin
- Mean corpuscular hemoglobin concentration
- White blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils, and others)
- Platelet count.

Serum Chemistry parameters:

- Urea, creatinine, total bilirubin, conjugated bilirubin
- Chloride, bicarbonate, sodium, potassium, calcium, inorganic phosphate
- Alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase
- Albumin, total protein, total cholesterol, triglycerides, fasting glucose.

Urinalysis parameters:

- pH, protein, ketones, bilirubin, blood, urobilinogen, nitrites, leukocytes, glucose and specific gravity

Laboratory results will be classified as low, normal, or high at each visit according to the laboratory supplied reference ranges. Abnormal values will be flagged (High [H], Low [L]) in the data listings. A list of clinically significant abnormal values will be presented by treatment group and subject ID.

Descriptive statistics will be presented for actual values and changes from study baseline at each scheduled assessment by treatment group.

The number and percentage of subjects will be summarised for clinical significance of each abnormal value.

For each scheduled post-baseline assessment visit, shift from study baseline tables of the number and percentage of subjects with low, normal or high values will be presented.

7.7.3 Antibody Test

Antibody testing results will be presented in a data listing. The listings for subjects with at least one positive neutralising (baseline or post baseline) will be provided separately.

The number and percentage of subjects with the presence of neutralising BTX-A antibodies at study baseline, and post-baseline visits will be presented in the shift tables. The number of neutralising BTX-A antibodies seroconverters (subjects having a negative result at study baseline and at least one positive result at one post-treatment time point) and the time by when the subjects seroconverted will be reported.

7.7.4 Vital Signs

The normal ranges for the vital signs are displayed in Table 2 below:

Table 2 Vital Signs Normal Ranges

Parameter	Low	Normal	High

Diastolic Blood Pressure (mmHg)	<40	40-110	>110
Systolic Blood Pressure (mmHg)	<60	60-190	>190
Heart Rate (bpm)	<50	50-130	>130
Height (cm)	<120	120-200	>200
Weight (kg)	<35	35-120	>120

Vital signs data will be presented in a listing by treatment group and subject. Any unscheduled vital signs assessment will be presented in the listings. Vital signs include blood pressure (systolic/diastolic), heart rate, respiratory rate and temperature.

Summary statistics will be presented for actual values and changes from study baseline at each scheduled assessment by treatment group.

The number and percentage of subjects with abnormal values (Low and High) will be presented by treatment group.

For the DBPC period and each Dysport Cycle, shift from study baseline tables of the number and percentage of subjects with low, normal or high values will be presented.

7.7.5 Electrocardiograms

Not applicable.

7.7.6 Other Safety Variables

Pregnancy test, urinary tract ultrasound and physical examination data will be presented in data listings.

7.8 Primary Analysis of the Study

CCI [redacted] The analysis will consist of all tables, figures and listings for the study described in this statistical analysis plan using all available data up to the cut-off date and a clinical study report will be written. A final analysis will occur when all subjects have completed the study (or at other timepoints if required to support regulatory agency submissions).

8 CHANGES IN PLANNED ANALYSES

Not applicable.

9 DATA ISSUES

Not applicable.

10 REFERENCES

1 ICH. *Statistical Principles for Clinical Trials*, Guideline E9, 1998.

2 CHMP. *Consider on Adjustment for Baseline Covariates*. EMEA: London, 2013

3 Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988;75:800-802.

4 ICH E3 Implementation Working Group. *ICH E3 Guideline: Structure and Content of Clinical Study Reports Questions & Answers (R1),* 6 July 2012

