Statistical Analysis Plan

Clinical Trial Number (CTN): 43USTH2201

Protocol Version and Date:
Version 4.0, 14 October 2024

A randomized, no-treatment-controlled, evaluator-blinded, multi-center study to evaluate the effectiveness and safety of Restylane Contour in the treatment of temple hollowing

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APPROVAL SIGNATURE PAGE

Protocol Title: A randomized, no-treatment-controlled, evaluator-blinded, multi-center study to evaluate the effectiveness and safety of Restylane Contour in the treatment of temple hollowing

Sponsor: Q-Med AB, part of the Galderma Group
Seminariegatan 21
SE-752 28 Uppsala, Sweden

Protocol Number: 43USTH2201

Advanced Clinical Author:

PPD

PPD

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Sponsor Signatory:

PPD

PPD

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ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC-2	Anatomical Therapeutic Chemical 2nd level
ATC-3	Anatomical Therapeutic Chemical 3rd level
BE	Blinded Evaluator
BMI	Body Mass Index
BOCF	Baseline Observation Carry Forward
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CTN	Clinical Trial Number
EOT	End of Treatment
EOS	End of Study
eCRF	Electronic Case Report Form
FST	Fitzpatrick Skin Type
CCI	[redacted]
GTVDS	Galderma Temple Volume Deficit Scale
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IPR	Independent Photographic Reviewer
IRB	Institutional Review Board
ITT	Intention-to-Treat
KM	Kaplan-Meier
LS	Least Squares
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
CCI	[redacted]
OC	Observed Cases
OR	Odds Ratio
PP	Per-Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAESI	Serious Adverse Event of Special Interest
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
CCI	[redacted]

Abbreviation	Definition
TI	Treating Investigator
VA	Visual Acuity
WHO	World Health Organization

1.0 INFORMATION FROM THE STUDY PROTOCOL

1.1 Introduction

Clinical trial number (CTN) 43USTH2201 is a randomized, no-treatment-controlled clinical study to collect safety and effectiveness data to support the use of *Restylane® Contour* in a new indication "correction of temple hollowing", in female and male subjects over the age of 21 years. Restylane Contour will be administered by needle and cannula injections in the temple area.

1.2 Study Objectives

This statistical analysis plan (SAP) describes the methods to be used in the analysis of study data from clinical protocol 43USTH2201, *A randomized, no-treatment-controlled, evaluator-blinded, multicenter study to evaluate the effectiveness and safety of Restylane Contour in the treatment of temple hollowing,* in order to answer the study objective(s), and is based on:

- Version 4.0 of the study protocol, dated 14 Oct 2024; and
- Version 3.0 of the electronic case report forms (eCRFs), dated 12 May 2023

Populations for analysis, data handling rules, statistical methods, and formats for data presentation are described within this document. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this study. The SAP outlines any differences in and details of data analysis methods relative to those planned in the study protocol. The analyses specified in this SAP supersede the analysis plan described in the study protocol and any previous versions of this SAP. Any changes to the data analysis methods after the SAP is finalized will be described in the CSR.

1.2.1 Primary Objective

The primary objective of the study is to evaluate the effectiveness of Restylane Contour versus a no-treatment control in correction of temple hollowing by comparing Galderma Temple Volume Deficit Scale (GTVDS) response rates.

1.2.2 Secondary Objectives

The secondary objective of the study is to further evaluate the effectiveness of Restylane Contour versus a no-treatment control in correction of temple hollowing.

1.2.3 Safety Objectives

The safety objective of the study is to evaluate the safety of Restylane Contour in treatment of temple hollowing.

1.3 Study Design

1.3.1 Overview of Study Design

Study 43USTH2201 is a randomized, no-treatment-controlled, evaluator-blinded, multi-center study to evaluate the effectiveness and safety of Restylane Contour in correction of temple hollowing. Restylane Contour will be administered by needle and cannula injections in the temple area.

A total of 225 subjects is planned to be included in the study. At the baseline visit, approximately 180 subjects will be randomized to the Restylane Contour Treatment group and approximately 45 subjects will be randomized to no-treatment (Control group). All subjects in the Treatment group will receive supraperiosteal injections using needle. Of these subjects, approximately 90 subjects will receive superficial (subdermal) injections using needle and 90 subjects will receive superficial (subdermal) injections using blunt cannula.

At least 45 subjects will be Fitzpatrick skin type (FST) IV-VI. This includes at least 23 subjects with FST V-VI, where at least 12 subjects will be FST V and at least 11 subjects will be FST VI.

After providing informed consent, eligible subjects randomized to receive treatment will be injected by the Treating Investigator at baseline (Day 1). A follow-up telephone call should be made 72 hours after treatment, and follow-up visits after 2 weeks and 1 month (4 weeks).

Optional touch-up treatment may be administered 1 month (4 weeks) after initial treatment, if deemed necessary by the Treating Investigator and the subject, to obtain optimal aesthetic improvement. Optimal aesthetic improvement is defined as at least 1 grade improvement from baseline in each temple on the GTVDS. If optional touch-up is performed, a 72-hour follow-up telephone call and follow-up visits after 2 weeks and 1 month (4 weeks) should be scheduled.

Follow-up visits are scheduled at 3 months (week 12), 6 months (week 24), 9 months (week 36), 12 months (week 48) and at 18 months (week 72) after baseline. Subjects in the Control group will be offered optional treatment after 3 months (12 weeks) from baseline (Day 1). A follow-up telephone call should be made 72 hours after treatment and follow-up visits at 2 weeks, 1 month (4 weeks), 3 months (12 weeks), 6 months (24 weeks), 9 months (36 weeks), and 12 months (48 weeks) after optional treatment should be scheduled. Subjects that decline optional treatment after 3 months (12 weeks) will end their study participation at the Month 3 visit.

Investigator blinding will be accomplished by using a Treating Investigator to administer the treatments and a Blinded Evaluator, to whom randomization and treatment are concealed, to conduct the blinded assessments. Safety assessments will be performed by non-blinded personnel.

Effectiveness and safety data will be collected for up to 18 months (72 weeks) after baseline. A subject will be involved in the study for up to 19 months (Treatment group) or up to 16 months (Control group), including a 21-day screening period. For subjects in the no-treatment Control group that do not receive treatment at 3 months (12 weeks), the study participation will be approximately 4 months, including the screening period.

1.3.2 Randomization Methodology

Approximately 225 subjects will be randomized to the either Restylane Contour (treatment group) or No Treatment (control group) in a 4:1 ratio. Approximately half of the subjects in the treatment group will receive injections with needle and the other half will receive injections with cannula.

Randomization will be stratified by Fitzpatrick Skin Type (FST) (I-III, IV, or V-VI). Subjects in the FST I-III stratum will be further stratified by study center; subjects in the FST IV or FST V-VI strata will not be further stratified by study center due to the smaller sample size in these groups.

Full details can be found in the Randomization Plan.

1.3.3 Sample Size Justification

A total sample size of 225 subjects is planned to be included in this study; approximately 180 subjects will be randomized to treatment with Restylane Contour (90 subjects with needle and 90 subjects with cannula for superficial [subdermal] injections) and approximately 45 subjects will be randomized to no-treatment.

Using a two-sided Fisher's Exact Test, in needle and cannula subjects separately (at the 2.5% level of significance to account for multiplicity), the power will be approximately 90% for each test (assuming the same responder rate of 70% in both needle and cannula and 35% in the no-treatment Control group). This yields 76 treated subjects and 38 control subjects. Since the control group is the same between needle and cannula subjects, 76 (needle) + 76 (cannula) + 38 (control) + dropout = 225 total subjects.

This calculation assumes an allocation ratio of 2:1 for both the needle and cannula groups of subjects to the no-treatment group of subjects, since approximately half of subjects in the treatment group will receive treatment with needle and approximately half will receive treatment with cannula. The total sample size accounts for 15% dropouts at month 3 after baseline. As described in Section 7, this sample size

justification corrects and clarifies the sample size justification provided in the study protocol.

1.3.4 Participation of Independent Committees

No independent committees are planned for this study.

1.4 Effectiveness and Safety Endpoints

1.4.1 Effectiveness Endpoints

1.4.1.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is the responder rate based on the Blinded Evaluators' live assessment of the GTVDS, at 3 months after baseline. A responder is defined as a subject with at least 1 grade improvement from baseline in both temples concurrently on the Month 3 GTVDS.

1.4.1.2 Secondary Effectiveness Endpoints

The secondary effectiveness endpoints include the following:

1. Responder rate, as assessed by the Blinded Evaluator at Month 3 after baseline for the Treatment group, compared to a reference standard responder rate of 50%. A responder is defined as a subject with at least 1 grade improvement from baseline in both temples concurrently on the GTVDS.

2. Responder rates, as assessed by the Blinded Evaluator at 6, 9 and 12 months after baseline for the Treatment group only. A responder is defined as a subject with at least 1 grade improvement from baseline in both temples concurrently on the GTVDS for a respective visit.

3. Responder rates, as assessed by the Blinded Evaluator at 18 months after baseline for the Treatment group only. A responder is defined as a subject with at least 1 grade improvement from baseline in both temples concurrently on the Month 18 GTVDS.

CCI [redacted]

CCI

1.4.2 Safety Endpoints

Safety evaluations performed during the study include the monitoring of adverse events, subject pain assessments, visual function assessments, and palpation, jaw functionality, and motor and sensory tests.

The safety endpoints of the study include the following:

1. Incidence, intensity, time to onset and duration of AEs collected throughout the study period.

CCI

CCI [redacted]

1.5 Effectiveness and Safety Assessments

1.5.1 Effectiveness Assessments

The following are the methods that will be used to collect effectiveness data. Certain assessments will be collected for both the Treatment group and the no-treatment Control group, while others will be collected for the Treatment group only. See Table 1 below for this categorization.

Table 1: Effectiveness Assessments by Treatment Group

Assessment	Assessed For
Independent Photographic Reviewer (IPR) Assessment of Improvement	Treatment group and no-treatment Control group
Galderma Temple Volume Deficit Scale (GTVDS) – Treating Investigator	Treatment group and no-treatment Control group
Galderma Temple Volume Deficit Scale (GTVDS) – Blinded Evaluator	Treatment group and no-treatment Control group
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

1.5.1.1 Photography

Photographs will be taken prior to the first injection of the study product, before treatments, and at every physical follow-up visit in order to document treatment effect. Photographs may also be taken to document AEs at the Investigator's discretion.
CCI [redacted]

1.5.1.2 Independent Photographic Reviewer (IPR) Assessment of Improvement

At the end of the study, the IPR will review photographs of each temple for each subject at:

- CCI [redacted]
- [redacted]

Baseline and post-baseline visit photographs will be paired and randomized in presentation order (i.e., Baseline image on the right and post-baseline image on the left or vice versa).

