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Statistical Analysis Plan

A Prospective Clinical Study to Evaluate Safety and Effectiveness of *Restylane® Kysse* for Lip Augmentation in Chinese Subjects

Clinical Trial Number: 05DF2007

Study Product: Restylane® Kysse

NCT ID: NCT05342753

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Version: 1.0

Revision History

Version	Date	Comments
1.0	26SEP2023	1. Initial Version

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1 Study Information

1.1 Background

This statistical analysis plan (SAP) describes the analysis variables and statistical procedures that will be used to analyze and report the results from Protocol 05DF2007 (v2.0), dated 02 FEB 2023.

The SAP was written in accordance with the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH-E3 Guideline entitled "Guidance for Industry: Structure and Content of Clinical Study Reports".

1.1.1 Study Design

This is a prospective, open-label, multi-center study to evaluate the safety and effectiveness of *Restylane Kysse* for lip augmentation and correction of perioral rhytids, if applicable, in subjects with both biological parents of full Chinese descent.

Approximately 50 subjects with a score of 1 (Very Thin) or 2 (Thin) on the Medicis Lip Fullness Scale (MLFS) will be enrolled. The upper lip and lower lip scores do not have to be equal as long as each score is either 1 or 2 at baseline.

Following the informed consent and screening process, eligible subjects will be injected in the lips by the investigator at baseline. The method of injection is at the discretion of the investigator and will be recorded. Sufficient amount of product should be injected to achieve optimal aesthetic improvement as determined by the investigator and subject. Optimal aesthetic improvement is defined as at least 1-point improvement from baseline using the MLFS and the best correction that can be achieved as agreed by the investigator and the subject.

Subjects in the US meeting the Wrinkle Assessment Scale (WAS) inclusion criteria may also receive optional treatment with *Restylane Kysse* in the perioral rhytids at baseline. Treatment of the upper perioral lines, vermillion border, philtral columns, Cupid's bow, and/or oral commissures may be performed to obtain optimal aesthetic improvement, as agreed by the investigator and subject.

Touch-up treatment of the lips and perioral area, if treated at baseline, may be administered 4 weeks after baseline treatment if deemed necessary to obtain optimal aesthetic improvement; this decision should be agreed upon by the investigator and the subject. Touch-up treatment will not be performed if the subject has a disease or condition described in the exclusion criteria or is experiencing an ongoing treatment-related AE that, in the opinion of the investigator, would be worsened by touch-up treatment.

The recommended maximum injected volume per subject per treatment visit is 6 mL (i.e. 1.5 mL for the upper lip, 1.5 mL for the lower lip, and 3 mL for perioral area, if treated). Treatment will be performed according to the approved Instructions for Use (IFU).

Subjects will have in-clinic follow up visits at 2, 4, 8, 16, 24, 32, 40, and 48 weeks after the last injection. If a touch-up is deemed necessary and performed at 4 weeks post-baseline, a second 2-week and 4-week follow-up visits should be scheduled.

1.1.2 Number of Subjects and Randomization

Subjects will be recruited from up to 5 study sites; 4 sites in the US CCI [redacted]. Approximately 50 subjects of full Chinese descent will be included in the study. The study is open-label and is not randomized.

1.2 Study Objectives

1.2.1 Effectiveness Objectives

The effectiveness objectives are:

1. To evaluate the effectiveness of *Restylane Kysse* for lip augmentation as assessed by the investigator using the Medicis Lip Fullness Scale (MLFS) for the upper and lower lips.
2. To evaluate the aesthetic improvement of the upper perioral rhytids and oral commissures after treatment with *Restylane Kysse* as assessed by the investigator using the Wrinkle Assessment Scale (WAS). *Note: After baseline, WAS will only be assessed for subjects who have been treated in the perioral area.*
3. To evaluate the aesthetic improvement (overall appearance) of the upper and lower lips after treatment with *Restylane Kysse* as assessed by the subject and the investigator, independently, using the Global Aesthetic Improvement Scale (GAIS).