5 Rubin, D. B. (1987). *Multiple Imputation for Nonresponse in Surveys*. New York: John Wiley & Sons.

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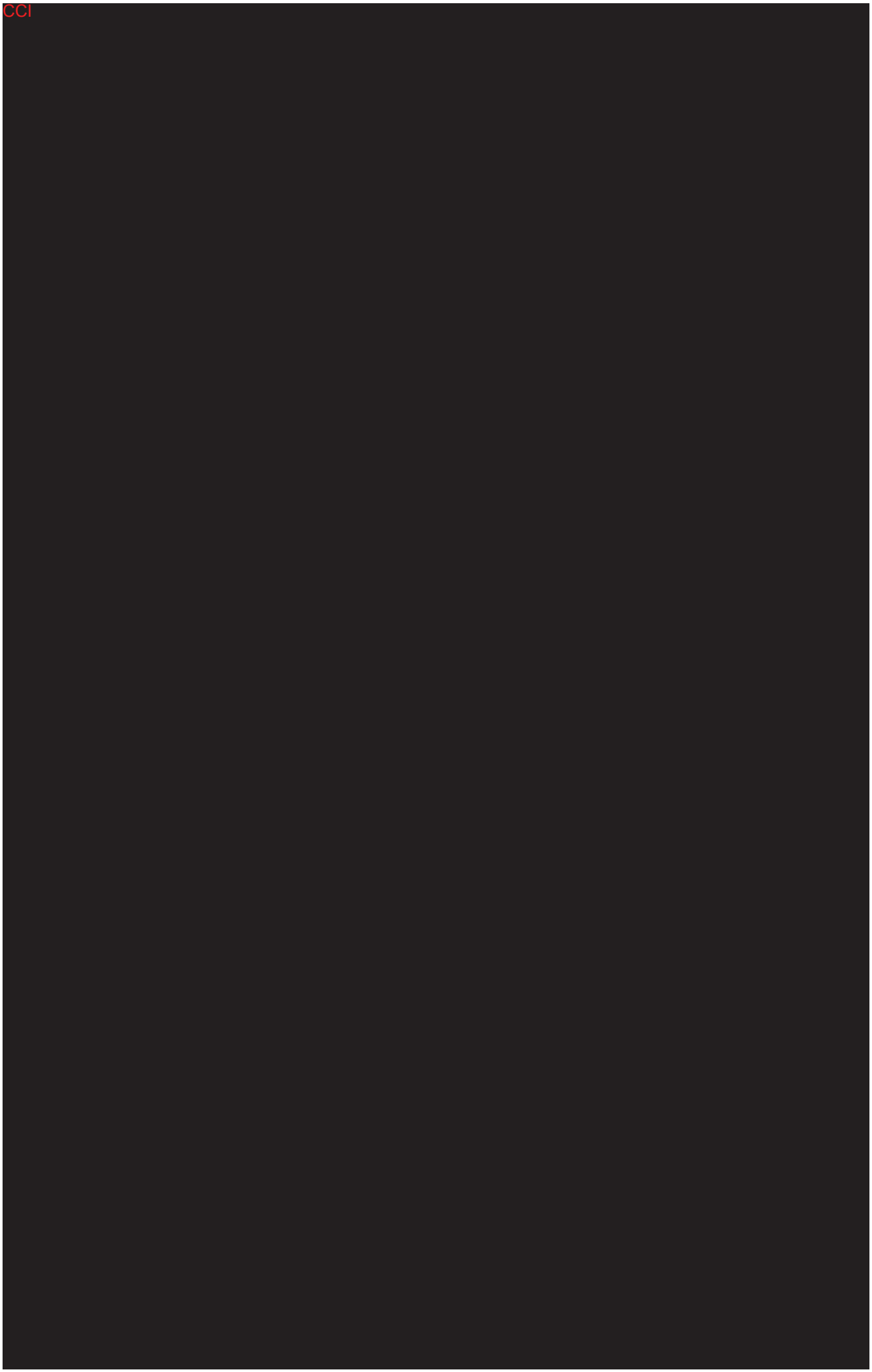
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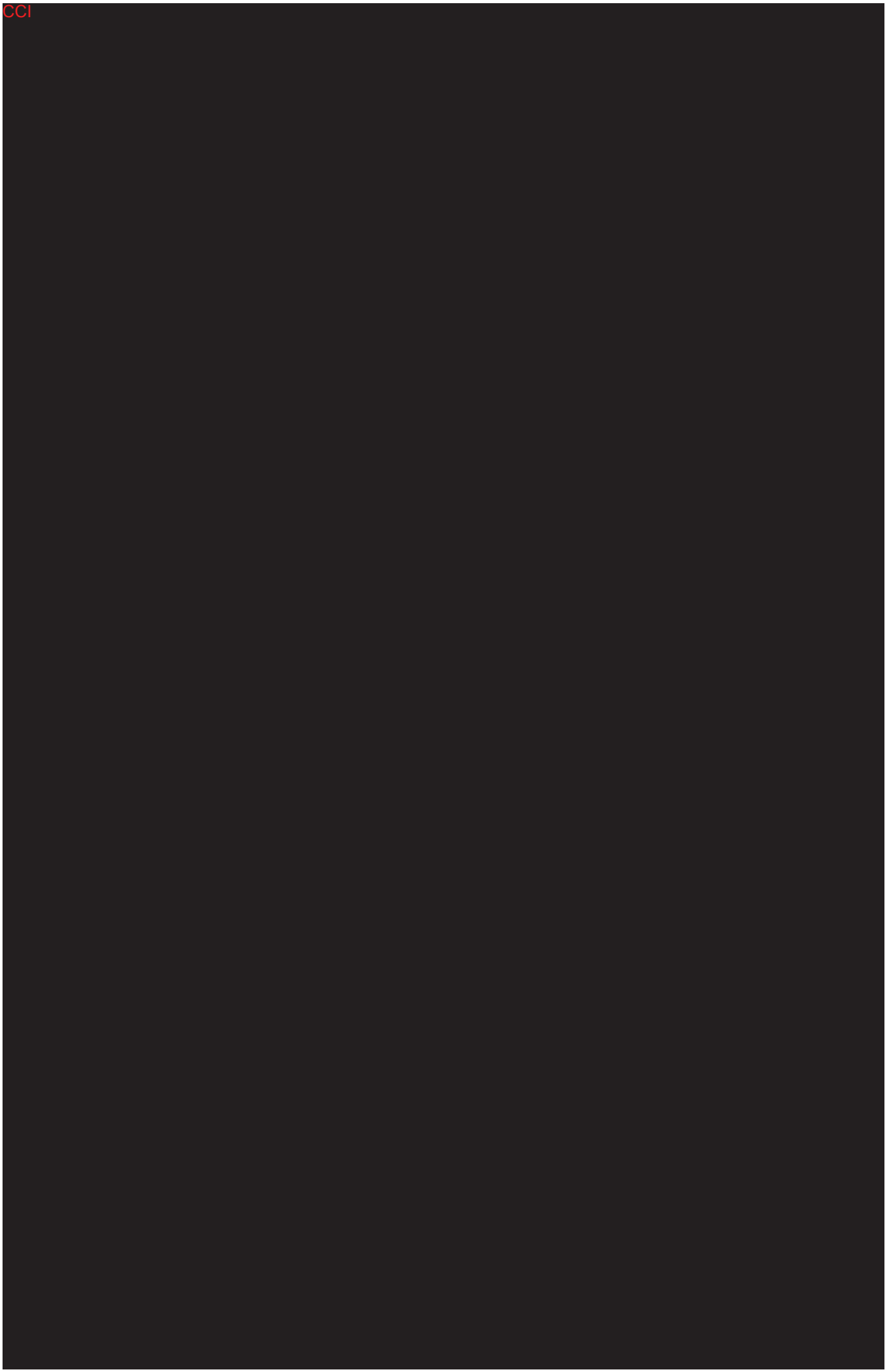
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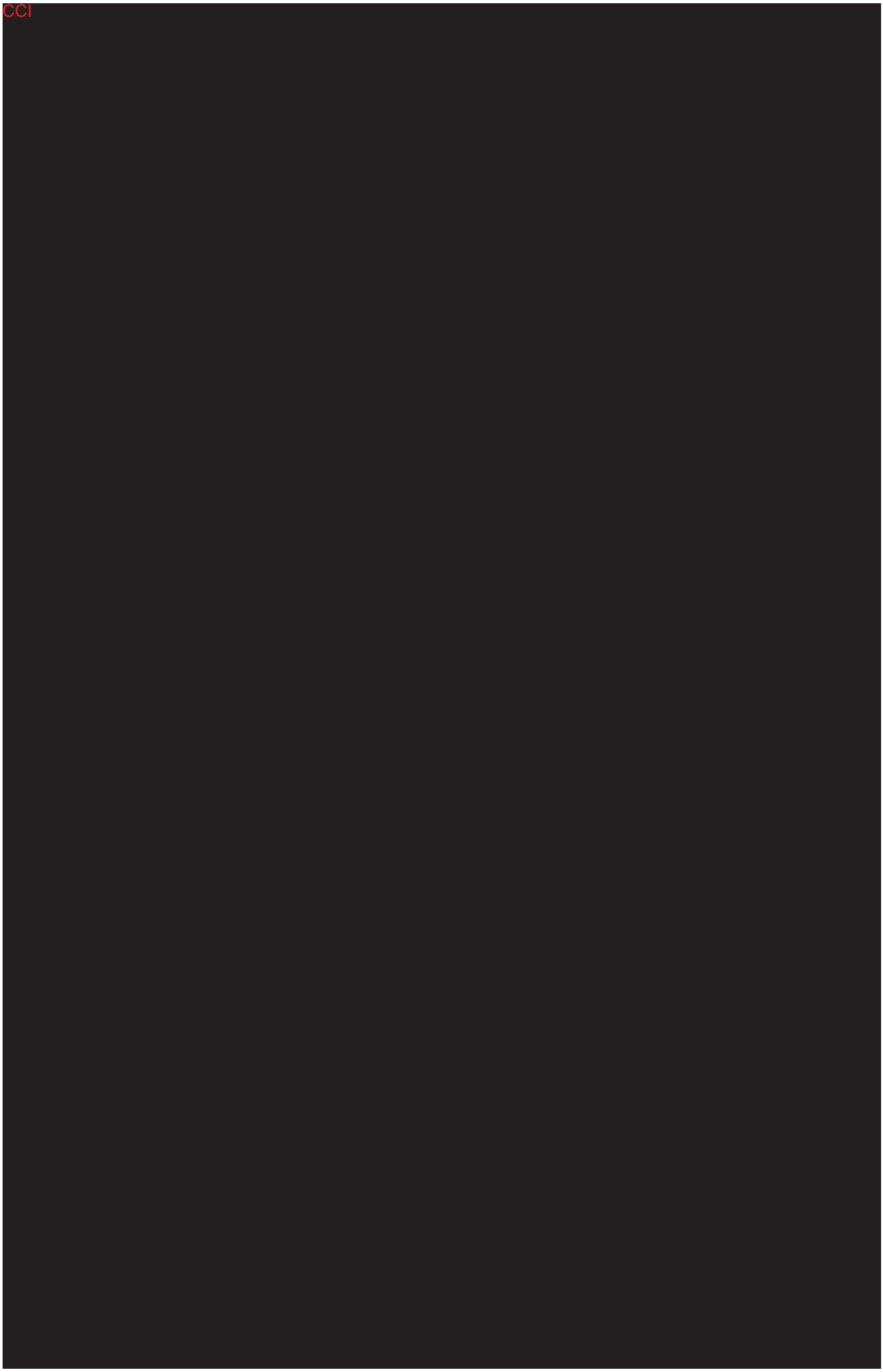
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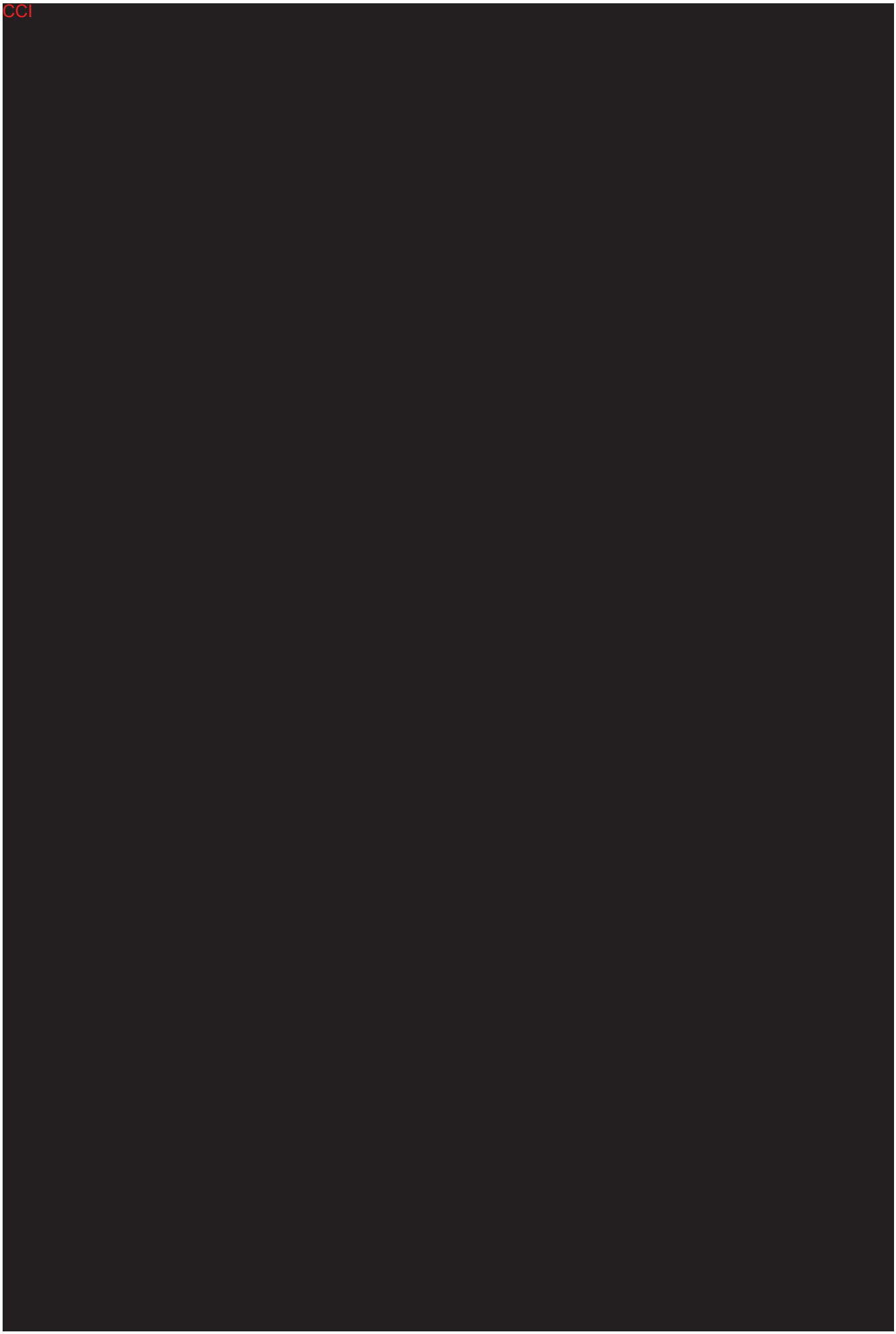