CCI [redacted]

[redacted]

CCI [redacted]

1.5.1.3 Galderma Temple Volume Deficit Scale (GTVDS)

The magnitude of temple hollowing correction will be assessed using the GTVDS, CCI [redacted]

[redacted]

CCI [redacted]

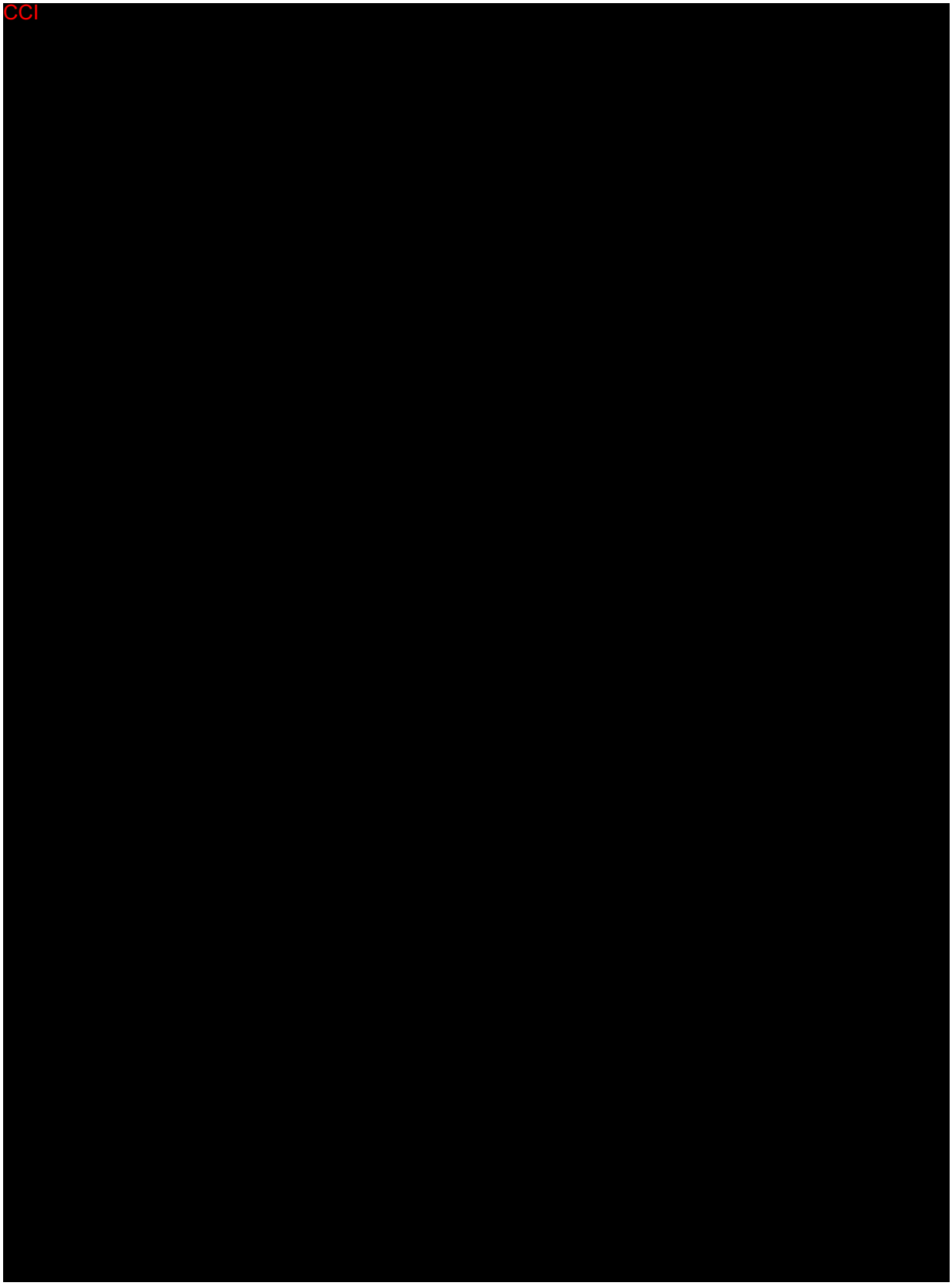
The Treating Investigator will perform GTVDS assessment:

- CCI [redacted]

The Blinded Evaluator will perform GTVDS assessment:

- CCI [redacted]

CCI [redacted]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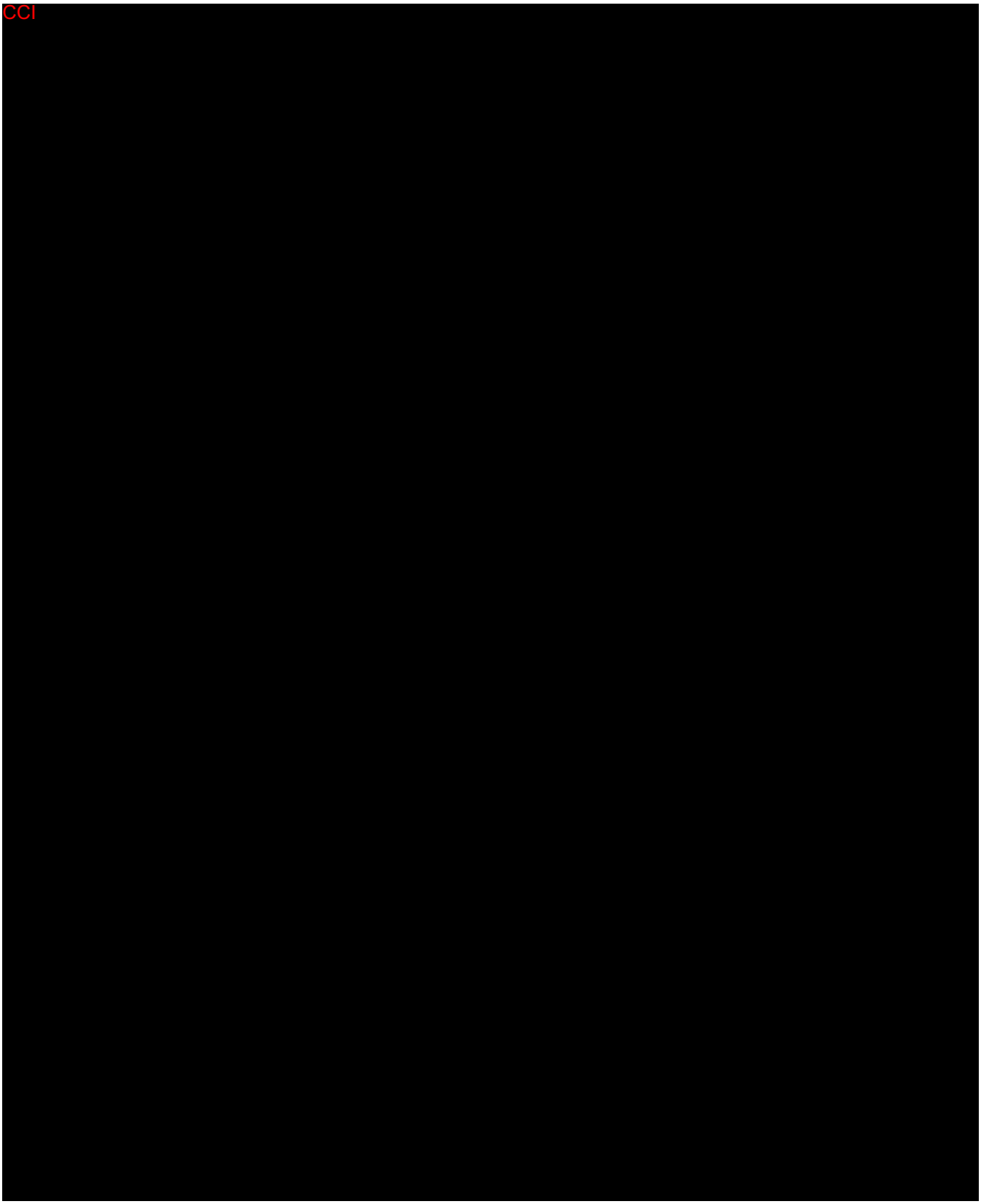

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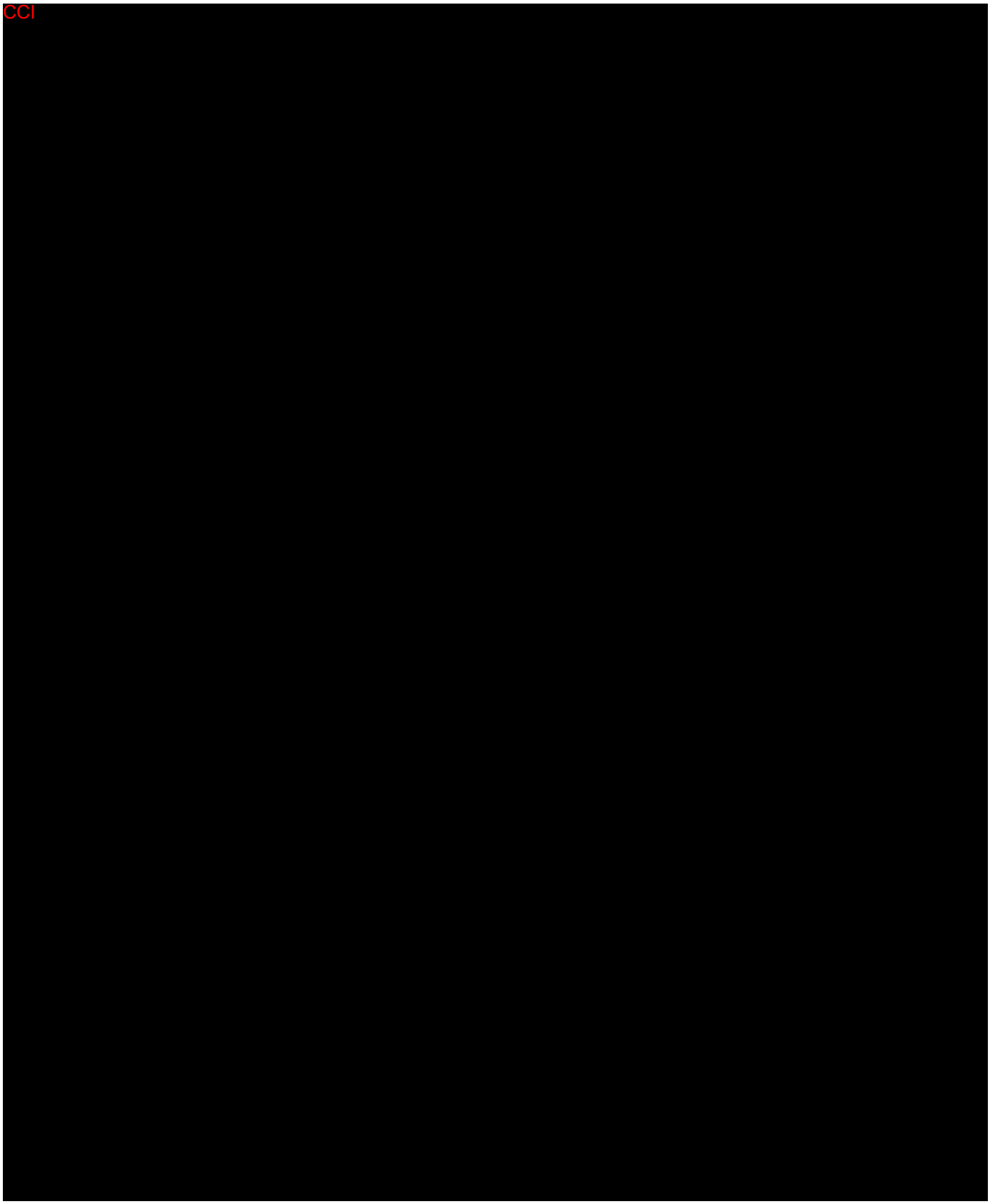