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1.2.2 Safety Objectives

To evaluate the safety of *Restylane Kysse* for lip augmentation in Chinese subjects via assessment of:

- AEs at all study visits.
- Pre-defined, expected, post-treatment events reported during the first 28 days after treatment as recorded in the subject diary.
- Lip safety assessments as evaluated by a qualified staff member including:
  - Presence of any unexpected resistance by palpation of each lip at baseline and at each physical follow-up visit.
  - Lip texture and symmetry according to pre-defined methods, for each lip at baseline and at each physical follow-up visit.
  - Lip movement, function, and sensation (on three different locations per lip) according to pre-defined methods, at baseline and at each physical follow-up visit.

1.3 Effectiveness Assessments

For all assessments, baseline will be defined as the observation that is closest to but prior to study treatment on Day 1 for treated subjects. Change from baseline will be calculated as the value at a given time point minus the baseline value.

1.3.1 Medicis Lip Fullness Scale

The MLFS is a validated photograph-based outcome instrument that is designed specifically for quantifying lip fullness. Scoring of lip fullness (see Table 1 below) will be based on visual live assessment by the investigator at defined time points, and not on a comparison to the baseline

appearance. Change from baseline (Day 1, pre-treatment) in MLFS will be calculated for each post baseline assessment.

This study will assess the magnitude of lip fullness augmentation using the two separate 5-grade MLFS photo guides (one scale for upper lip and one scale for lower lip).

Table 1. Medicis Lip Fullness Scale

Grade	Description
1	Very Thin
2	Thin
3	Medium
4	Full
5	Very Full

1.3.2 Wrinkle Assessment Scale

The WAS is a validated photograph-based outcome instrument that is designed specifically for quantifying facial folds. Scoring of fold severity is based on visual assessment of the length and apparent depth of the wrinkle at a certain time-point. Scoring of the upper perioral rhytids and oral commissures according to Table 2 will be based on visual live assessment by the investigator at defined time points, and not on a comparison to the baseline appearance. Change from baseline (Day 1, pre-treatment) in the WAS will be calculated for each post baseline assessment.

After the baseline visit, WAS will only be assessed for subjects who have been treated in the perioral area.

Table 2. Wrinkle Assessment Scale for Evaluation of Upper Perioral Rhytids and Oral Commissures

Grade	Description
0	No wrinkles
1	Just perceptible wrinkle
2	Shallow wrinkles
3	Moderately deep wrinkle
4	Deep wrinkle, well-defined edges
5	Very deep wrinkle, redundant fold

1.3.3 Global Aesthetic Improvement Scale (GAIS)

The 7-graded GAIS will be used to assess the appearance of the lips (upper and lower lip combined) compared to what they looked like before treatment (see Table 3).

Investigator assessment: The investigator will rate, in a live assessment, the global aesthetic improvement of the lips using the following categorical scale and responding to the question:

"With respect to the appearance of the subject's lips, how would you describe the result of the lip treatment compared to the photos taken before treatment?"

The subject's photographs from pre-treatment are compared to live assessment during the present visit.

Subject assessment: Subjects will rate, in live assessment, the global aesthetic improvement of their lips using the following categorical scale and responding to the question:

"With respect to the appearance of your lips, how would you describe the result of the lip treatment compared to the photos taken before treatment?"

The subject's photographs from pre-treatment are compared to live assessment using a mirror during the present visit.

Table 3. Global Aesthetic Improvement Scale (GAIS)

Grade	Rating	Definition for Investigator
3	Very much improved	Optimal aesthetic result for the implant for this subject.
2	Much improved	Marked improvement in appearance from the initial condition, but not completely optimal for this subject.
1	Improved	The appearance is improved from the initial condition.
0	No change	The appearance is essentially the same as baseline.
-1	Worse	The appearance is worse than the initial condition.
-2	Much worse	Marked worsening in appearance from the initial condition.
-3	Very much worse	Obvious worsening in appearance from the initial condition.

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1.4 Effectiveness Endpoints

The effectiveness endpoints include:

1. MLFS change from baseline and response rates at 8, 16, 24, 32, 40 and 48 weeks after last injection.
2. WAS change from baseline and response rates at 8, 16, 24, 32, 40 and 48 weeks after last injection.
3. GAIS response rates at 8, 16, 24, 32, 40 and 48 weeks after last injection.