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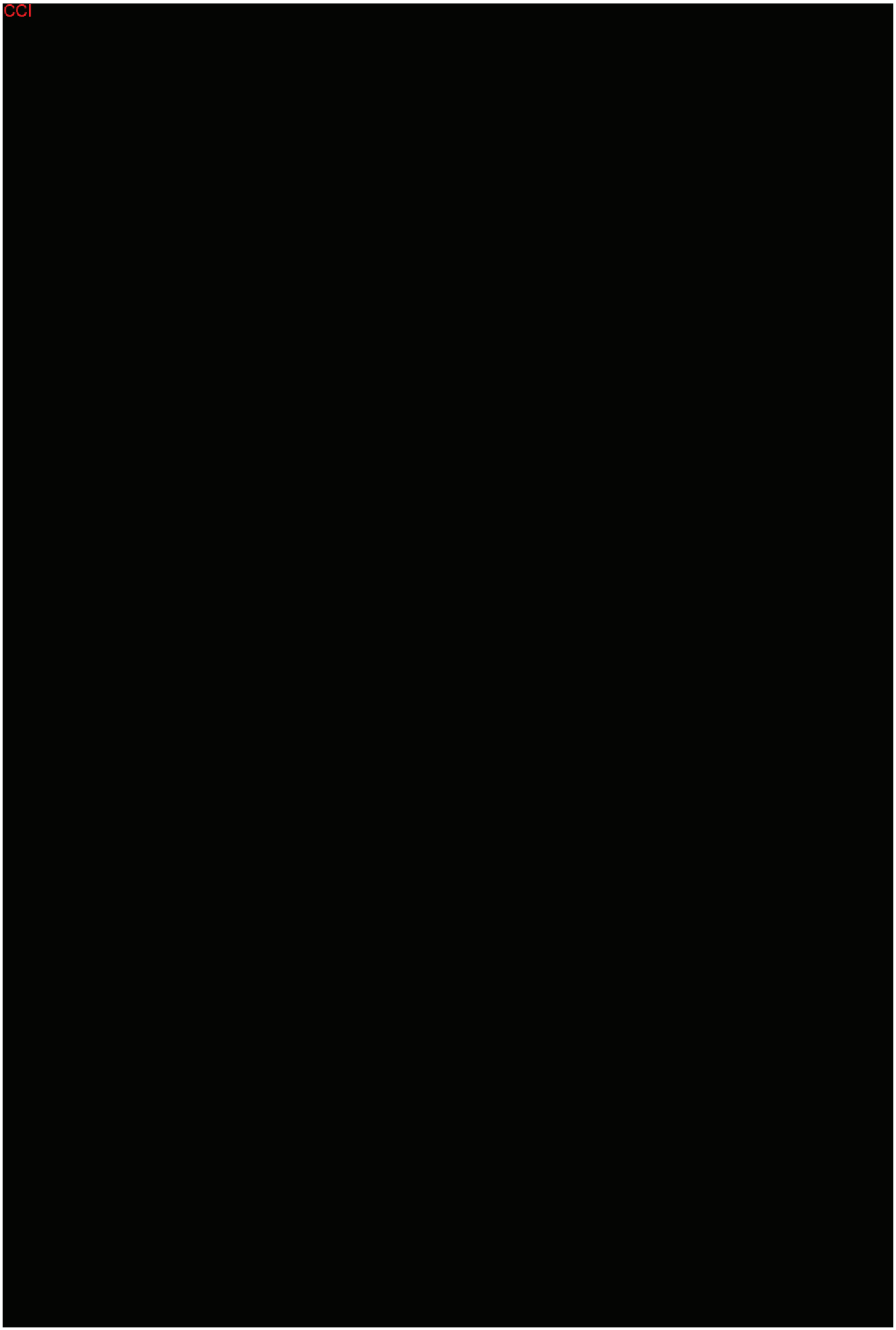
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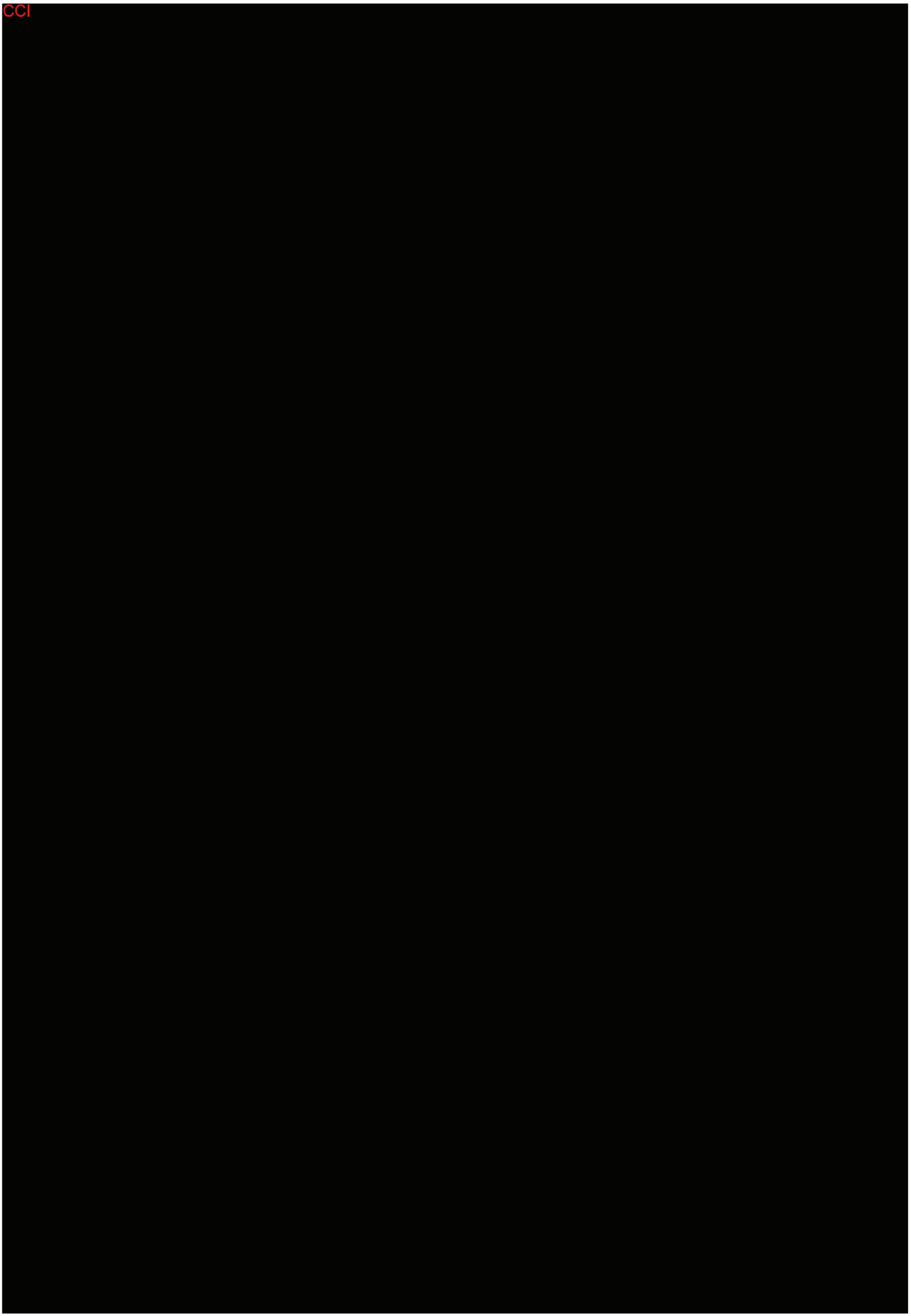
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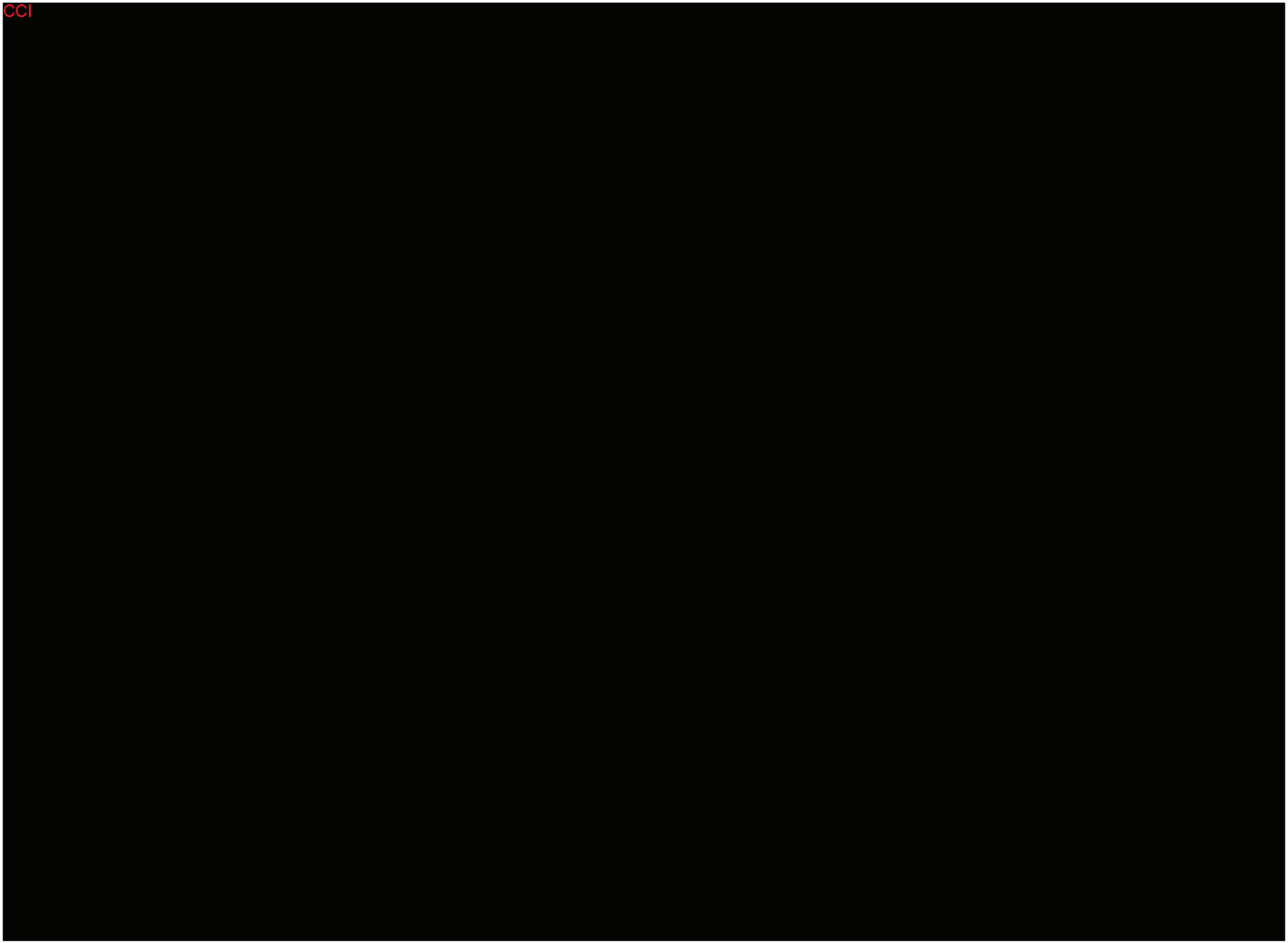
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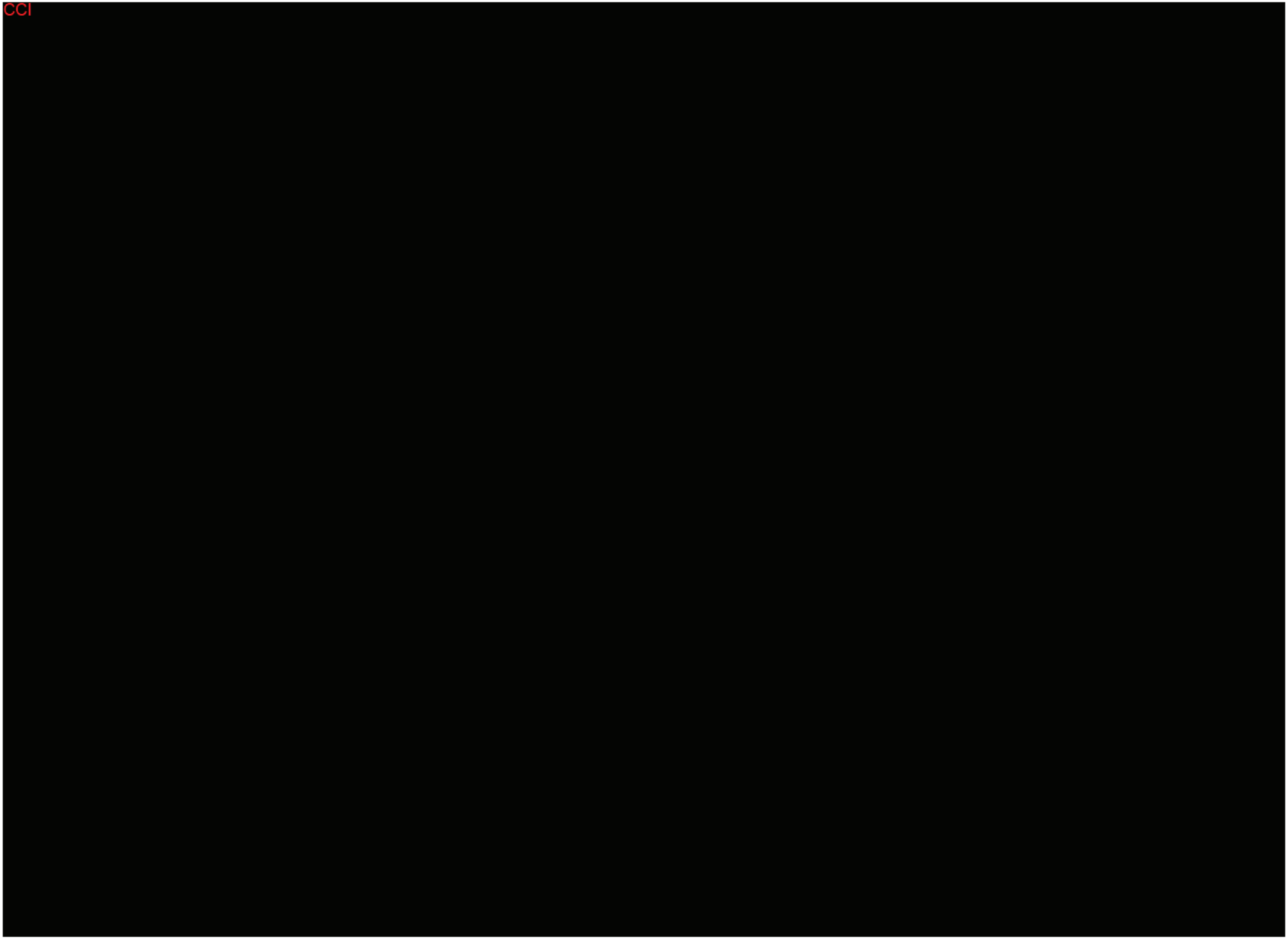
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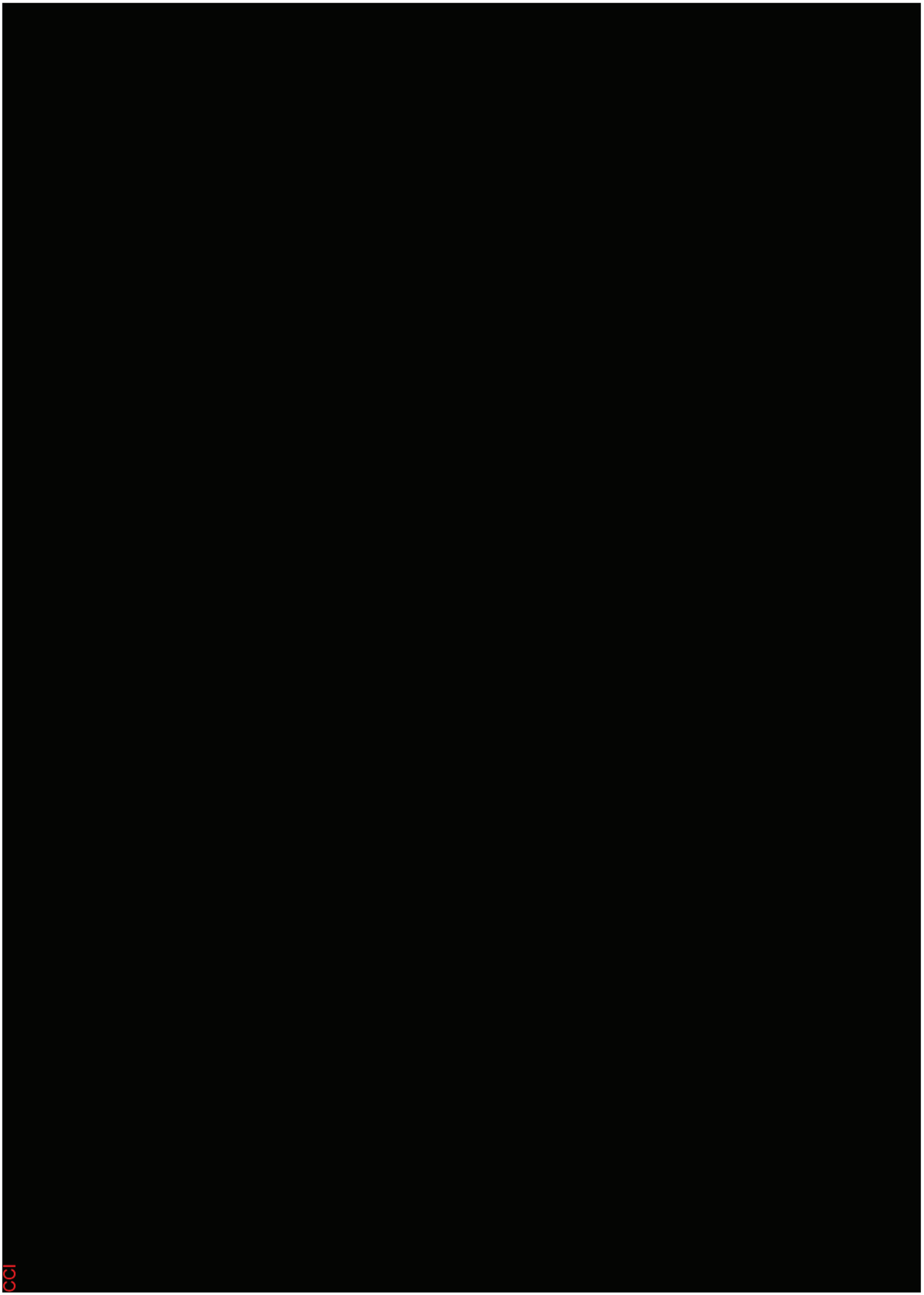