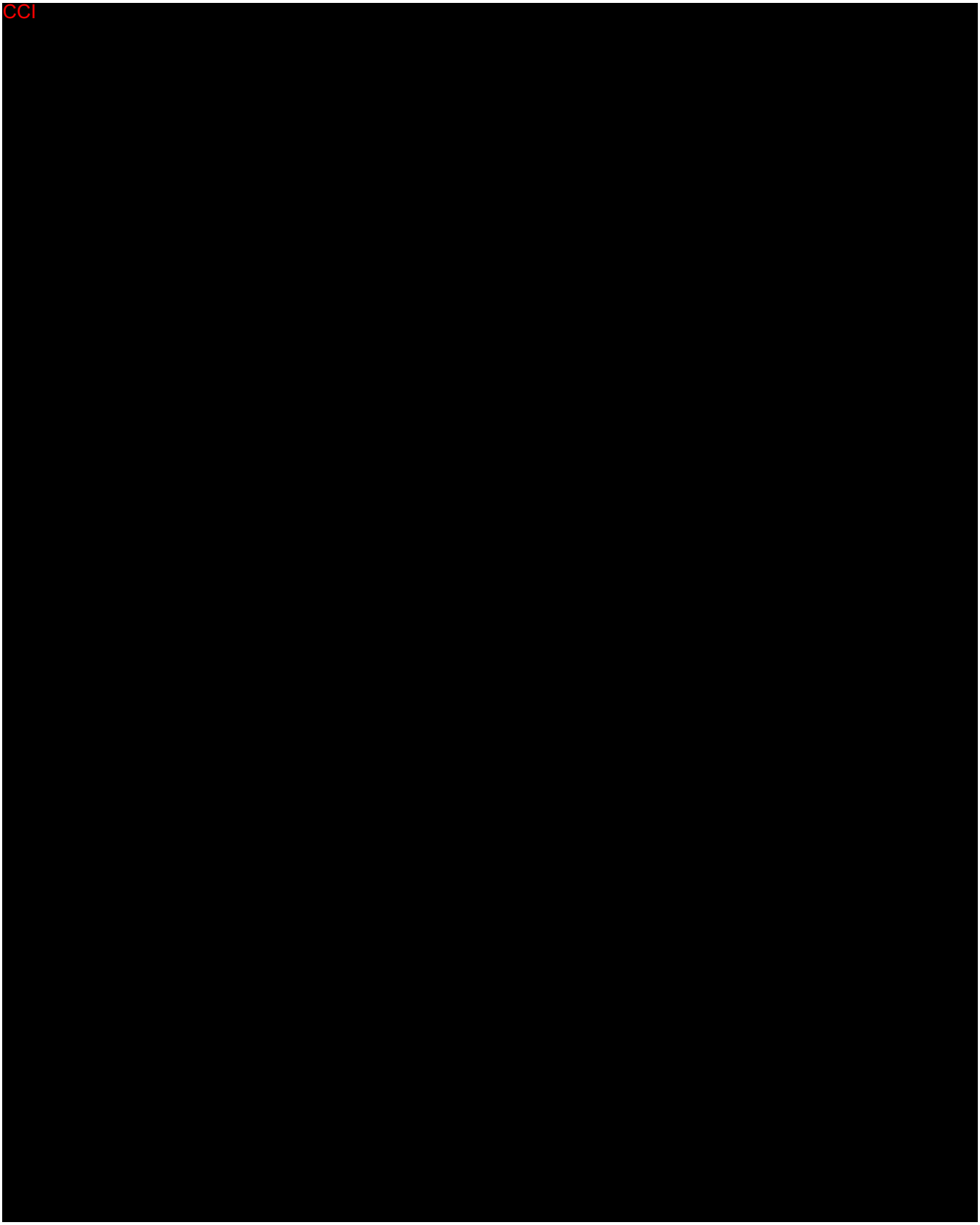
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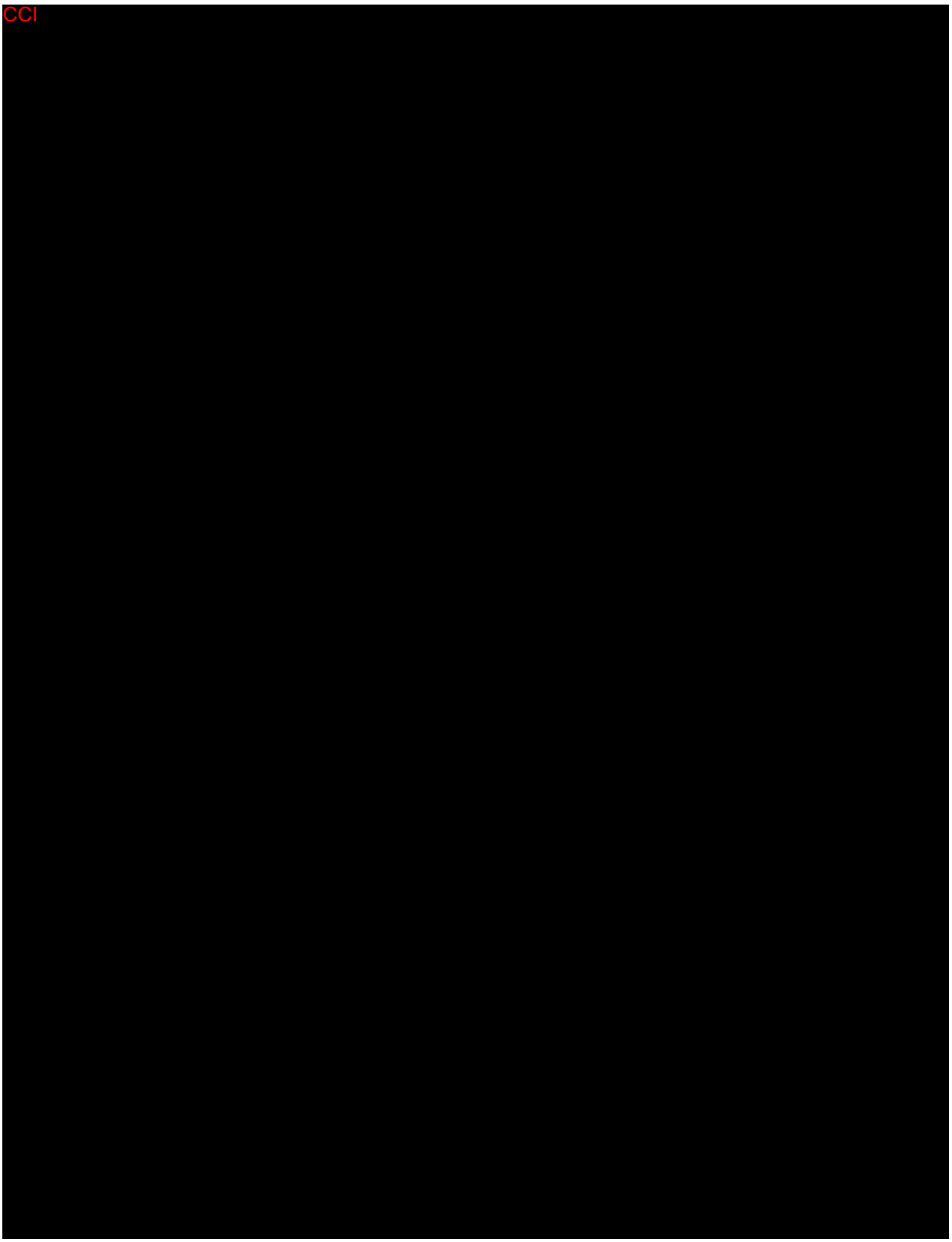
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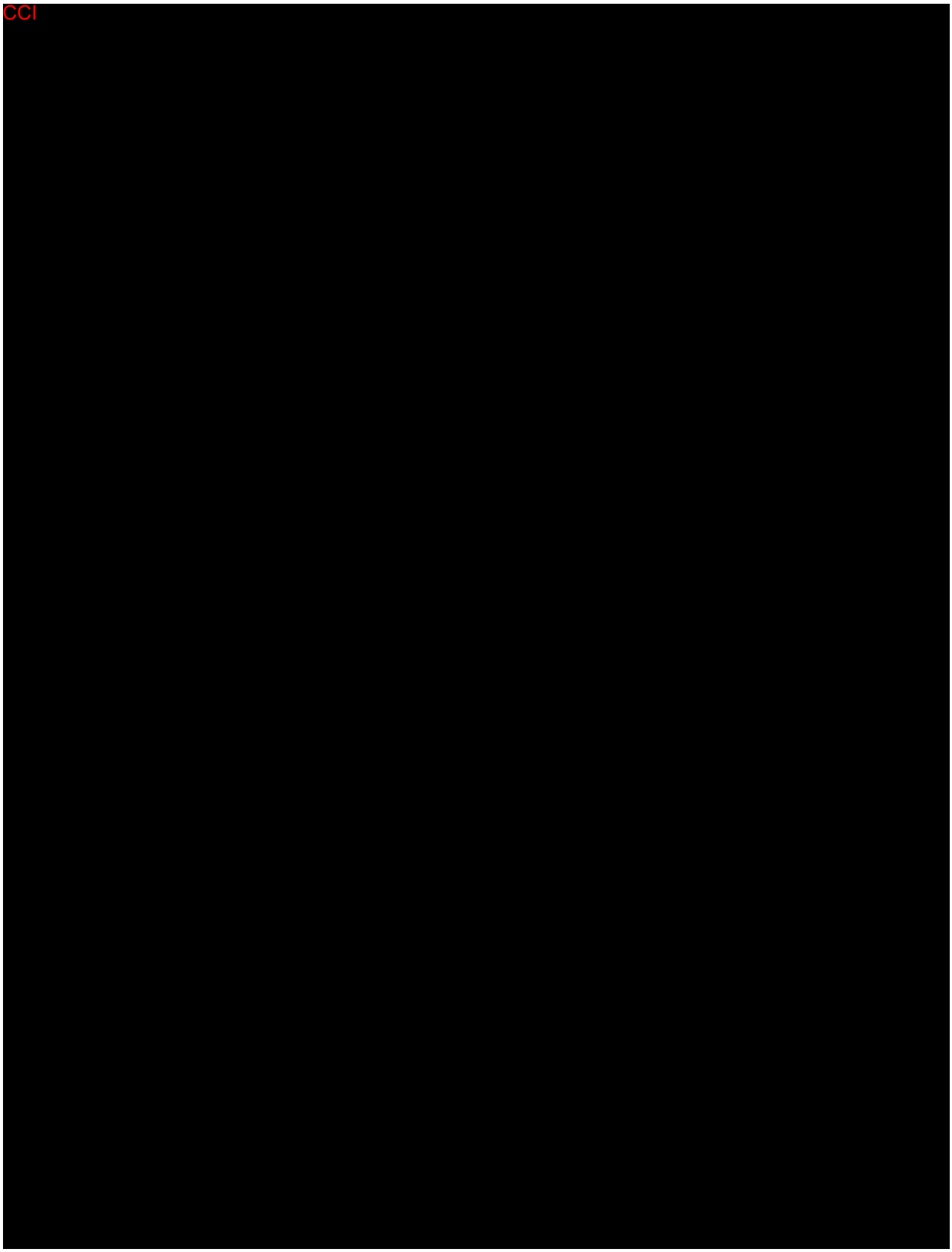

2.0 ANALYSIS POPULATIONS

2.1 Intention-to-Treat Population

The Intention-to-Treat (ITT) population includes all subjects who are randomized and will be analyzed according to the randomization scheme. The ITT population is the primary population for the analysis of effectiveness endpoints.

2.2 Per-Protocol Population

The Per-Protocol (PP) Population includes all subjects in the ITT population who complete the primary endpoint assessment at 3 months after baseline without any deviations considered to have substantial impact on the primary effectiveness. The PP population will be used to support primary analyses performed on the ITT population if the PP population contains less than 90% of the subjects in the ITT population.

2.3 Safety Population

The Safety Population includes all subjects who were treated with Restylane Contour or randomized to the no-treatment Control group and will be analyzed according to the as-treated principle. The Safety population is the primary population for the analysis of safety endpoints.

3.0 GENERAL ANALYSIS CONVENTIONS

3.1 Timing of Analyses

All analyses used for the CSR will be performed when all subjects have either completed the study or discontinued early from the study, and all data from the study are in the clinical database, and the database is locked.

3.2 General Methods

All data listings that contain an evaluation date will contain a study day. For the Restylane Contour group, study day is relative to the date of first dose, designated as Day 1. For the No Treatment group, study day is relative to the day of randomization, designated as Day 1. Both pre-treatment and on-treatment study days are numbered relative to Day 1, and the day prior to the first administration of study drug (for the Restylane Contour group) or day of randomization (for the No Treatment group) will be Day -1 (there will be no Day 0).

The Screening Visit (Day -21 to Day 1) will be considered the visit prior to administration of study drug (for subjects randomized to Restylane Contour) or randomization visit (for subjects randomized to No Treatment). Because the Screening visit and Baseline visit (Day 1) may be performed on the same day, the Screening visit can also be Day 1.

All output will be incorporated into Microsoft Word or Adobe Acrobat PDF files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

3.2.1 Descriptive Statistics

All data collected in the eCRFs as well as external sources will be presented in by-subject listings.

Tabulations will be produced for appropriate demographic, baseline, effectiveness, and safety variables. For categorical variables, summary tabulations of the number and percentage of subjects within each category of the variable will be presented. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum, and maximum values will be presented. Unless otherwise specified, confidence intervals (CIs) will be two-sided and constructed at a confidence level of 95%.

Assuming raw or derived variables are to 'x' decimal places, the data will be presented as follows:

- Minimum, maximum, and range to x decimal places
- Mean and median to 'x+1' decimal places
- SD to 'x+2' decimal places

- 'x+2' should be no greater than 4 decimal places

3.2.2 Hypothesis Testing

Formal statistical hypothesis testing for the primary effectiveness analysis will be conducted at the 2-sided, 0.025 level of significance for the needle and cannula treatment groups separately. The null and alternative hypothesis, for both needle and cannula treatment groups, can be written as

H_0: Probability of response is independent of treatment group
$(p_{TRT} = p_C)$

versus

H_1: Probability of response is higher in the Restylane Contour group (Treatment group) compared to the Control group or Probability of response is higher in the Control group compared to the Restylane Contour group (Treatment group)
$(p_{TRT} \neq p_C)$

where p_{TRT} and p_C are the population proportion of responders in the Treatment group and no-treatment Control group, respectively. See Section 5.1.2 for the complete description of the primary effectiveness analysis.