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1.5 Safety Assessments

The methods for collecting safety data are described in Section 7 of the Clinical Study Protocol. Data to be collected include the following:

- Adverse events.
- Subject diaries to be completed daily for 28 days following each treatment session.
- Lip Safety Assessments.
- Device deficiencies.
- Urine pregnancy test performed at screening and all treatment visits (prior to treatment).

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2 Statistical Methods

2.1 General Methods

Any change made to the finalized SAP before database lock will result in an SAP amendment. Otherwise, changes will be documented in the Clinical Study Report (CSR). However, if additional supportive or exploratory analyses are requested after SAP approval, this will not require amendment of the SAP, but these additional analyses will be described in the CSR.

Some of the analyses detailed here may be more explicit or in some respects different from those stated in the protocol. In case of differences, this SAP supersedes the statistical sections in the protocol.

2.1.1 Programming Conventions

EMB Statistical Solutions will have responsibility for performing analyses. All computations for statistical analyses will be performed using SAS® software, Version 9.4 or later. All SAS programs used in the production of statistical summary outputs will be validated with independent programming prior to finalization. In addition, all program outputs will be independently reviewed. The validation process will be used to confirm that all data manipulations and calculations were accurately done. Once validation is complete, a senior statistical reviewer will perform a final review of the documents to ensure the accuracy and consistency with this plan and consistency

within tables. Upon completion of validation and quality review procedures, all documentation will be collected and filed by the project statistician or designee.

The electronic case report form (eCRF) data for all subjects will be provided in Standard Data Tabulation Model (SDTM) datasets. Analysis Data Model (ADaM) datasets will be developed from the SDTM datasets for use in table and figure production.

2.1.2 Reporting Conventions

The formats for the tables, listings, and figures described in this SAP will be provided in a companion document. Changes to the formats of these reports that are decided after the finalization of the SAP will not require an amendment. In addition, any additional supportive or exploratory analyses requested after SAP approval will not require amendment of the SAP. These additional analyses will be described in the CSR.

Study data from the eCRFs as well as derived variables will be provided in subject data listings. An indication of specific listings for each data type will not be indicated in the text of subsequent SAP sections. Data listings supplied as part of the CSR will be sorted by study site number concatenated with subject number, assessment dates, and/or time point.

The following conventions will be applied to all data presentations and analyses:

- Confidence intervals (CIs) will be two-tailed and constructed at a confidence level of 95%. Statistical tests will be performed at a significance level of 5%, and p-values will be two-sided, unless otherwise specified.
- Quantitative variables will generally be summarized by the number of subjects, mean, standard deviation, median, minimum, and maximum. Unless otherwise specified, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the standard deviation will be displayed to two extra decimal places compared to the raw data.
- Categorical variables will be summarized by the number and percentage of subjects (and number of events where appropriate) within each category. Unless otherwise specified, the percentage will be presented in parentheses to one decimal place. Frequency and percentage values of 0 will be presented as '0' rather than '0 (0)'.
- All summary tables will include the analysis population sample size (i.e., number of subjects) in each treatment group.
- Date variables will be formatted as DDMMMYYYY for presentation.

2.1.3 Data Transformations

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2.2 Analysis Populations

The statistical analyses will be performed based on the following subject populations.

2.2.1 Modified Intent-to-Treat (MITT) Population

The MITT population includes all subjects who were treated in both lips. All effectiveness variables will be analyzed based on the MITT population.

2.2.2 Safety Population

The Safety population includes all subjects who were treated with *Restylane Kysse* in at least one lip, and will be analyzed according to the treatment actually received. All safety data will be summarized descriptively based on the Safety population.

2.3 Study Subjects

Demographic endpoints and subject characteristics will be summarized using descriptive statistics overall based on the MITT population using observed cases. There are no planned inferential statistical analyses of demographic endpoints or subject characteristics.

2.3.1 Subject Disposition

The number of subjects screened will be shown in total.

The number of subjects in each study population (i.e., MITT, and Safety) will be summarized by country and in total.