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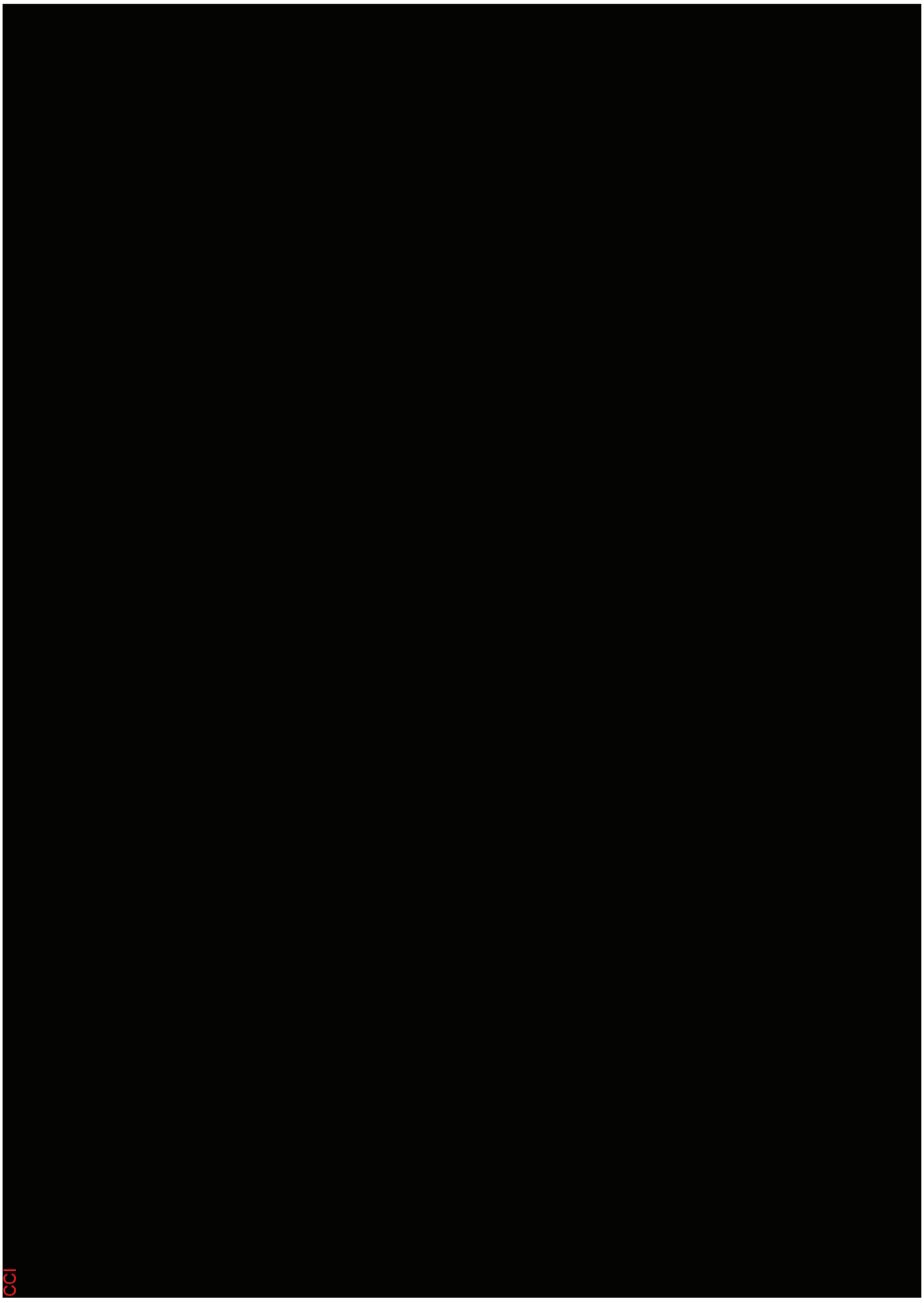