3.3 Computing Environment

All analyses will be performed using SAS statistical software Version 9.4 or higher, unless otherwise noted. Medical history and adverse events will be coded using the Medical Dictionary for Regulator Activities (MedDRA) Version 25.1 or higher. Concomitant therapies will be coded using the WHO Drug Dictionary Global B3/Sep 2022 or higher.

3.4 Baseline Definitions

For the Restylane Contour group, baseline is defined as the last non-missing measurement prior to the first administration of study product, including unscheduled visits prior to study treatment. For the No Treatment group, baseline is defined as the day of randomization.

3.5 Subgroup Analyses

3.5.1 Effectiveness

For consistency of the results of the primary effectiveness analysis, the primary endpoint will be evaluated across different subgroups:

- Study site
- Race (possibly pooled based on subject counts within categories)
- Ethnicity
- Sex at birth
- Age (≤ ITT Population median age vs > ITT Population median age)
- FST I-III vs IV-VI (using cohort at randomization)
- Injection volume (≤ ITT median total injection volume vs > ITT median total injection volume)

These subgroup analyses will be identical to the primary effectiveness analysis (i.e., the subgroup analyses will also be split into separate hypothesis tests for the needle and cannula treatment groups). As in the primary analysis, the ITT population will be used and multiple imputation (MI) will be used for imputation of missing data. However, adjustments for multiple comparisons will not be made for the subgroup analyses.

Additionally, a subgroup analysis will be conducted to compare the responder rates at 3 months after baseline between subjects that received the 1 month touch-up treatment against those that did not receive the 1 month touch-up treatment.

3.5.2 Safety

The consistency of AE data across different subgroups will be evaluated. The following subgroup factors will be used for the Related AEs summarized by SOC, PT and maximum intensity:

- Injection tool for superficial (subdermal) injections (needle or cannula)
- Study site
- Race (possibly pooled based on subject counts within categories)
- Ethnicity
- Sex at birth
- Age (≤ Safety Population median age vs > Safety Population median age)
- FST I-III and IV-VI (using cohort at randomization)
- Injection volume (≤ Safety Population median total injection volume vs > Safety Population median total injection volume)

3.6 Methods of Pooling Data

As this is a multi-center study, it is possible that some sites may only enroll a small number of subjects. Since this study plans to conduct site-level analyses, the number of subjects at each site may need to be considered for reliable and accurate results. If any site enrolls 5 or fewer subjects, the site will be removed from analyses. Sites enrolling 5 or fewer subjects will still be presented in descriptive statistics analyses.

If no sites enroll 5 or fewer subjects, then the efficacy site-level analyses will be presented for all sites.

3.7 Adjustments for Multiple Comparisons

The Bonferroni correction will be applied to the primary effectiveness analysis. The overall significance level for the primary effectiveness analysis is set to 0.05, with each individual test (for the needle and cannula treatment groups) having a significance level of 0.025.

There will be no adjustments for multiplicity for the secondary effectiveness analyses or subgroup analyses; p-values obtained for any endpoint other than the primary will only be provided for ease of interpretation of results.

3.8 Missing Data Handling

The number of missing values will be summarized and reported as appropriate.

3.8.1 Effectiveness Data

For ITT analysis of the responder rate based on the Blinded Evaluators' live assessment of the GTVDS, at 3 months after baseline, the analysis will be performed using multiple imputation (MI) as the primary imputation method.

Missing values for Month 3 Blinded Evaluators' assessment of the GTVDS will be imputed. The imputed values will then be used to derive the responder status of subjects at Month 3 after baseline. The MI procedure will be conducted under the assumption of missing at random (MAR) and will be performed as follows:

1. Regardless of the actual pattern of missing data, the Markov Chain Monte Carlo (MCMC) method of the SAS PROC MI procedure will first be used to make it monotone. The single chain method will be used. The minimum values for imputed variables will be set to 0, to force PROC MI to redraw another value for imputation when an intended imputed value is less than the 0, the maximum value for imputed variables will be set to 3, to force PROC MI to redraw another value for imputation when an intended imputed value is greater than the 3. Imputed values will be rounded to the nearest integer. The seed number will be set to 2201.
    a. Repeat Step 1 but using the right temple. The seed number will be set to 18.
2. The SAS PROC MI procedure will be used for imputing missing values of data with monotone missing pattern. A linear regression will be employed to model the missing GTVDS values with the following covariates included in the imputation model: treatment group and Baseline GTVDS for the left temple. The minimum value for the imputed variables will be set to 0 and the maximum will be set to 3. Imputed values will be rounded to the nearest integer. The seed

number will be set to 31 and five (5) imputations will be created for the left temple.

   a. Repeat Step 2 for the right temple. The seed number will be set to 108.

3. The Month 3 GTVDS responder variable will then be calculated using the imputed GTVDS values from Steps 1 and 2.

4. The imputed datasets will be analyzed using a Chi-Square test as specified in Section 5.1.2.

5. The resulting Chi-Square statistics will be transformed to approximate normality using the Wilson-Hilferty transformation and combined using PROC MIANALYZE to produce a pooled Chi-Square statistic and p-value (Ratitch et al [1]). The proportion of responders for each treatment group, the difference in proportions between treatment groups, and standard errors will also be combined using SAS PROC MIANALYZE.

6. The resulting pooled proportion of responders, difference in proportions, and standard errors will be used to produce 97.5% confidence intervals based on the large-sample approximation method for binary data without using continuity correction.

Additionally, in order to further assess the impact of missing data on the primary endpoint, the primary analysis will be repeated using the following methods of missing data handling: observed cases, baseline observation carry forward (BOCF), and a tipping point method, each of which are described below:

1. Observed Cases: Repeat the primary analysis without imputation of missing Month 3 GTVDS values.
2. BOCF: Repeat the primary analysis but impute missing Month 3 GTVDS values by carrying forward the baseline observation.
3. Tipping Point method: Tipping point analysis will be used to check how severe departures from the MAR missing data assumption need to be in order to "tip" the primary endpoint results in the opposite direction (i.e. significant to non-significant). The following steps will be employed:
   a. Determine the number of missing Month 3 GTVDS observations in the Restylane Contour group (n_{1m}) and no-treatment Control group (n_{2m})
   b. Let s_1 represent the number of GTVDS Responders in the missing Restylane Contour group. Let s_2 represent the number of GTVDS Responders in the missing no-treatment Control group
   c. Set both $s_1 = 0$ and $s_2 = 0$
   d. From 0 to n_{1m}, calculate the difference in proportion of responders between treatment groups and corresponding p-value, where each iteration is $s_1 = s_1 + 1$, using a Chi-Square test

e. From 0 to n_{2m}, calculate the difference in proportion of responders between treatment groups and corresponding p-value, where each iteration is $s_2 = s_2 + 1$, using a Chi-Square test
f. Present the p-values from each analysis combination of s_1 and s_2 in steps (d) and (e) in a heatmap
g. Determine the "tipping point" of the results where the difference in proportions is significant at the 0.025 level

All other effectiveness endpoints will be evaluated based on the observed cases in ITT; no imputation will be done.

3.8.2 Safety Data

Descriptive statistics of all safety data will be performed on observed cases in the Safety Population. Missing or partial dates for adverse event and prior/concomitant therapy data will be imputed according to the table below for summary tabulations; dates as collected will be presented in the listings.

Table 4: Imputation Criteria for Missing/Partial Dates

Variable	Missing Day	Missing Month or Day and Month	Missing Year, Month and Year, or Day and Year	Missing Day, Month, Year
Adverse Event/Medication Start Date	Assign to the first of the month (i.e., UNK-JAN-2019 becomes 01-JAN-2019)	Assign to the month of 'June' (i.e., 01-UNK-2019 becomes 01-JUN-2019), provided the imputed date is on or after the patient's Baseline study treatment date; otherwise, the subsequent month after study treatment will be used.	Assign to year of study treatment will be used (i.e., 01-JAN-UNK becomes 01-JAN-2019), provided the imputed date is on or after the patient's study treatment date; otherwise, the subsequent year after treatment will be used.	Assign to Baseline study treatment date
Adverse Event/Medication End Date	Assign the last day of the month (i.e., UNK-JAN-2019 becomes 31-JAN-2019).	Assign to the subsequent month after the start date.	Assign to the year of Baseline study treatment (i.e., 01-JAN-UNK becomes 01-JAN-2019), provided the imputed date is after the start date; otherwise, the subsequent year after start date will be used.	Assumed medication is ongoing; no imputation

3.9 Visit Windows

It is expected that all visits should occur according to the protocol schedule. All data will be tabulated per the evaluation visit as recorded on the CRF even if the assessment is outside of the visit window. In data listings, the relative day of all dates will be presented. There will not be any windowing for unscheduled visits in the analysis, and unscheduled visits will not be included in any analyses, unless used for Baseline determination. Unscheduled visits, if any, will be presented in listings only.

3.10 Data Presentation

3.10.1 Effectiveness

For the primary and secondary effectiveness endpoints, the data presentation will have the following header:

Restylane Contour (N=xx)	No Treatment (N=xx)

An overall column is not planned for any effectiveness output, however it may be added, if warranted.

3.10.2 Safety

The primary data presentation for all safety analyses will have the following table header:

Restylane Contour (N=xx)	No Treatment (N=xx)	Overall (N=xx)

3.11 Interim Analysis

There is no interim analysis planned for this study.

4.0 DISPOSITION, PROTOCOL DEVIATIONS, DEMOGRAPHICS AND BASELINE ANALYSES

All analyses in this section will be performed using the ITT Population and presented using the data presentation described in Section 3.11, unless otherwise indicated.

4.1 Subject Disposition

Subject disposition will be summarized in a table. The number of screened, randomized, treated, completed, and withdrawn subjects will be presented with percentages, as well as the number and percentages of subjects in each analysis population set (ITT, PP and Safety Populations). Percentages will be based on the ITT Population. The numbers and percentages of subjects associated with withdrawal reasons will be presented, with percentages based on the number of withdrawn subjects per treatment. A subject disposition table by study site will also be presented, with the same variables reported.

Subject accountability by visit will be summarized by the following:

- Number of subjects expected at each visit
- Number of subjects performed each visit
- Number of subjects missed at each visit
- Number of subjects withdrawn at each visit

Subjects who were excluded from the study will be presented in a data listing, along with reasons for exclusion. All subjects' completion and discontinuation information will be presented in a data listing that will report the last visit performed with date, the date of completion or discontinuation and the reason for discontinuation.

A study visit listing will include the reason for missing the study visit and how the remote visit was conducted when it applies. The study visits listing will also include any changes in concomitant therapies or adverse events and if the subject has been interviewed regarding diary completion and reported post-treatment events.

An informed consent and randomization data listing will include the date and version of the initial consent and re-consent if it applies, the date and time of randomization and the assigned treatment.

4.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be tabulated and will be summarized for the ITT population using descriptive statistics.

Demographic variables include the following:

- Age (years)
- Age Category (≤ ITT median age or > ITT median age)
- Sex at Birth
- Gender Identity
- Ethnicity

- Race
- Fitzpatrick Skin Type (cohort at randomization)

Baseline characteristic variables include the following:

- Baseline GTVDS for left and right temples, as evaluated by the Blinded Evaluator

Demographic and baseline characteristics, as well as the childbearing potential and breastfeeding status for female subjects, will be provided in data listings.

In the event that Fitzpatrick Skin Type (FST) scores are updated post-randomization, FST cohorts at randomization will be used in all outputs. FST scores as recorded in the demographics CRF will also be included in the demographics listing.

4.3 Medical History

Subjects' medical history will be collected at Screening and Baseline visits. An event that occurs after the subject signs the Informed Consent Form (ICF) but before enrollment will be recorded in the subject's medical history.

Medical history summaries will be reported using the ITT Population. The number and percentage of subjects reporting medical history and the number of events will be summarized by MedDRA System Organ Class (SOC) and Preferred Term (PT). System Organ Classes and PTs will be sorted in descending frequency first, based on the Restylane Contour group, and then alphabetically if there are ties. Each subject will only be counted once within each SOC and SOC/PT combination. The MedDRA version used will be noted as a footnote in the tables and listings.

Medical history information will also be reported in a data listing presenting the SOC, the PT, the description, and the onset and stop date (or if ongoing).

4.4 Prior Dermatologic Procedures and Implant History

Subjects' prior dermatologic procedures and implant history will be collected at Screening and at Baseline visits and summarized using the ITT Population in the same way as for subject's medical history.

Prior dermatologic procedures and implant history will be reported in a data listing presenting the SOC, the PT, the procedure or product name, the location and the date.