The disposition of subjects will be presented by country and in total, including numbers of subjects who were completed and withdrawn (including primary reason for withdrawal).

The number of subjects expected, completed, withdrawn, and missed will be summarized by scheduled visit, using the following definitions:

- Expected = all subjects at screening minus subjects who have withdrawn up to that visit.
- Completed = subjects who showed up at that visit.
- Withdrawn = all subjects who have withdrawn up to that visit (cumulative).
- Missed = expected subjects minus completed subjects.

All withdrawn subjects will be listed individually, including at least subject number, date and reason for withdrawal, and last visit performed.

2.3.2 Protocol Deviations

Subjects with any protocol deviations will be summarized by type for each country and overall.

2.3.3 Demographic Characteristics

Age and body mass index will be summarized as continuous variables.

Gender, race, ethnicity, Fitzpatrick Skin Type (FST), baseline MLFS (upper and lower lip) and childbearing potential will be summarized as categorical variables.

Demographics will be summarized by country and overall.

2.3.4 Medical History, Medications, and Procedures

Prior and concomitant medications and vaccines will be coded using the World Health Organization Drug Dictionary (WHODD). Medical history, prior cosmetic treatments/procedures, and concomitant procedures/treatments will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

Prior medications/procedures are the medications/procedures with stop dates prior to first study treatment session. Medications/procedures after the first study treatment session will be considered concomitant.

Subjects reporting medical history, prior cosmetic treatments/procedures, and concomitant procedures/treatments will be summarized by System Organ Class (SOC) and Preferred Term (PT).

Subjects reporting prior and concomitant medications will be summarized separately, by WHODD Anatomical Therapeutic Chemical (ATC) Class Level 3 (if Level 3 is not available, the highest class available will be used) and WHODD preferred name.

2.4 Effectiveness Analysis

2.4.1 Datasets Analyzed

The MITT population is primary for all effectiveness analyses. The MITT population will be split into two subgroups for analysis by country.

2.4.2 Handling of Missing Data

Number of missing values will be summarized and reported as appropriate.

All effectiveness endpoints will be evaluated based on observed cases in the MITT population. Sensitivity analyses will be performed for the MLFS. The first sensitivity analysis will replace all missing values with the most negative answer (1). The second sensitivity analysis will replace all missing values with the most positive answer (5). MLFS tables will be repeated for both sensitivity analyses.

2.4.3 Primary Effectiveness Analysis

2.4.3.1 Medicis Lip Fullness Scale

MLFS will be presented with number of subjects and percentage for each category of the scale. The proportion of responders based on MLFS (defined as at least 1-point improvement from baseline) as assessed by the investigator at weeks 8, 16, 24, 32, 40, and 48 after last injection will be calculated and presented with their 95% confidence intervals (calculated via Clopper-Pearson). Response rates will be calculated for the upper and lower lip separately as well as for both lips combined. A bar plot of the percentage of responders for each upper lip, lower lip and combined by visit also will be produced for each.

In addition, the change from baseline at weeks 8, 16, 24 32, 40, and 48 after last injection will be calculated for the upper and lower lip separately. The number of subjects and percentage for each point change (+4, +3, +2, etc.) from baseline will be presented.

2.4.3.2 Wrinkle Assessment Scale

WAS will be presented with number of subjects and percentage for each category of the scale. The proportion of responders based on the WAS (i.e., at least a one point improvement from the investigator baseline assessment of the upper perioral rhytids and oral commissures at weeks 8, 16, 24, 32, 40, and 48) will be calculated and presented along with their 95% confidence intervals (calculated via Clopper-Pearson). A bar plot of the percentage of responders for each upper perioral rhytids and oral commissures by visit also will be produced for each.

In addition, the change from baseline at weeks 8, 16, 24 32, 40, and 48 after last injection will be calculated. The number of subjects and percentage for each point change (+3, +2, +1, 0, etc.) from baseline will be presented.