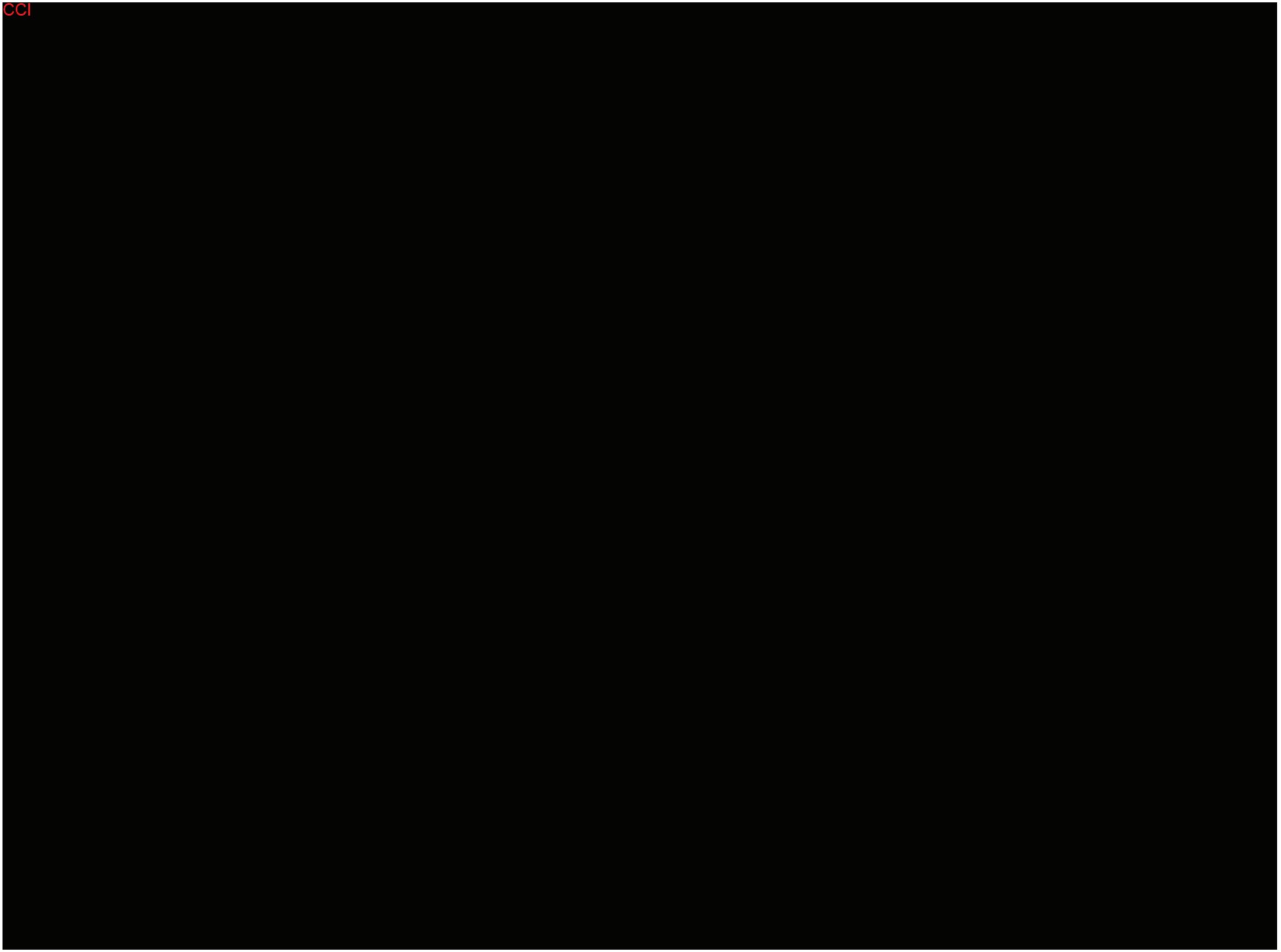
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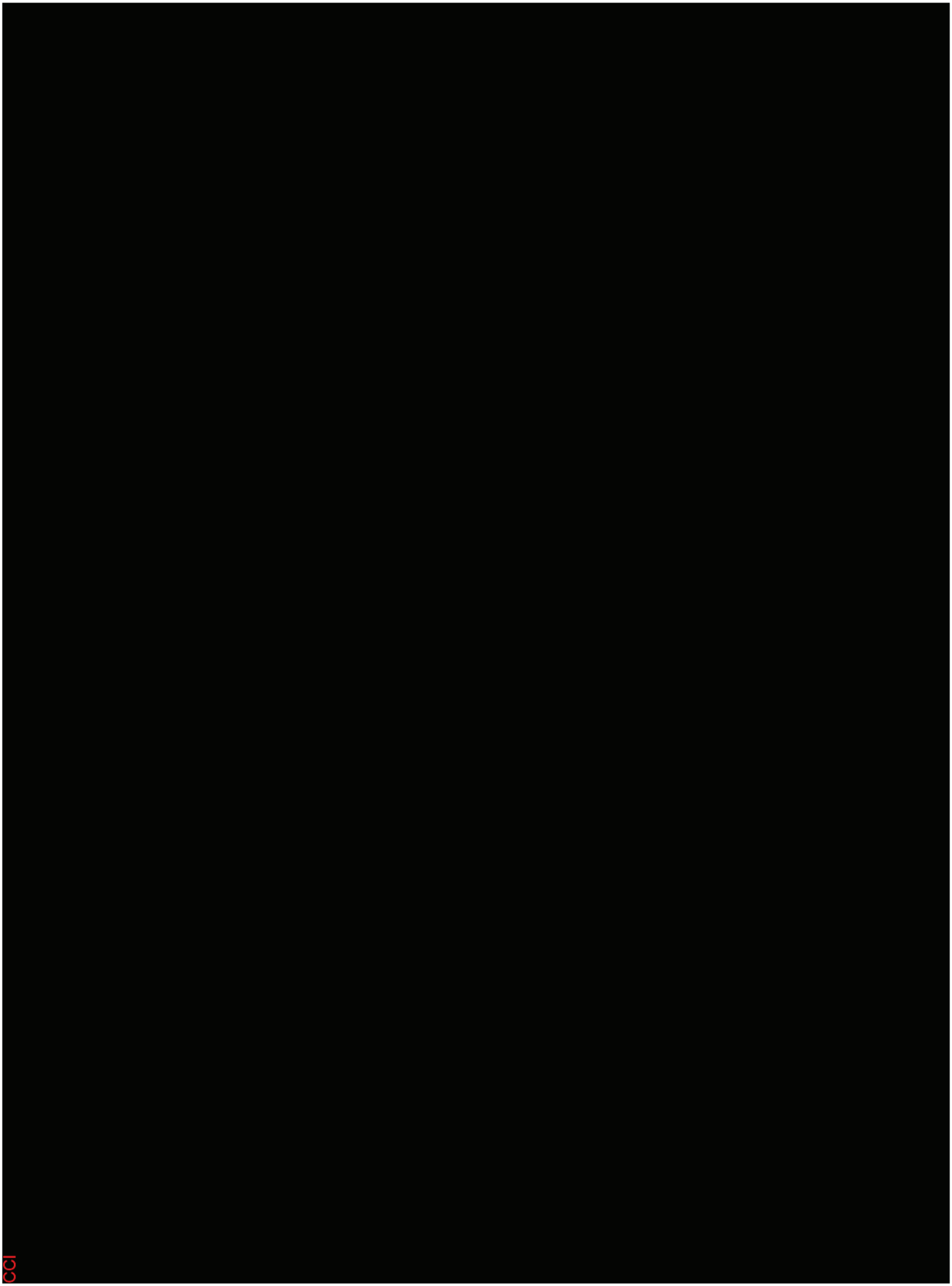