4.5 Concomitant Procedures/Treatments

Subjects' concomitant procedures/treatments will be collected at all study visits.

Concomitant procedures/treatments will be summarized using the ITT Population in the same way as subjects' medical history. The subset of concomitant procedures administered for treatment-related adverse events will be summarized in the same way in an additional table.

Concomitant procedures/treatments will be reported in a data listing and will include the SOC, the PT, the procedure name, the start and stop date, the reason for procedure, and the related medical history and/or adverse event when it applies.

4.6 Prior and Concomitant Therapies

Prior therapies are defined as therapies that have been used within 30 days preceding the baseline visit or within the timelines specified in the inclusion and exclusion criteria, and then stopped prior to the baseline visit.

Concomitant therapies are defined as follows:

- Any existing therapies ongoing at the time of the baseline visit
- Any changes to existing therapies (such as changes in dose or formulation) during the course of the study
- Any new therapies received by the subject since the baseline visit

Prior and concomitant therapy summaries will be reported using the ITT Population in two different tables. The number and percentage of subjects reporting prior/concomitant therapies and the number of events will be summarized by the WHO Drug Dictionary Anatomical Therapeutic Chemical 3rd level (ATC-3) and the Preferred Term (PT). If the 3rd level term is not available, the next available level (e.g., ATC-2) will be used. Anatomical Therapeutic Chemical 3rd level and PTs will be sorted in descending frequency first, using the Restylane Contour group, and then alphabetically if there are ties. Each subject will only be counted once within each ATC and ATC/PT combination. The subset of concomitant therapies administered for treatment-related adverse events will be summarized in the same way in an additional table.

Prior and concomitant therapies will be reported in a data listing that will present the name of the therapy, the ATC and PT, the total daily dose, the route, the start and end date, the reason for administration, and the related medical history and/or adverse event when it applies.

4.7 Protocol Deviations

A protocol deviation occurs when a subject deviates from the protocol procedures. Depending on the seriousness of the deviation, the subject might be excluded from the PP analysis. Since PP will be used for the primary analysis at Month 3 only, the focus will be on deviations occurring before and on the Month 3 visit day, as they might

compromise the primary endpoint. For this study, the protocol deviations that will exclude subjects from PP are identified (but not limited to) in Table 5 below.

Table 5: Protocol Deviations

Deviation
Any subject that conducts their Month 3 visit significantly out of window.
Any subject not treated according to the assigned treatment.
Any subject that does not have a Blinded Evaluator GTVDS onsite live assessment at the primary endpoint visit (Month 3).
Any subject that does not have an available screening or Baseline Blinded Evaluator GTVDS onsite live assessment.
Any subject that has grade 1 on either the Blinded Evaluator or Treating Investigator GTVDS onsite live assessment at Baseline.
Any subject with prohibited concomitant treatments/procedures prior to Month 3 visit considered to have a substantial impact on the primary effectiveness outcome.
Any subject with a prohibited medical history, unstable medical history condition, or medical history condition that worsens prior to Month 3 visit considered to have a substantial impact on the primary effectiveness outcome.

Protocol deviations will be presented descriptively. The number and percentage of subjects who have protocol deviations, the total number of deviations and the type of protocol deviation will be summarized using the ITT population. The above summary of protocol deviations will be repeated by site as well. Protocol deviation listings will be reviewed, and each patient will be classified as belonging to the per-protocol set or not. Exclusions from the per-protocol set will be identified and documented prior to database lock.

Protocol deviations will be presented in a data listing that will display the visit where the deviation was reported, the date where the deviation occurred, the deviation type and description, the action taken, if it was reported to the IRB and if the deviation was due to COVID-19. Patients who are excluded from the PP population will also be presented in a data listing, along with their reason(s) for exclusion.

4.7.1 Out of Window Visit Duration

When a subject performs a planned study visit outside of the protocol-specified visit windows (Appendix 1 and Appendix 2), the subject has an out of window study visit, which is considered a type of protocol deviation for this study. Knowing a subject's

Screening visit (Visit 1) and Baseline visit (Visit 2) and using the protocol-specified visit windowing, one can calculate a subject's target study visit window date range for each planned study visit. Then, by comparing a subject's actual study visit date to the target study visit window date range, one can calculate the days over/under the actual study visit is in relation to the target study visit date, corresponding to the study visit out of window duration.

The duration, in days, a study visit is out of window will be summarized by treatment group, overall, and by visit. Out of window visit durations will also be presented by site. Duration will be split into the following below categories. Duration categories will include both days before and days after the target planned visit date.

- +/- 1-2 days;
- +/- 3-7 days;
- +/- 8-20 days;
- +/- 21 or more days.

The number and percentage of subjects within each out of window duration category will be presented descriptively. For the overall analysis, percentages will be calculated using the number of subjects with an out of window visit at the respective visit as the denominator; for the by site analysis, percentages will be calculated using the number of subjects at the respective site as the denominator.

5.0 EFFECTIVENESS ANALYSIS

5.1 Primary Effectiveness

All analyses in this section will be conducted primarily using the ITT population, and presented as described in Section 3.11, unless otherwise indicated. The primary analysis will be reproduced using the PP Population if the PP population contains less than 90% of the subjects in the ITT population.

All source data for all effectiveness endpoints will be provided in by-subject data listings. All effectiveness measurements over time will also be tabulated using descriptive statistics.

5.1.1 Primary Effectiveness Estimand

The primary estimand is the difference in the proportion of responders for the Blinded Evaluator's assessment of the GTVDS at 3 months after baseline between the Restylane Contour group (Treatment group) and no-treatment group (Control group), in all randomized subjects (ITT population).

Primary Endpoint	**Estimand**

<table>
<tr><td rowspan="4">Responder rate based on the Blinded Evaluators' live assessment of the GTVDS, at 3 months after baseline</td><td colspan="2">Treatment: Initial and optional touch-up treatment of Restylane Contour (Treatment group) or no treatment (Control group)</td></tr>
<tr><td colspan="2">Population: All randomized subjects (ITT Population)</td></tr>
<tr><td colspan="2">Endpoint: Responder rate based on the Blinded Evaluators' live assessment of the GTVDS, at 3 months after baseline</td></tr>
<tr><td>Intercurrent Events:
1. Missing Month 3 GTVDs observation
2. Use of prohibited treatment in or near the treatment area prior to Month 3
3. Administered treatment not according to randomization</td><td>Handling of Intercurrent Events:
1. Imputation using Multiple Imputation (MI)
2. Use observed response
3. Use observed response</td></tr>
<tr><td colspan="2">Summary measure: The difference in the proportion of responders at 3 months after baseline between the Restylane Contour group (Treatment group) and no-treatment group (Control group)</td></tr>
</table>

Note: Intercurrent events are defined as events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question.

5.1.2 Primary Analysis Methods

The primary endpoint is the responder rate based on the Blinded Evaluators' live assessment of the GTVDS, at 3 months after baseline.

A responder will be defined as a subject with at least 1 grade improvement from baseline to Month 3 (in both temples concurrently) based on the GTVDS scale.

The proportion of responders will be compared between Restylane Contour group (Treatment group) and the Control group using a Chi-Square test to assess the null hypothesis of independence between the treatment groups and the outcome in terms of response.

The null and alternative hypotheses for needle:

- H_0: Probability of response is independent of treatment group $(p_{TRT} = p_C)$
- H_1: Probability of response is higher in the Restylane Contour needle group (Treatment group) compared to the Control group or Probability of response is higher in the Control group compared to the Restylane Contour needle group (Treatment group) $(p_{TRT} \neq p_C)$

where p_{TRT} and p_C are the population proportion of responders in the Treatment (needle) group and no-treatment Control group, respectively. The test will be two-sided and performed at the 0.025 significance level.

The null and alternative hypotheses for cannula:

- H_0: Probability of response is independent of treatment group $(p_{TRT} = p_C)$
- H_1: Probability of response is higher in the Restylane Contour cannula group (Treatment group) compared to the Control group or Probability of response is higher in the Control group compared to the Restylane Contour cannula group (Treatment group) $(p_{TRT} \neq p_C)$

Where p_{TRT} and p_C are the population proportion of responders in the Treatment (cannula) group and no-treatment Control group, respectively. The test will be two-sided and performed at the 0.025 significance level.

The study success criterion is defined so that:

1. At least one of these tests has to result in a p-value <0.025, i.e., applying the Bonferroni correction, the overall study significance level is set to 0.05.
2. The corresponding two-sided 97.5% CI around the responder rate at Month 3 (for needle and/or cannula) needs to be completely above 50%.

The 97.5% CI for the responder rate, as well as the difference in responder rates, will be calculated using the normal approximation (Wald) method.

Multiple Imputation (MI) will be used for imputation of missing data in the primary effectiveness analysis; details of the MI methodology are outlined in Section 3.8.1.

5.1.3 Sensitivity Analysis

The following sensitivity analyses are planned to assess the robustness of the primary analysis:

- The primary analysis will be repeated using the PP population if the PP population contains less than 90% of the ITT population
- The primary analysis will be repeated on the Safety population (i.e., subjects will be analyzed as treated) to assess the impact of potential errors in randomization
- The primary analysis will be repeated using the following methods of missing data handling (see Section 3.8 for detailed descriptions of these analyses):

    1. Using the baseline observation carry forward (BOCF) method
    2. Using observed cases (OC)
    3. Using a tipping point method

5.1.4 Poolability Analysis

A poolability analysis will be performed to assess the consistency of the primary results across sites. Homogeneous association of responder rate and treatment group across sites will be tested using a Breslow-Day Test of the Odds Ratios (ORs) estimated from a Cochran-Mantel-Haenszel (CMH) test stratified by site. The Breslow-Day Test will be conducted separately for both the needle and cannula treatment groups.

The null and alternative hypotheses, for both needle and cannula groups, can be written as:

H_0: The ORs are equal for all sites $(\theta_1 = \theta_2 = \cdots = \theta_k)$

versus

H_1: The ORs are unequal for at least one pair of sites $(\theta_l \neq \theta_{k)}$

where θ_k is the OR for site k.

If the resulting p-value is less than or equal to 0.10, it will be concluded that the combining of data across sites for the primary analysis may not be justified, and the primary analysis (the Chi-Square test of responder status using Multiple Imputation and the ITT Population) will be presented separately by site in addition to pooled across sites. P-values obtained from the pooled analysis will be presented, but may not be easily interpreted due to the lack of evidence of poolability. P-values obtained for the by-site analysis will be presented but will be not be used as confirmatory evidence of treatment effect for individual sites. Additional analysis may be performed to understand the nature of the differences between sites that may contribute to the non-homogeneous treatment effects across sites.

5.2 Secondary Effectiveness Analysis

All analyses in this section will be presented as described in Section 3.11, unless otherwise indicated. All analyses will be performed using the ITT population and using observed cases, unless otherwise noted.

No correction for multiplicity will be done; p-values obtained for any endpoint other than the primary will only be provided for ease of interpretation of the results. All other secondary effectiveness analyses will be done descriptively as appropriate.

5.2.1 Secondary Analysis Methods

5.2.1.1 GTVDS Responder Rate Assessed by Blinded Evaluator at 3 Months Compared to Reference Standard (Treatment Group only)

The GTVDS responder rate as assessed by the Blinded Evaluator at 3 months after baseline for the Treatment group will be tested for non-inferiority to the minimum reference standard responder rate of 50%.

The null and alternative hypotheses to be tested are:

- H_0: Probability of response in the Restylane Contour group is less than 50% ($p_0 > p_1$, where p_0=0.5)
- H_1: Probability of response in the Restylane Contour group is greater than or equal to 50% ($p_0 \leq p_1$)

The exact p-value will be calculated using the binomial distribution and the test will be conducted at the 2.5% level of significance. The corresponding 97.5% confidence interval for the responder rate will be calculated using the normal approximation (Wald) method.

5.2.1.2 GTVDS Responder Rates Assessed by Blinded Evaluator at 6, 9, and 12 Months (Treatment Group only)

The GTVDS responder rates as assessed by the Blinded Evaluator at 6, 9, and 12 months after baseline for the Treatment group will be presented with their 97.5% CIs using the normal approximation (Wald) method. The responder rates over time will be displayed graphically.

The number and percentage of subjects in each response category of the GTVDS will also be summarized by visit and by right/left temple.

The Blinded Evaluator's GTVDS assessments, including the actual GTVDS ratings, and the responder status (yes/no), will be presented in a data listing.