2.4.3.3 Global Aesthetic Improvement Scale

GAIS will be presented with number of subjects and percentage for each category of the scale. For the GAIS, response rate is defined as a subject with a rating of at least "improved". The response rates based on the GAIS as assessed by the investigator and the subject, respectively, at Week 8, 16, 24, 32, 40, and 48 after last injection will be calculated and presented along with their 95% confidence intervals (calculated via Clopper-Pearson). A bar plot of the percentage of responders (at least "Improved") by visit also will be produced for each evaluator type (investigator and subject).

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2.5 Safety Analysis

Safety endpoints will be summarized using descriptive statistics based on the safety population using observed cases. There are no planned inferential statistical analyses of safety endpoints.

2.5.1 Treatment Administration and Procedural Anesthetics

Treatment administration endpoints that will be summarized by treatment session, treatment location and overall include (but are not limited to): injection volume, injection method, and depth of injection.

The number of subjects with any procedural anesthetics will be summarized by anesthetic type.

2.5.2 Adverse Events (AEs)

All AEs will be coded according to MedDRA and summarized by System Organ Class (SOC), and Preferred Term (PT), including number of subjects with at least one event, associated percentage, and number of events.

For subject counts, a subject will only be counted once per SOC and once per PT in cases where multiple events are reported for a subject within SOC or PT. For event counts, subjects with multiple events in a category will be counted for each event.

The number of subjects with AEs related to study product or study product injection procedure, as well as the number of events, will be presented by SOC, PT, and maximum intensity. Action taken for related AEs will also be summarized by SOC and PT using number of events. Serious AEs will be listed. AEs related to study product or injection procedure with late onset (> 21 days after most recent treatment session) will be listed.

AEs unrelated to study product or injection procedure will be summarized by SOC, PT, and maximum intensity.

For AEs related to study product or study product injection procedure, the number of days to onset and the duration of event will be summarized by SOC and PT using mean, standard deviation, median, minimum, and maximum. Days to onset of an AE will be derived as the start date minus the date of most recent treatment session. Duration of an AE will be derived as the stop date minus the start date + 1.

For the purpose of deriving days to onset and duration, the following date imputation rules will be used.

Start Date

- If start date is completely missing, it will be assumed that the AE started at baseline.
- If the start date is missing the day, the baseline day will be used provided the imputed date is on or after the subject's first treatment date; otherwise, the day of first treatment will be used.
- If the start date is missing the month, the first treatment month will be used. provided the imputed date is on or after the subject's first treatment date; otherwise, the subsequent month after first treatment will be used.
- If the start date is missing the year, the baseline year will be used provided the imputed date is on or after the subject's first treatment date; otherwise, the subsequent year after first treatment will be used.

End Date

- If end date is completely missing, it will be assumed that the AE is still ongoing and will not be imputed.
- If the end date is missing the day, the last of the month will be used (i.e. UNK-JAN-2022 becomes 31-JAN-2022)
- If the end date is missing the month, the subsequent month after the start date will be used.
- If the end date is missing the year, the year of first treatment will be used, provided the imputed date is after the start date; otherwise, the subsequent year after start date will be used.

Adverse events with a completely missing start date will be considered treatment-emergent unless the event has a stop date prior to the date of the first dose of study drug. All AEs will be listed by treatment and subject. Dates will be presented as collected in the listings.

In addition, a summary of all AEs will be provided, which will include (but is not limited to):

- number of subjects with at least one AE and number of events (in total as well as serious AEs),
- number of subjects with at least one related AE and number of events (in total as well as serious AEs),
- number of subjects with at least one unrelated AE and number of events (in total as well as serious AEs),

- number of subjects who did not have an AE.

2.5.3 Pre-Defined, Expected, Post-Treatment Events

The number and percentage of subjects reporting each pre-defined, expected, post-treatment event, as collected in the 28-day diary, will be presented in total and by maximum intensity for each treatment session and overall. The number of days with the event for each treatment session will be summarized using mean, SD, min, max and median. The percentage of subjects with each event also will be plotted for each treatment session by day.

2.5.4 Other Safety Analyses

Palpation assessment, lip movement, function and sensation (on 3 different locations per lip), as well as lip texture and symmetry, will be presented in frequency tables by visit.

2.6 Interim Analysis

There are no planned interim analyses for this study.