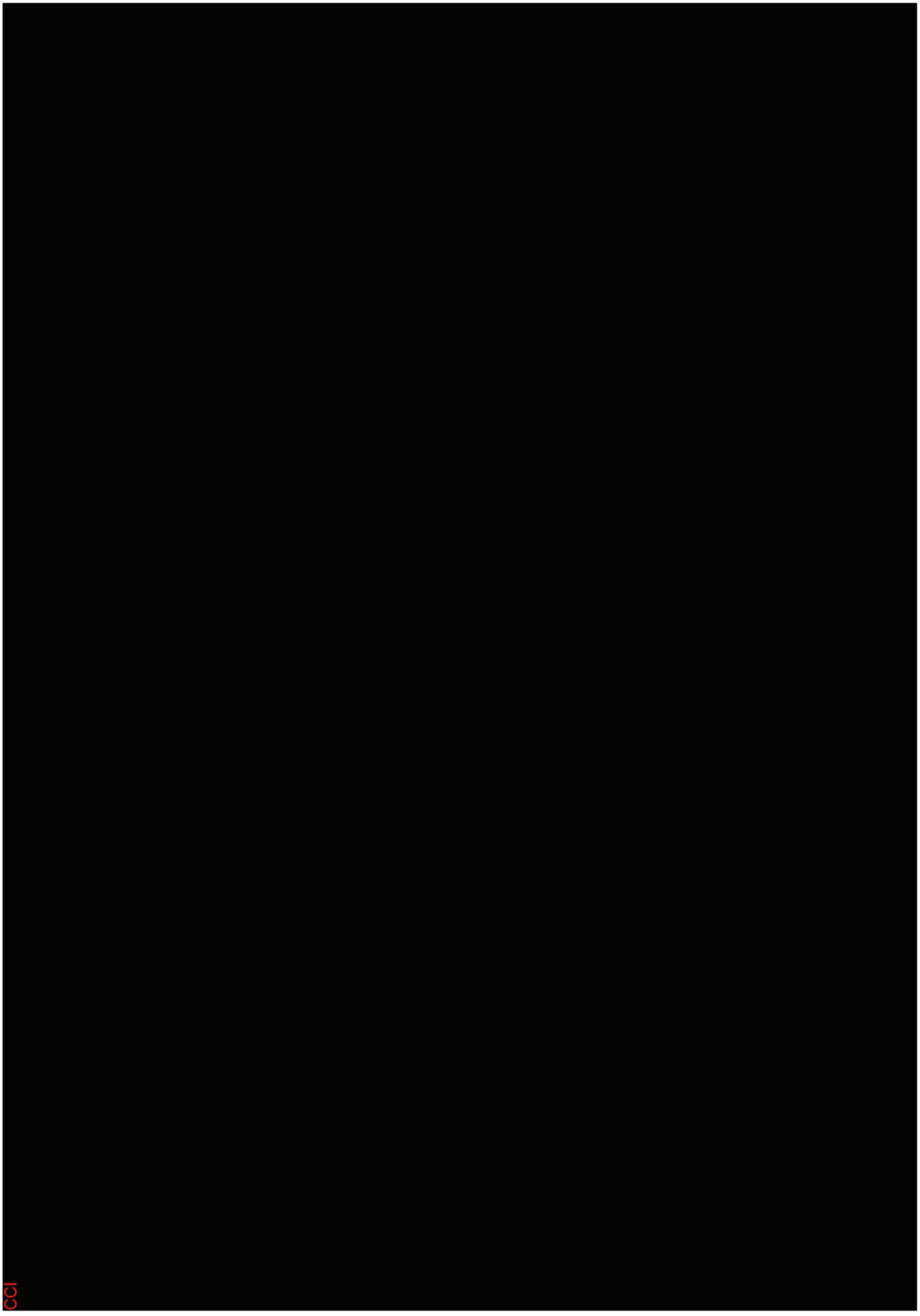

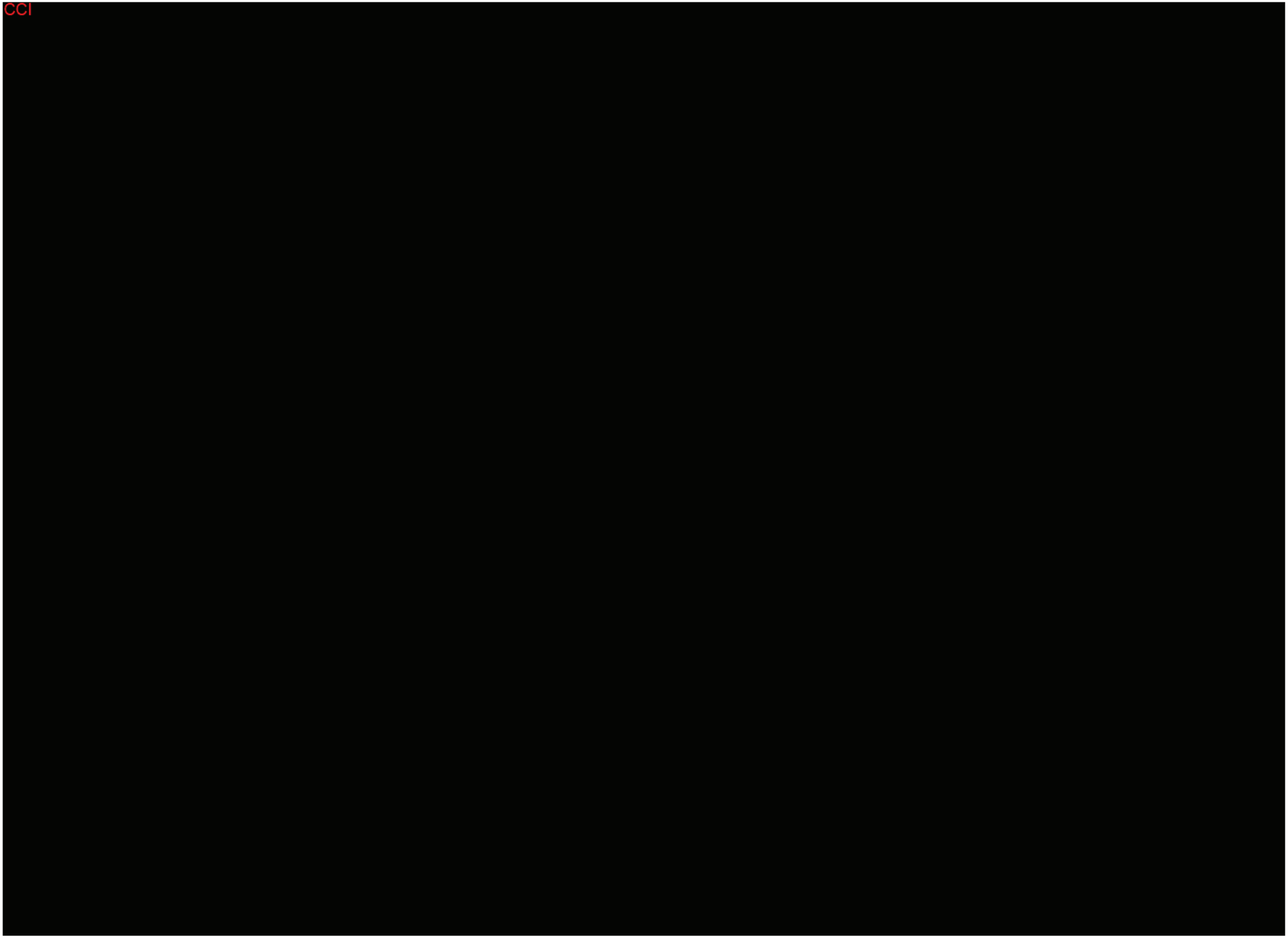
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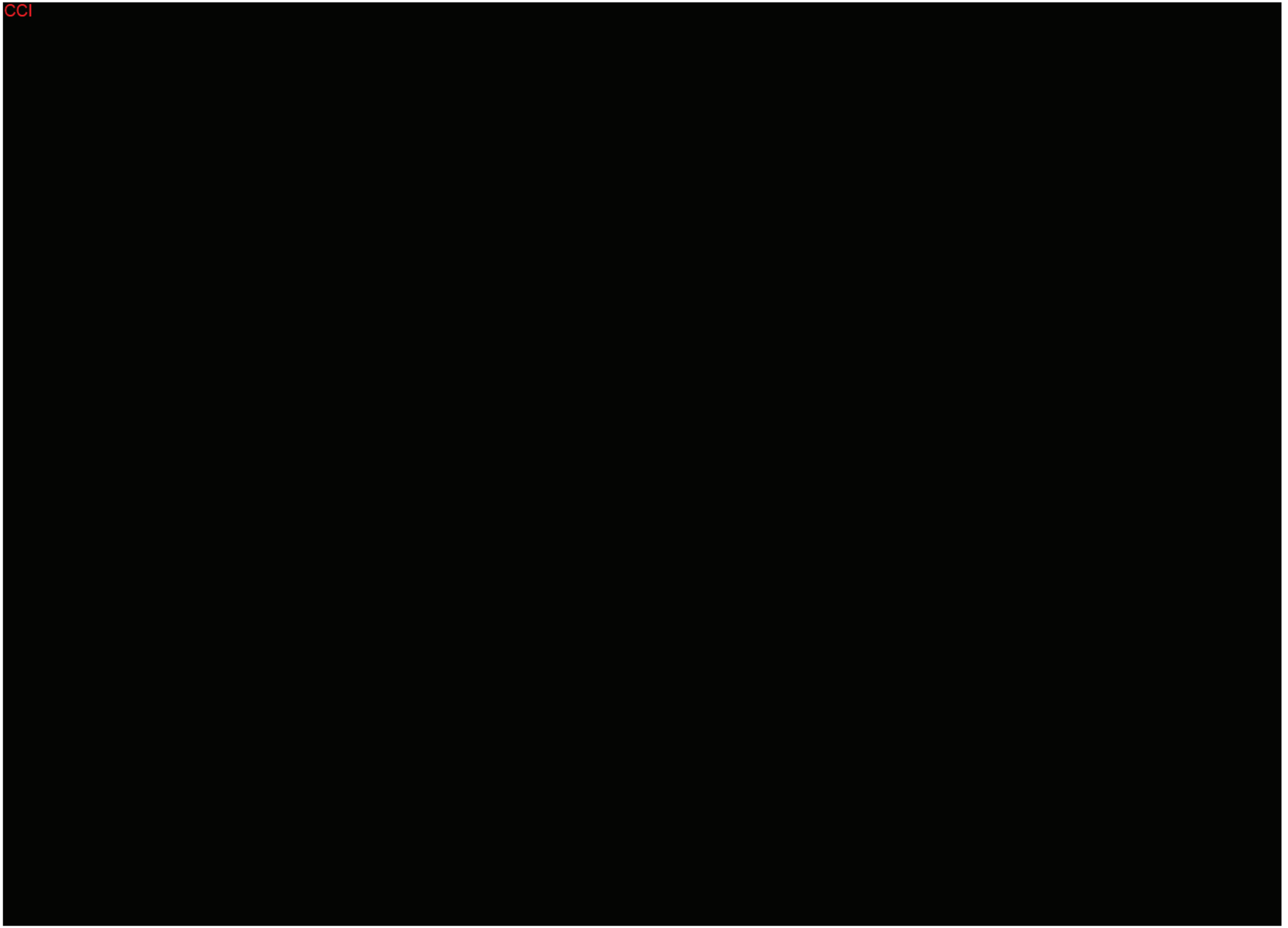
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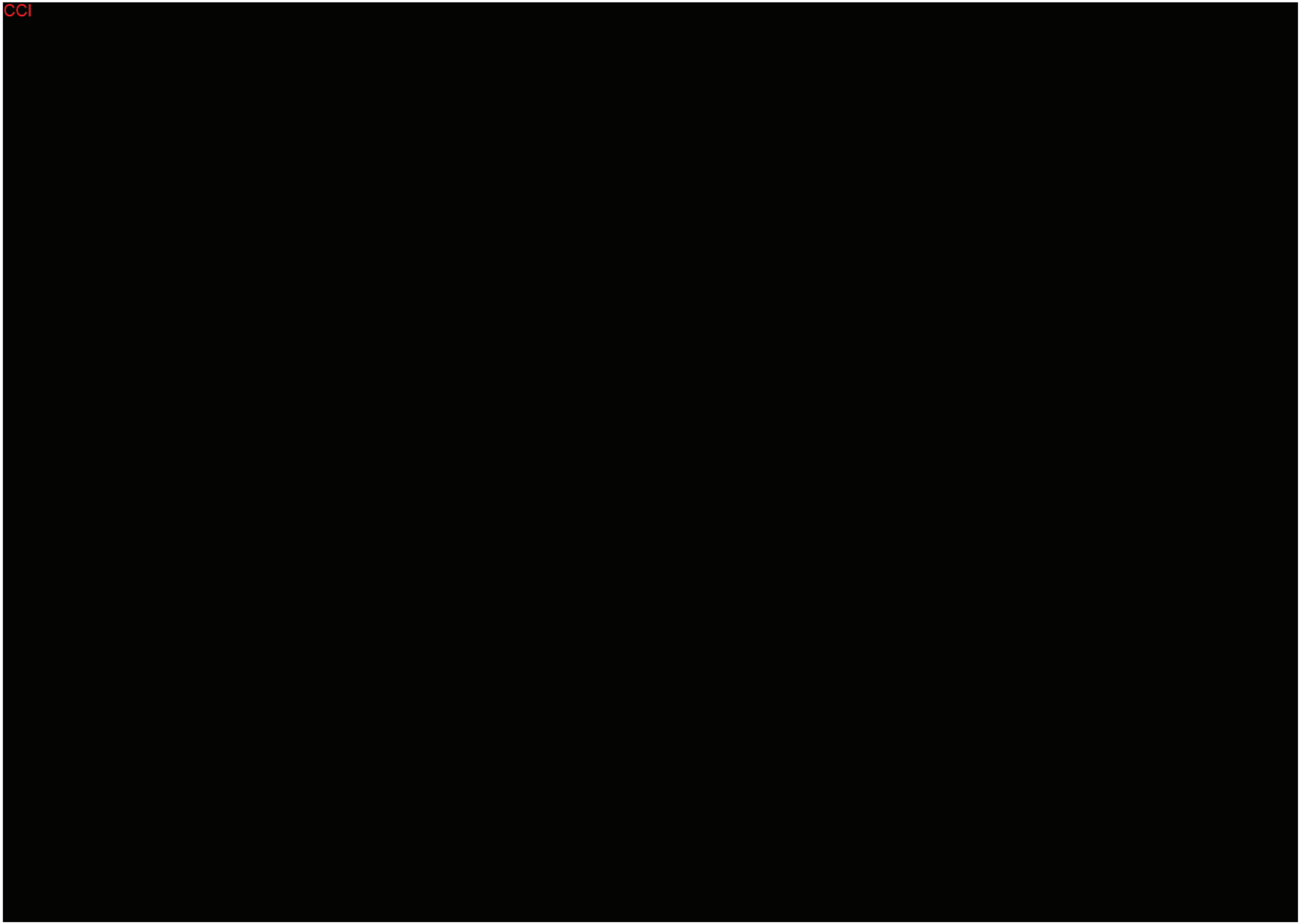
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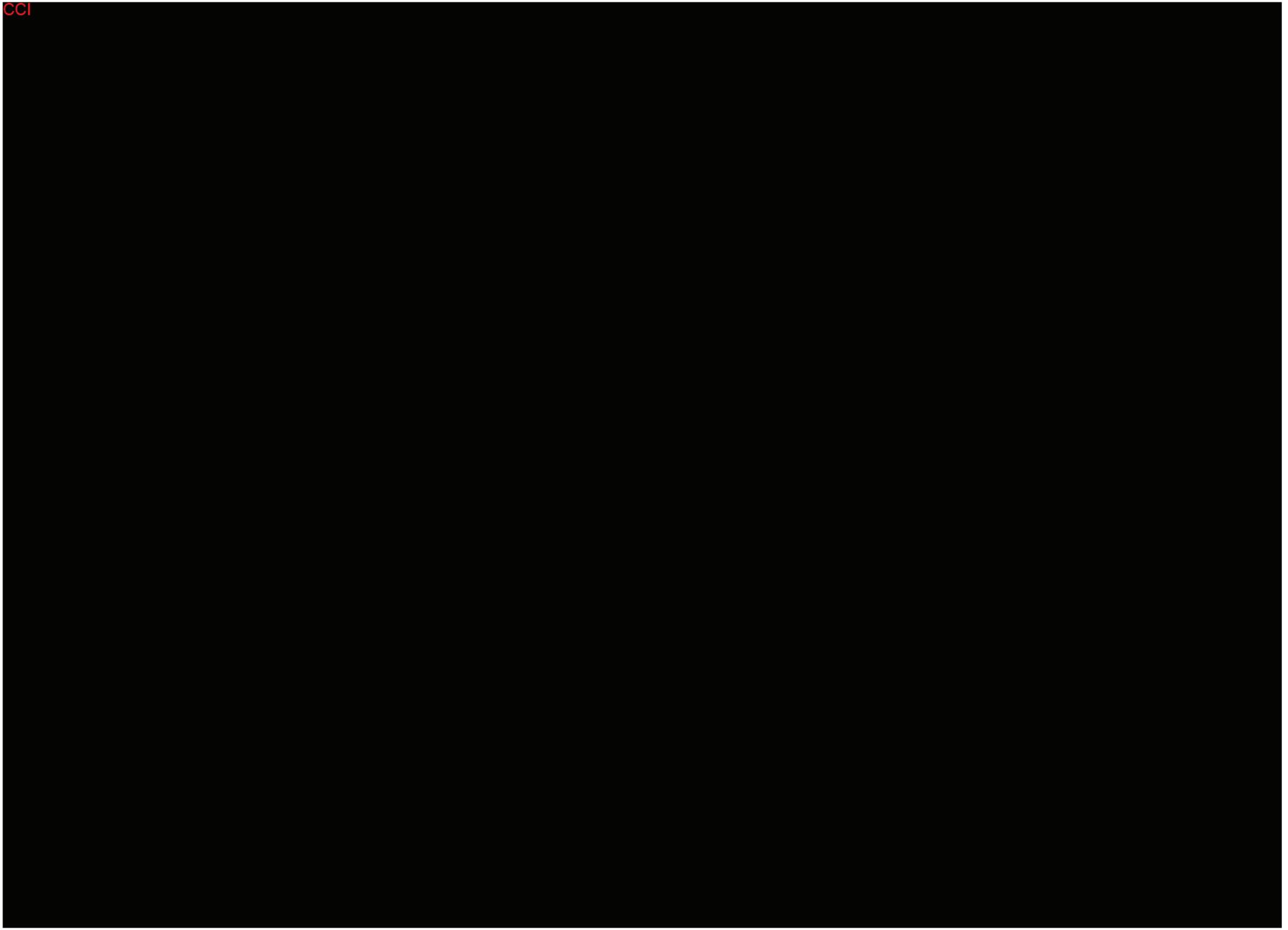