5.2.1.3 GTVDS Responder Rates Assessed by Blinded Evaluator at 18 Months (Treatment Group only)

The GTVDS responder rates as assessed by the Blinded Evaluator at 18 months after baseline for the Treatment group will be presented with the corresponding 97.5% CI using the normal approximation (Wald) method. The responder rates over time will be displayed graphically.

The number and percentage of subjects in each response category of the GTVDS will also be summarized by visit and by right/left temple.

The Blinded Evaluator's GTVDS assessments, including the actual GTVDS ratings, and the responder status (yes/no), will be presented in a data listing.

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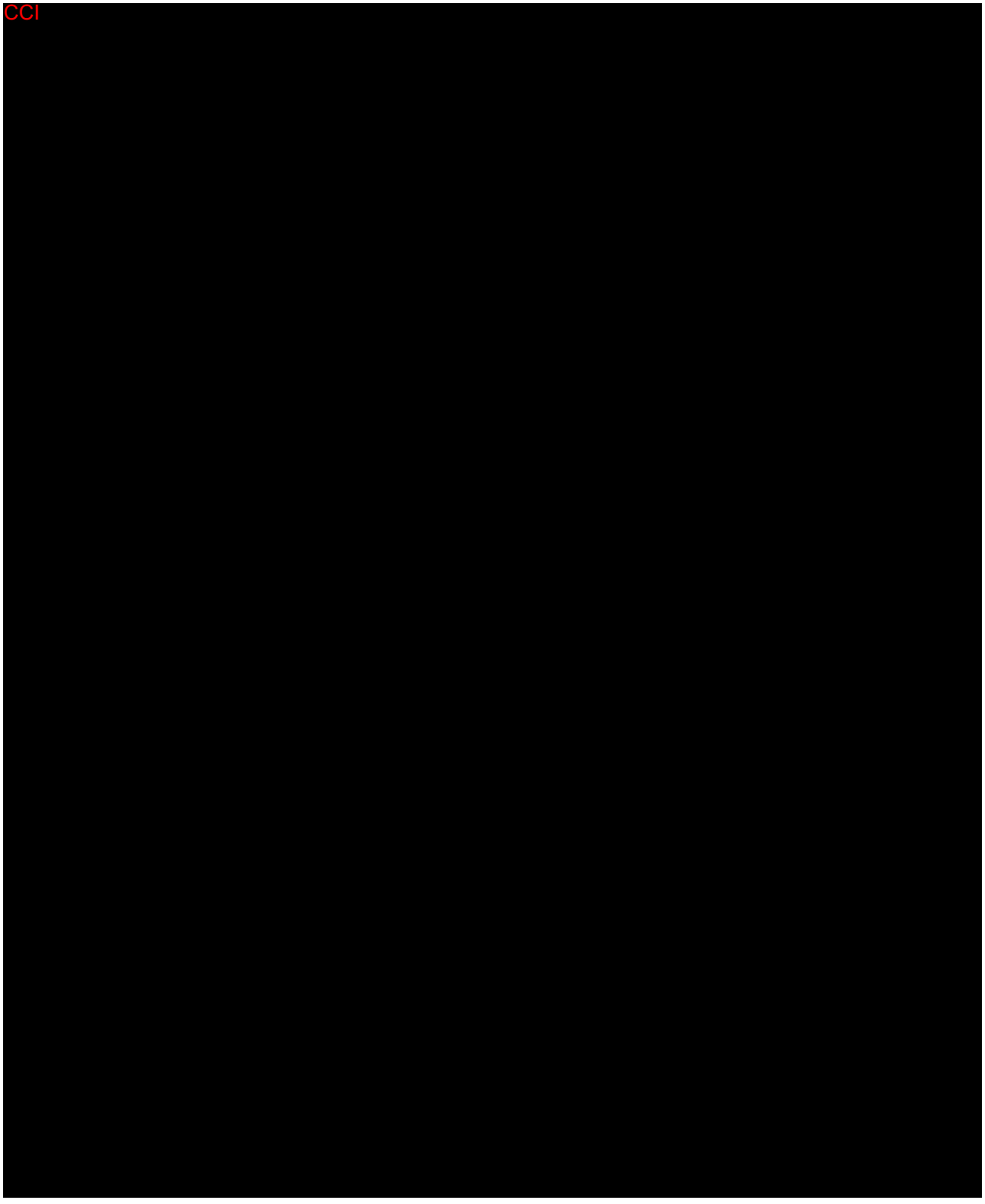

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6.0 SAFETY ANALYSIS

All analyses in this section will be performed using the Safety Population and presented as described in Section 3.11, unless otherwise indicated. Safety analysis will be descriptive only.

6.1 Study Drug Exposure

Data on extent of exposure and treatment procedure will be summarized separately for the initial treatment and for the optional touch-up.

6.1.1 Injection Characteristics

Injection characteristics include injection administration, procedural anesthetics, and post-injection concomitant procedures used. The following variables will be summarized for the left and right temples combined, separately for the initial treatment and for the optional touch-up:

- Total number of subjects treated
- Total number of syringes used

- Injection tool(s) used for superficial (subdermal) injections (needle or cannula)
- Injection method(s) used for deep supraperiosteal injection (bolus, linear threading, serial puncture, fanning, tunneling, other)
- Injection method(s) used for superficial (subdermal) injection (bolus, linear threading, serial puncture, fanning, tunneling, other)
- Depth(s) of injection for deep supraperiosteal injection (supraperiosteal, other)
- Depth(s) of injection for superficial (subdermal) injection (superficial, other)
- Use of procedural anesthetics (yes/no)
- Type of anesthetics (Topical or local injection)
- Post-injection procedures (none, massage, ice pack, other)

Injection characteristics will be presented by subject in a data listing for each visit with treatment. Procedural anesthetics will also be reported, specifying the anesthetic name, concentration, volume and type.

6.1.2 Injection Volume Administered

The injection volume (mL) administered throughout the study will be presented descriptively for the Treatment group for the following injection timepoints:

- Initial treatment – The amount of study product injected into subjects at the Baseline visit for the left and right temples separately
- Optional Touch-up – The amount of study product injected into subjects at the Month 1 visit for the left and right temples separately
- Total injected volume – The cumulative sum of study product injected into subjects for the initial and touch-up treatments, regardless of how many injections a subject got

Injection volume data will be presented by subject in a data listing for each visit with treatment.

For the optional touch-up, the eligibility and reason for not performing the injection will also be presented by subject in a data listing.

6.2 Adverse Events

Adverse Event reporting on each subject will start once a subject is enrolled (i.e., randomized and/or treated) in the study. All other events that occur after the subject signs the ICF but before enrollment will be recorded in the subject's medical history. The reporting will continue during each follow-up visit (including telephone contacts and extra visits between planned visits) until the last scheduled visit in the study. Missing

dates will be imputed as described in Section 3.8.2. Missing intensity, relationship, and seriousness will be imputed as described in the sections below.

The number and percentage of subjects with at least one AE and the number of events will be summarized by SOC and PT. System Organ Classes and PTs will be sorted in descending frequency using the Restylane Contour group and then alphabetically if there are ties. This sorting method will apply to all other AE tables described below.

All AEs reported will be listed, documenting the verbatim term, MedDRA Preferred Term (PT) and System Organ Class (SOC), affected area, event start and end date (or ongoing), seriousness (yes/no), intensity, relationship to study product (yes/no), relationship to injection procedure (yes/no), action taken, outcome, time to onset, duration and timing.

6.2.1 Summary of Adverse Events

A summary of AEs will be provided, which will include the number and percentage of subjects and number of events in the following categories:

- Any AE
- Any AE related to study product or injection procedure
- Any AE unrelated to study product or injection procedure
- Any SAE
- Any SAE related to study product or injection procedure
- Any SAE unrelated to study product or injection procedure
- Any AE leading to study discontinuation
- Any AESI
- Any Serious AESI
- Any AE ongoing at the end of the study
- Subjects who did not have any AE

6.2.2 Intensity of Adverse Events

The intensity of the AEs (mild, moderate or severe) will be recorded. If the intensity changes within one day, the maximum intensity of the AE during that day will be recorded. If the intensity assessment is missing, the intensity of 'Severe' will be assumed.

6.2.3 Relationship to Study Product or Injection Procedure

Each AE will be assessed by the Investigator for a reasonable possibility of a causal relationship with the study product and with its use (the injection procedure), both on a two-point scale (Yes or No). AEs related to either the study product or to the injection procedure will be considered related for the analysis. Missing relationships will be considered related.

Related AEs will be summarized by SOC, PT and maximum intensity. Unrelated AEs, as well as serious related AEs, will also each be summarized by SOC, PT and maximum intensity. If a subject has multiple occurrences of the same MedDRA SOC or PT, then only the most severe event will be summarized in the tables for that SOC and PT.

Finally, the number of subjects with related AEs will be summarized by SOC, PT, and action taken (none, medication treatment, non-pharmacological treatment, other procedures/tests, subject withdrawn). Subjects will be only counted in 'None' category if no other action was taken.

6.2.4 Time to Onset and Duration of AEs

Time to onset and duration of related AEs will be recorded. Time to onset of an AE will be derived as the AE start date minus the date of most recent prior treatment. If the AE start date is partially/completely missing, it will be imputed using the imputation rules specified in Section 3.8.2.

Duration of an AE will be derived as the AE stop date minus the AE start date + 1. If the AE start date is partially/completely missing, it will be imputed using the imputation rules specified in Section 3.8.2. A completely missing AE stop date will not be imputed and therefore no duration will be calculated in these cases.

The number of days to onset and the duration of each respective related AEs will be summarized by SOC and PT using the mean, standard deviation, min, max and median. These summaries are at the event level so that subjects will be counted once for each multiple related AE they experience. Related AEs with onset >21 days after the most recent treatment will be listed.

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6.2.6 Death, Serious Adverse Events, and Adverse Events Leading to Study Discontinuation

Serious AEs, AEs resulting in death on study and AEs leading to discontinuation of study will be reported in separate listings. These listings will include the same variables as the listing for all AEs, and the SAE listing will additionally include the SAE criteria.

If an AE has a missing seriousness assessment, the AE will be considered serious for analysis purposes.