2.7 Determination of Sample Size

The sample size of approximately 50 subjects is not based on a statistical calculation. The selected number of subjects is regarded as sufficient for an evaluation of the studied endpoints by using descriptive statistics.

2.8 Changes in the Analysis Planned in the Protocol

There have been no substantial changes from the statistical methods described in the protocol.

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3 Reference List

There are no other references beyond those that are included in the protocol.

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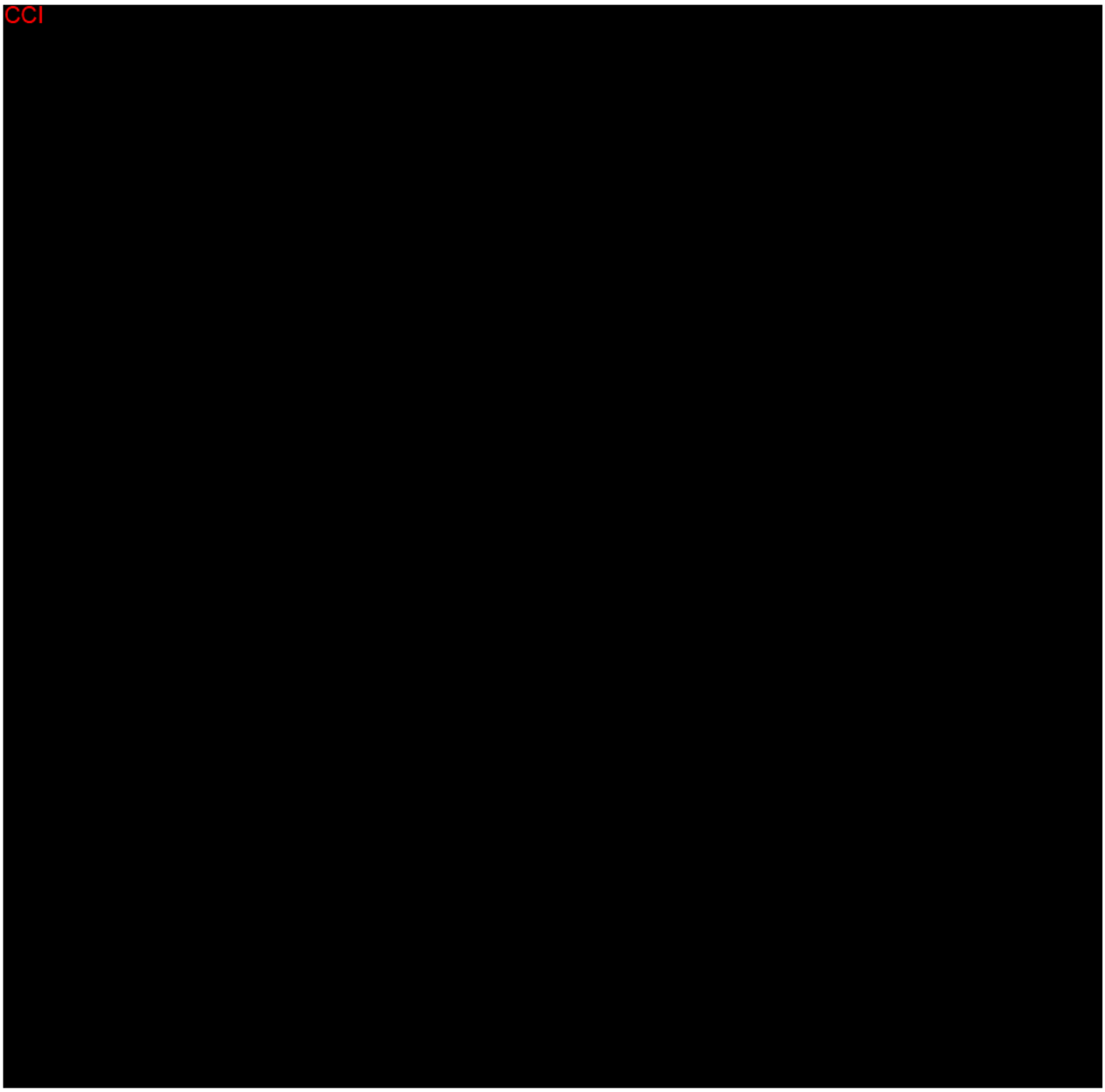