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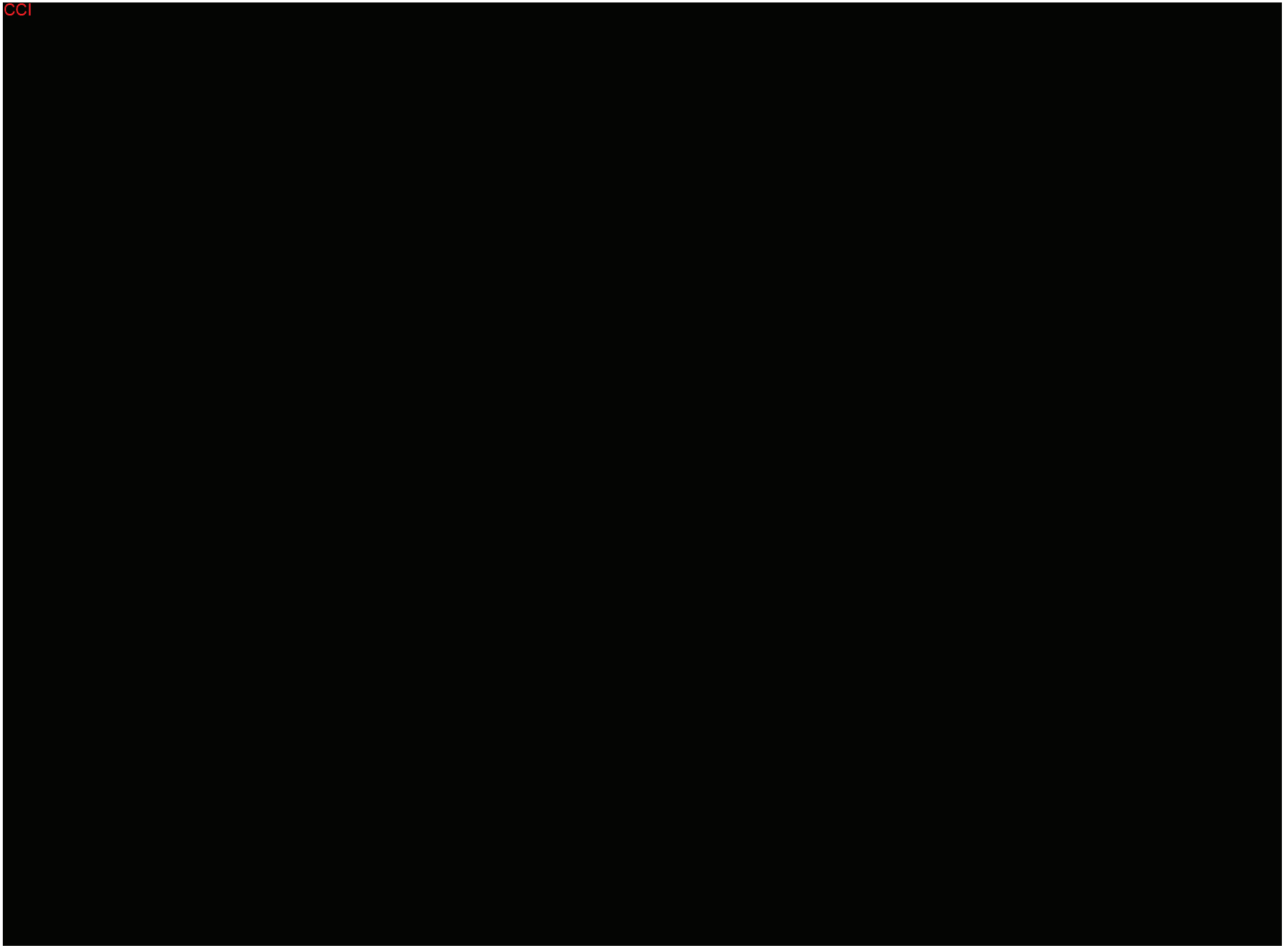
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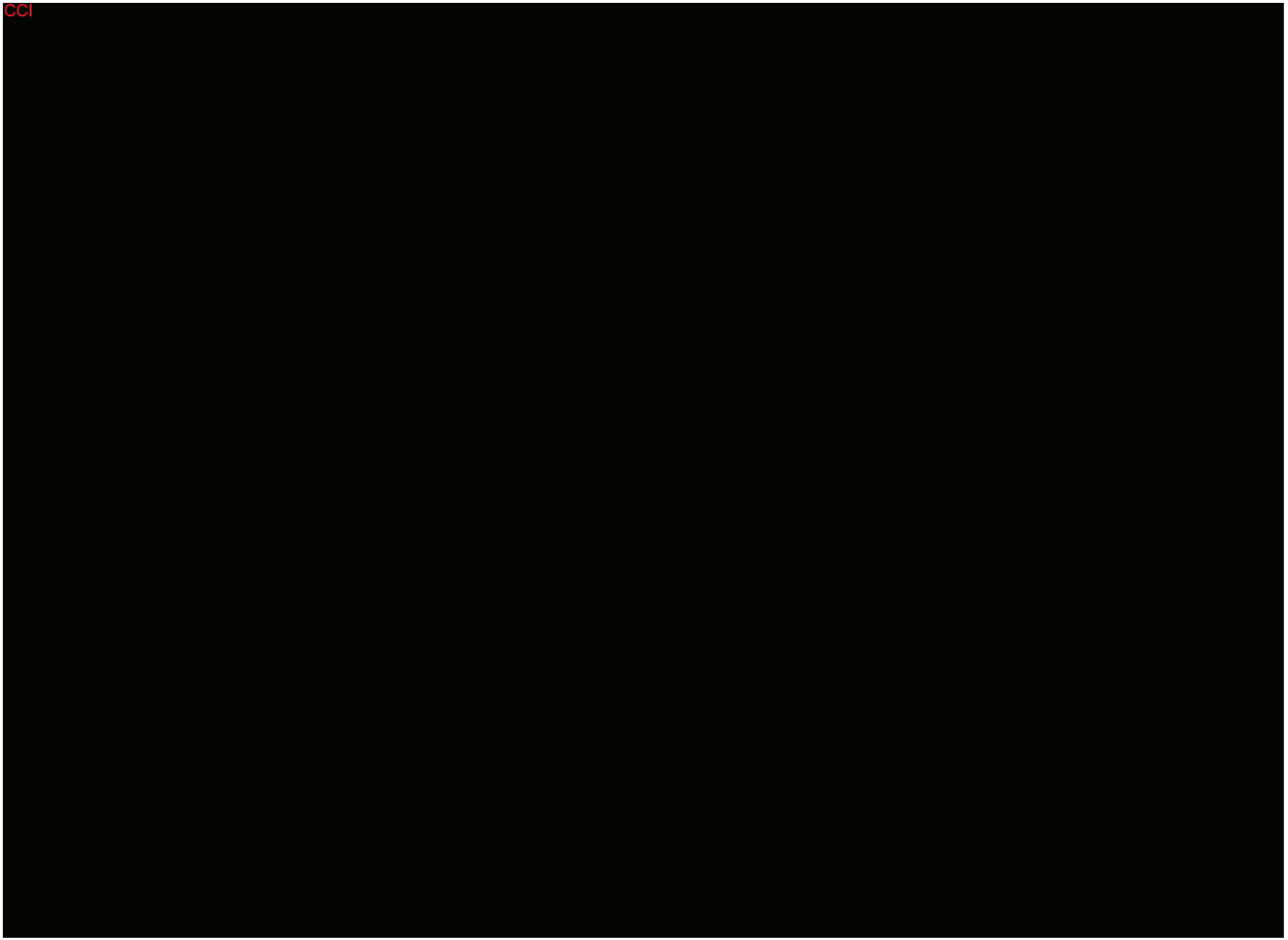
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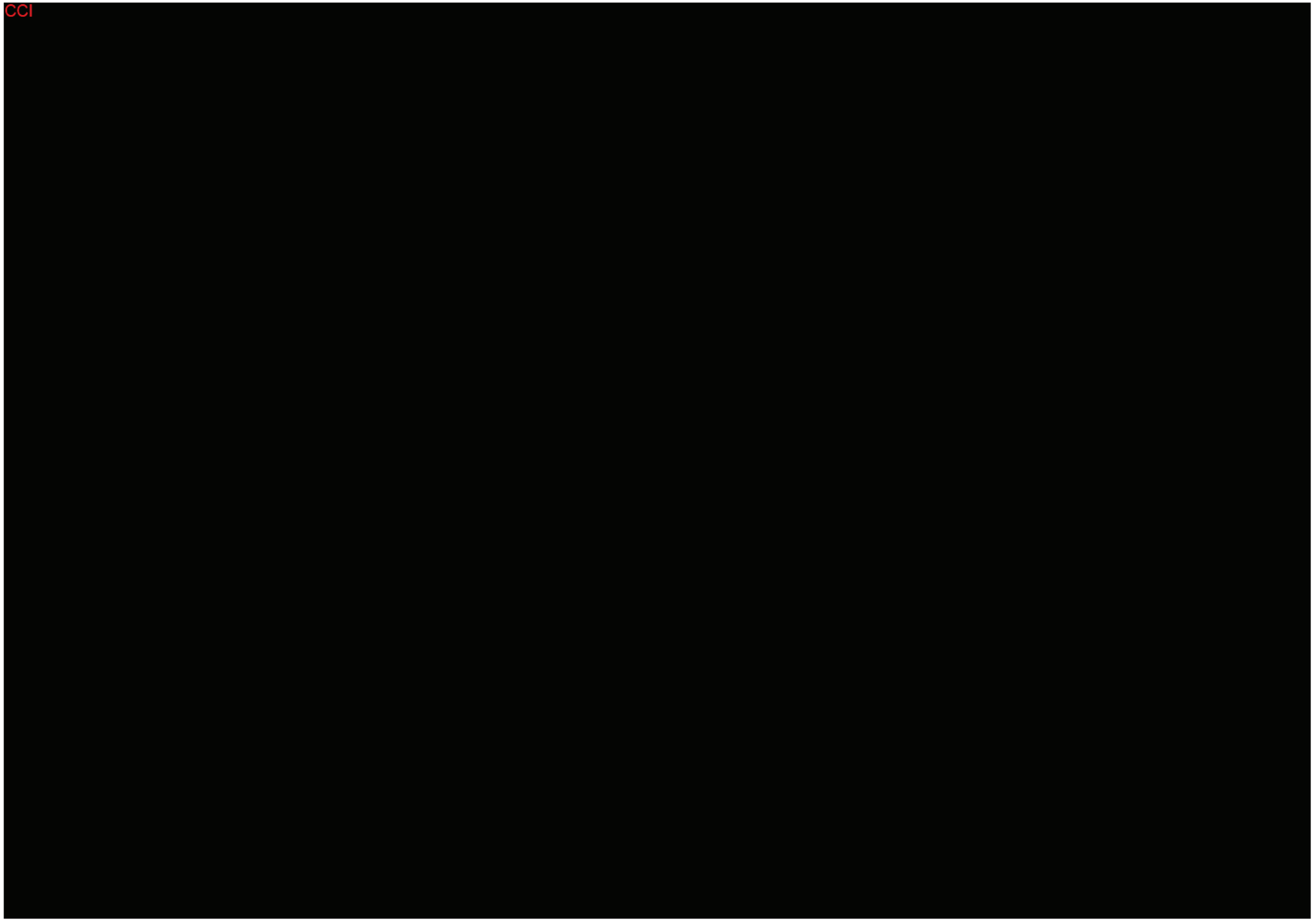
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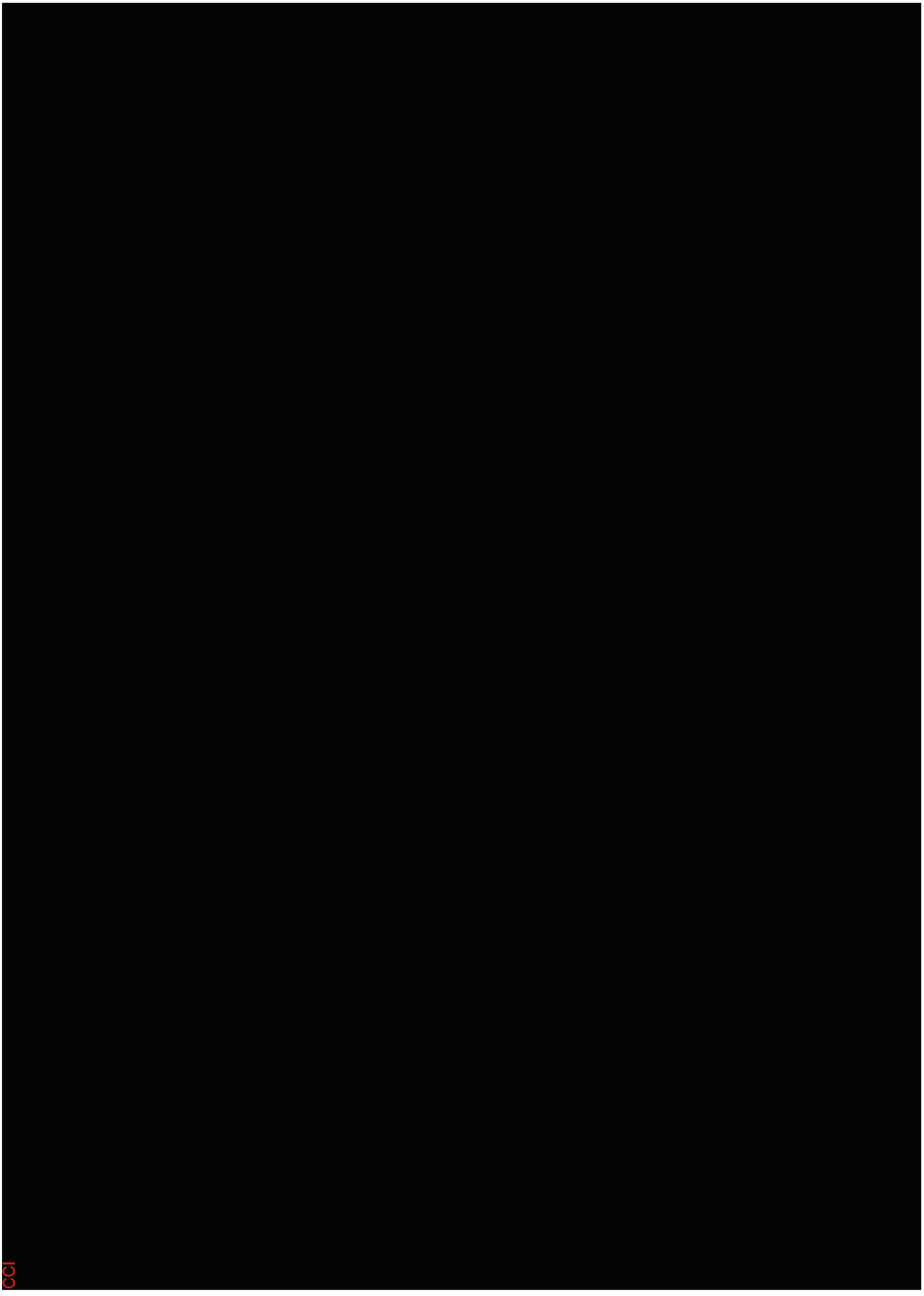