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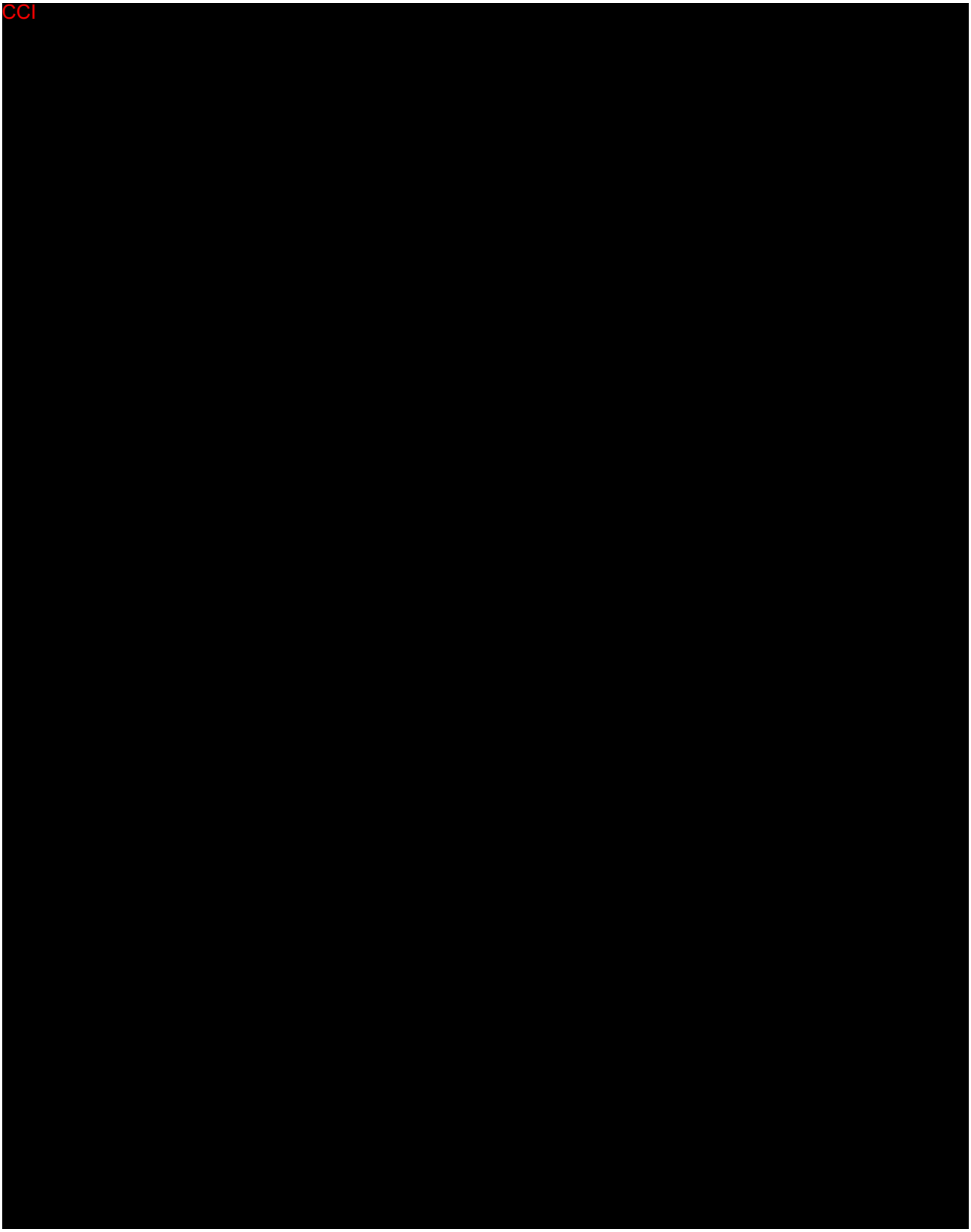
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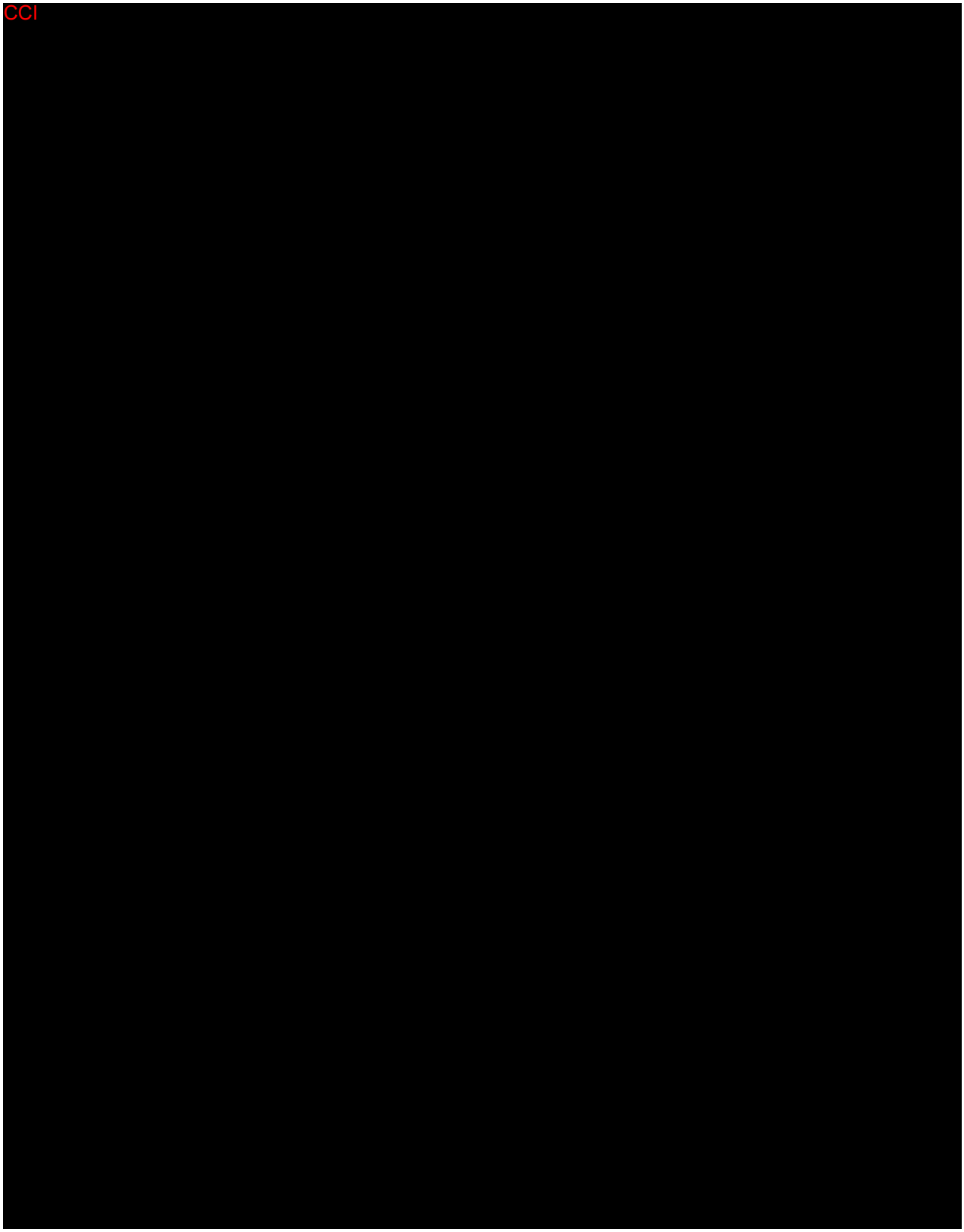
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7.0 CHANGES TO PLANNED ANALYSES

There are no changes to protocol planned analyses.

8.0 REFERENCES

1. Bohdana Ratitch, et al. "Combining Analysis Results from Multiply Imputed Categorical Data", 2013, PharmaSUG Proceedings, Paper SP-03

9.0 CHANGE HISTORY

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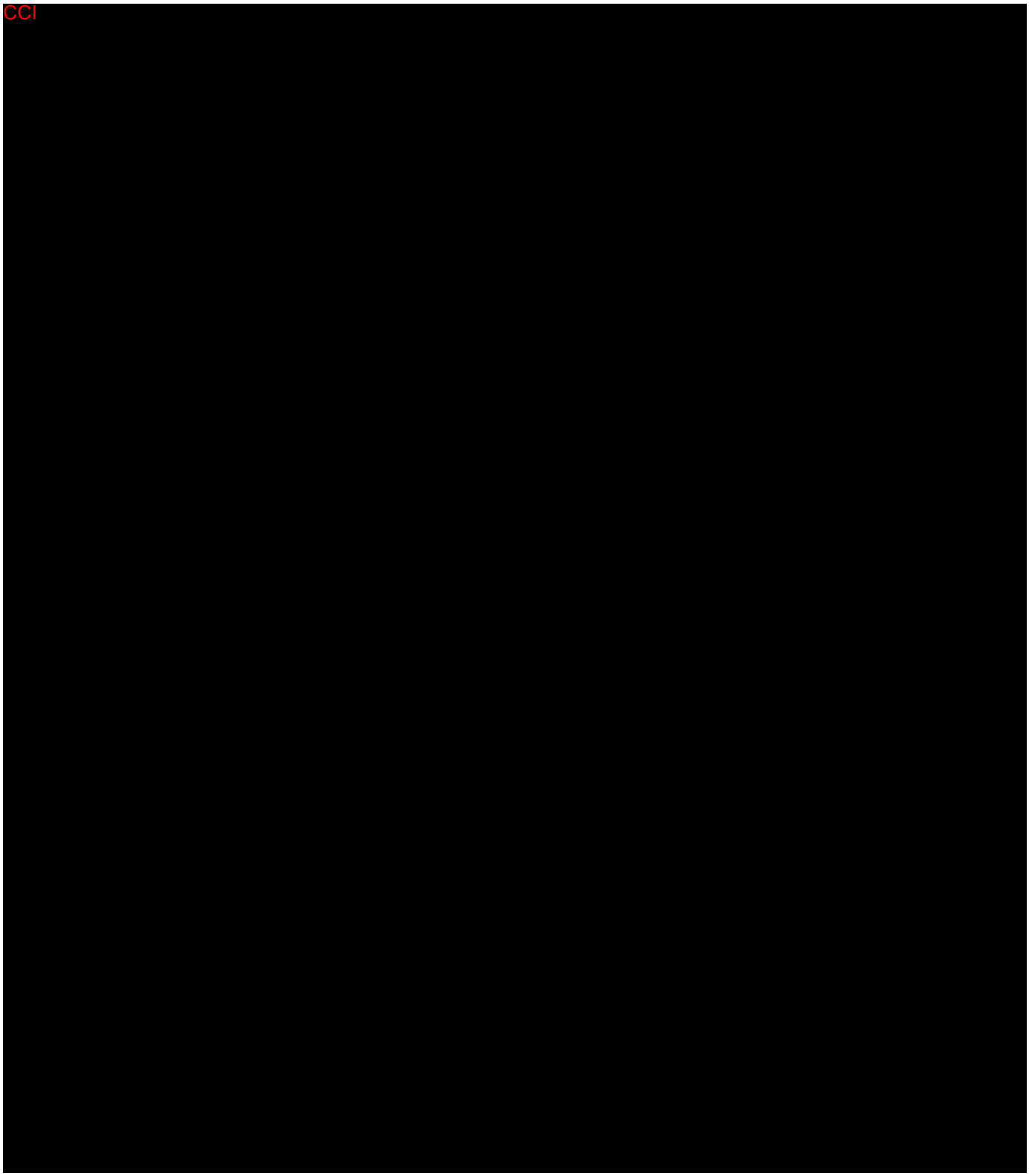

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10.0 APPENDICES

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10.2 Appendix 2: Study Schedule of Events for No-Treatment Control Group