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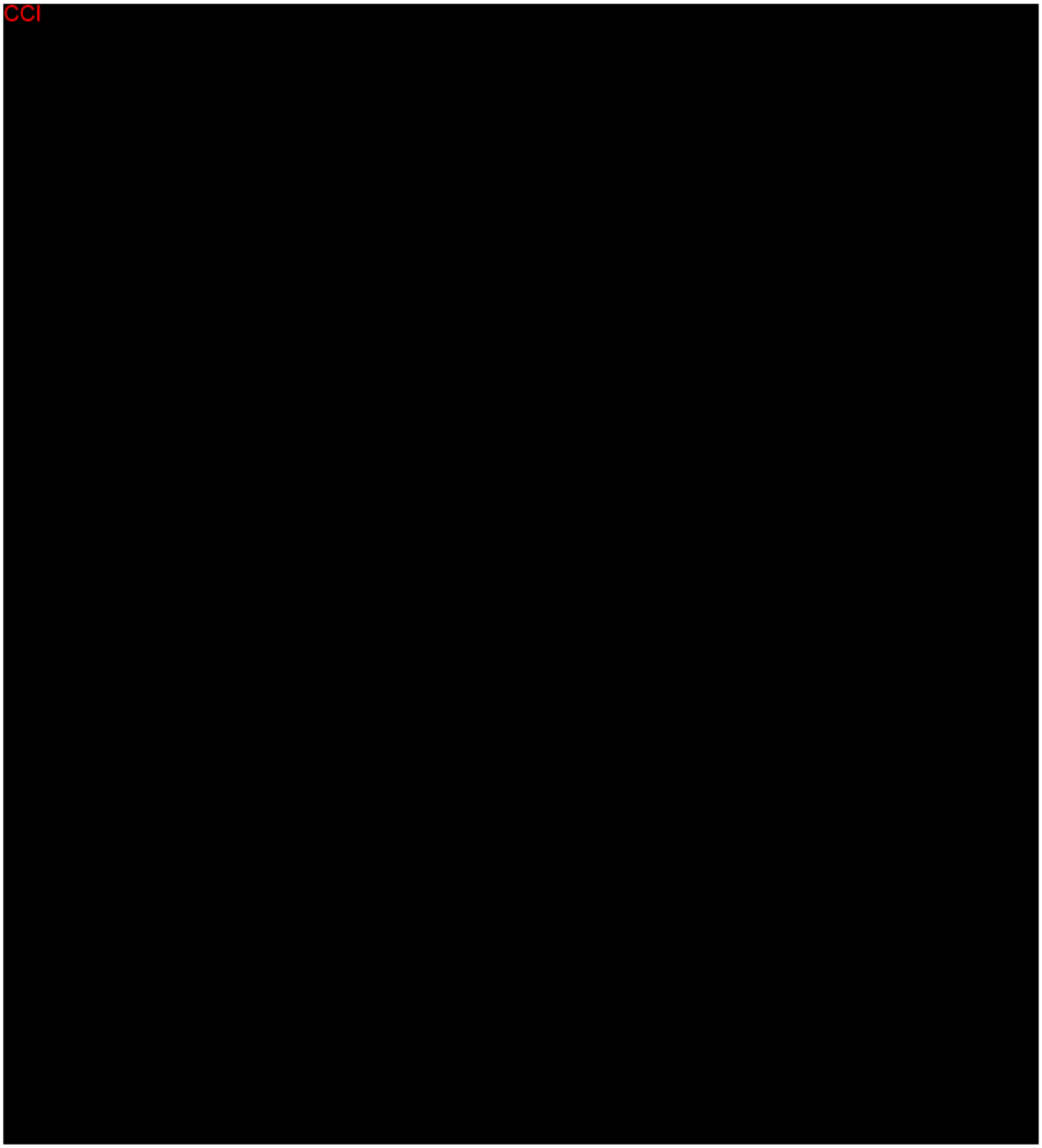

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