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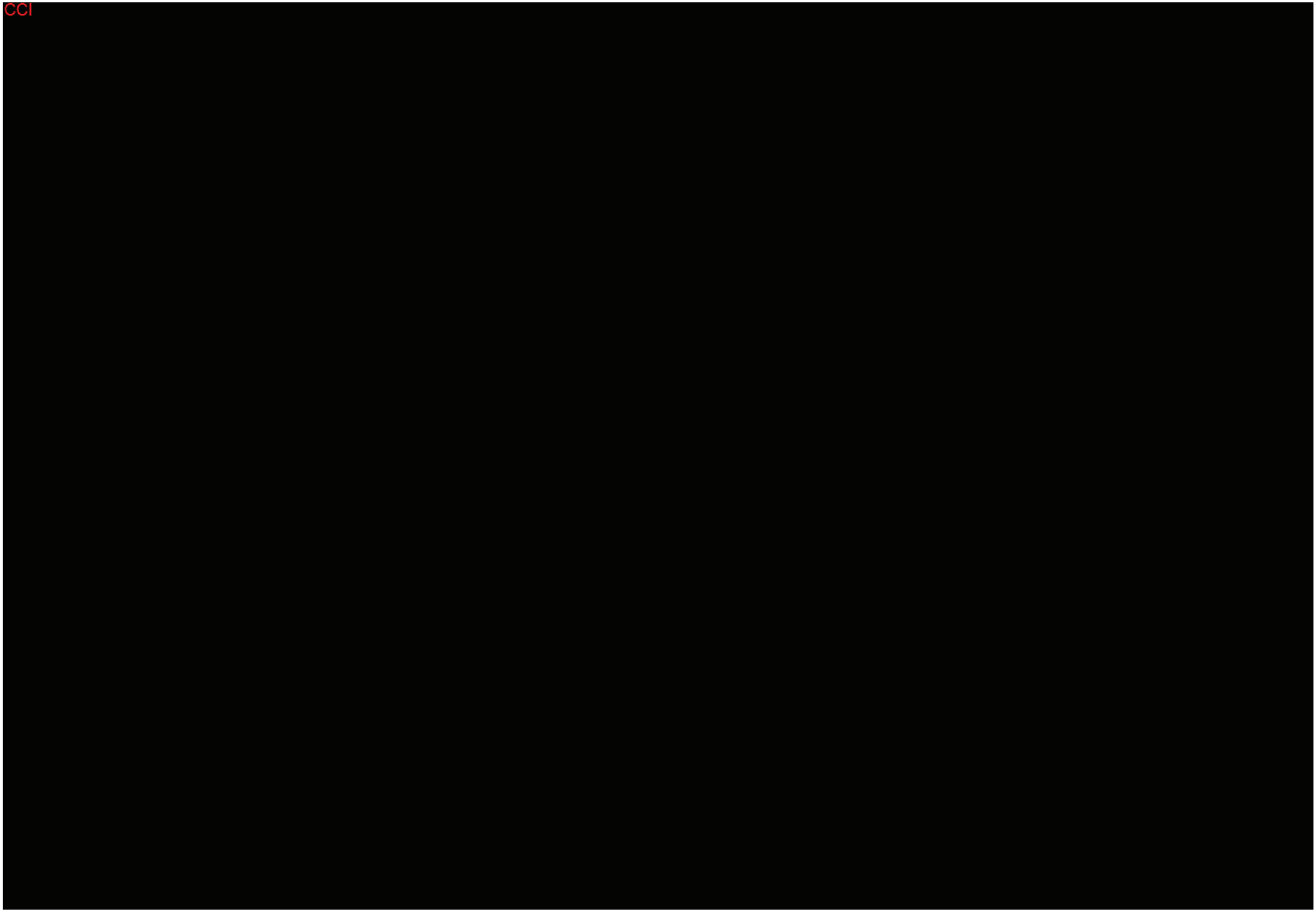
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