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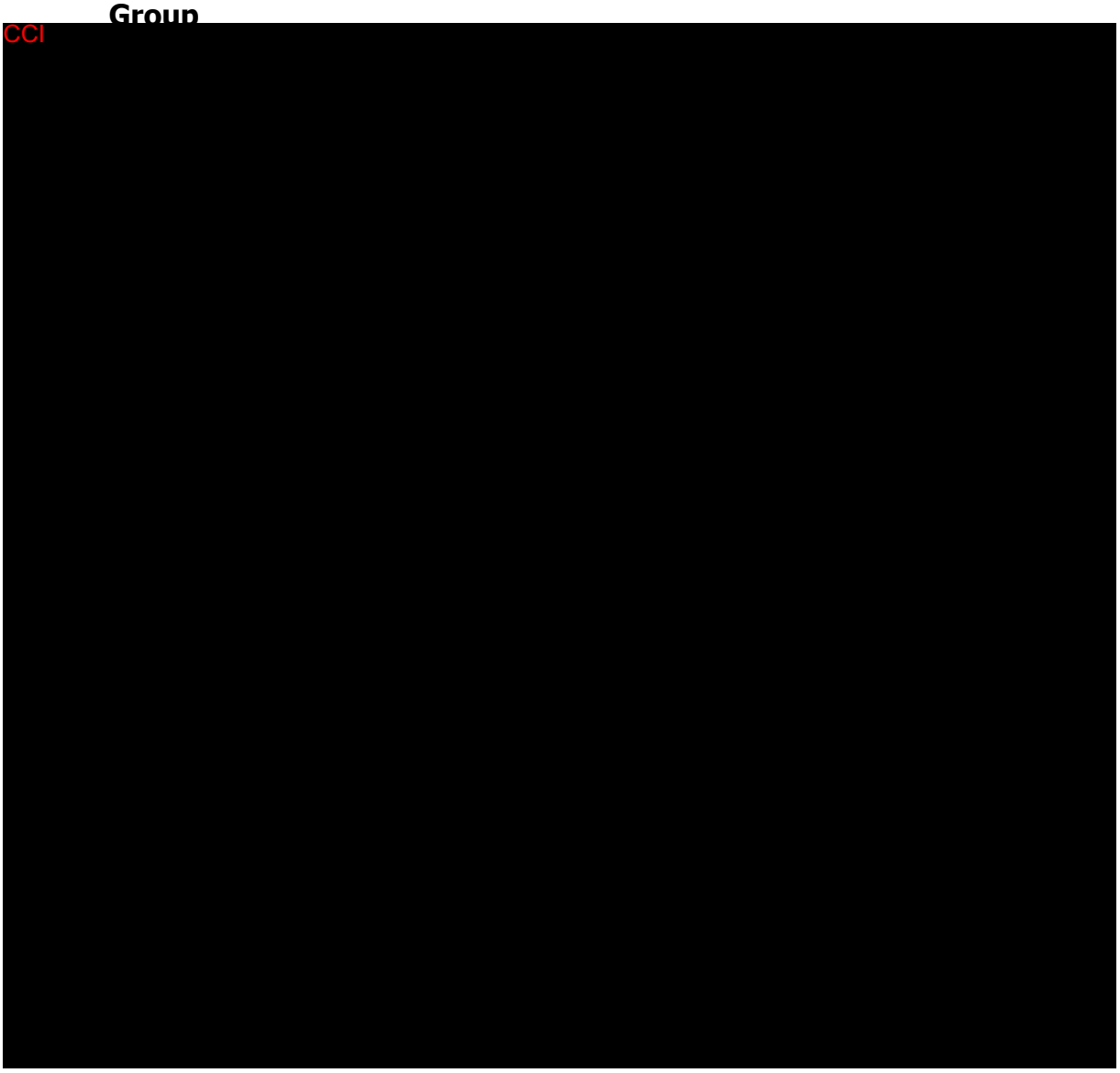
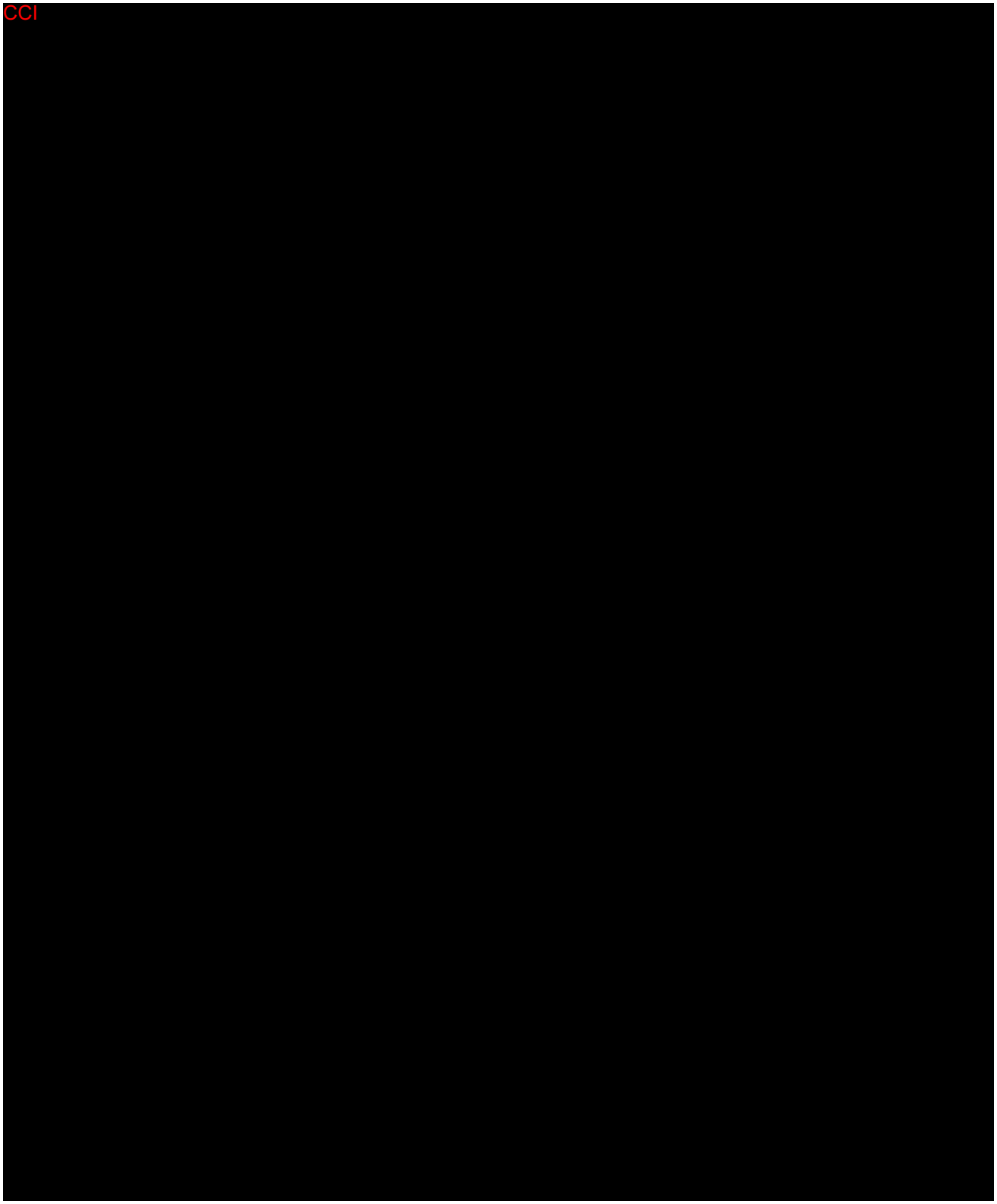
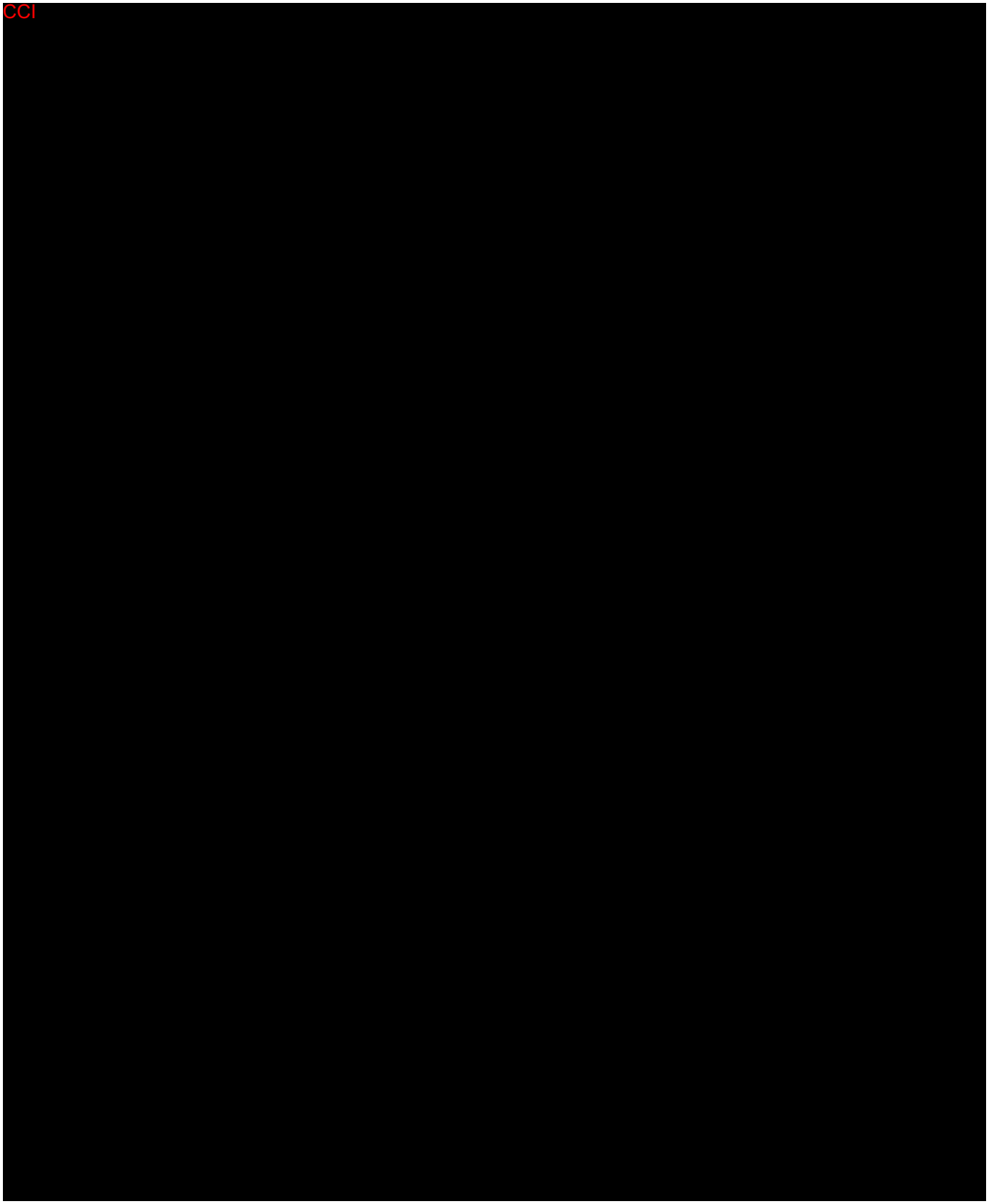


10.3 Appendix 3: Subject Satisfaction Questionnaire (SSQ)

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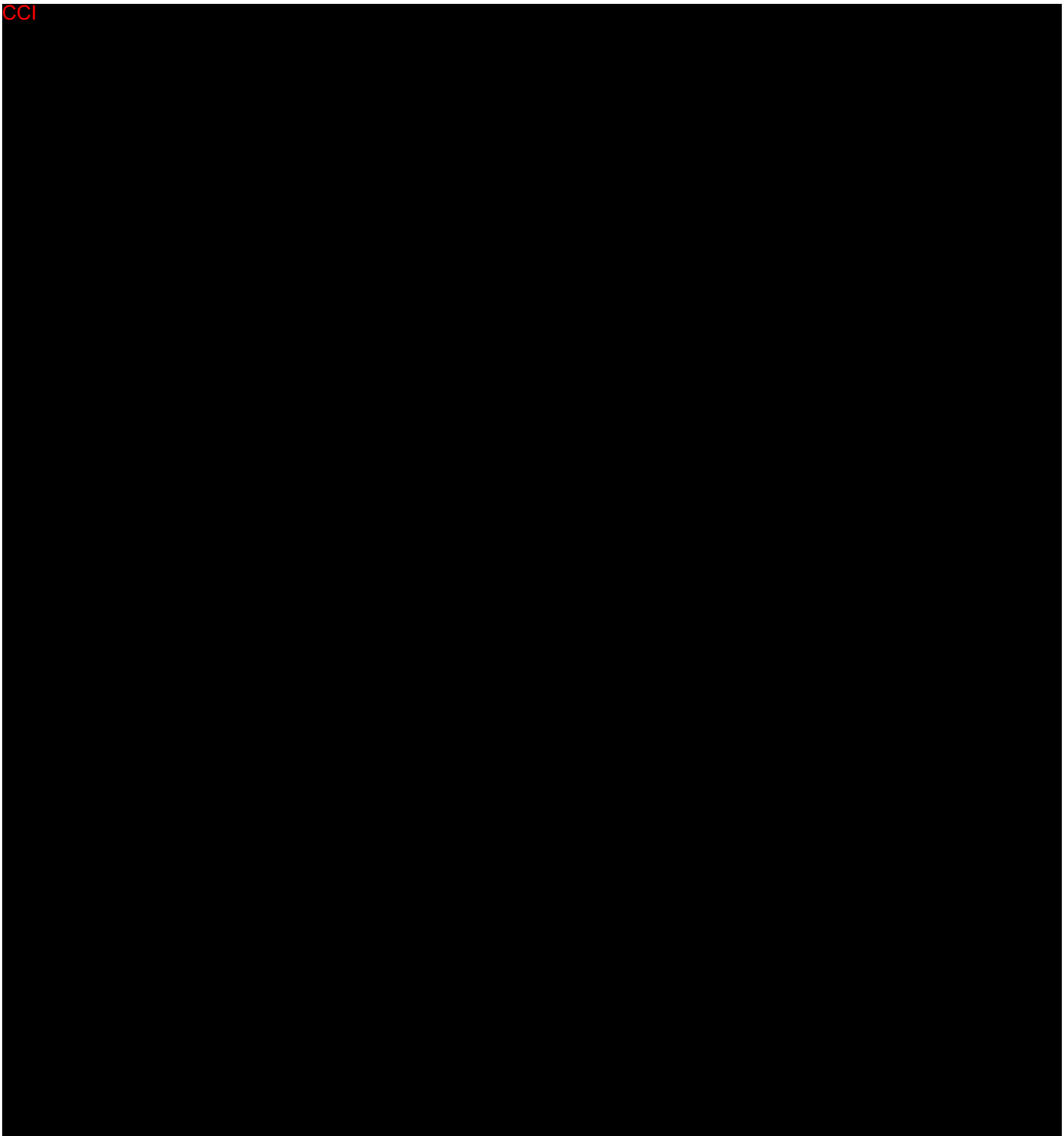
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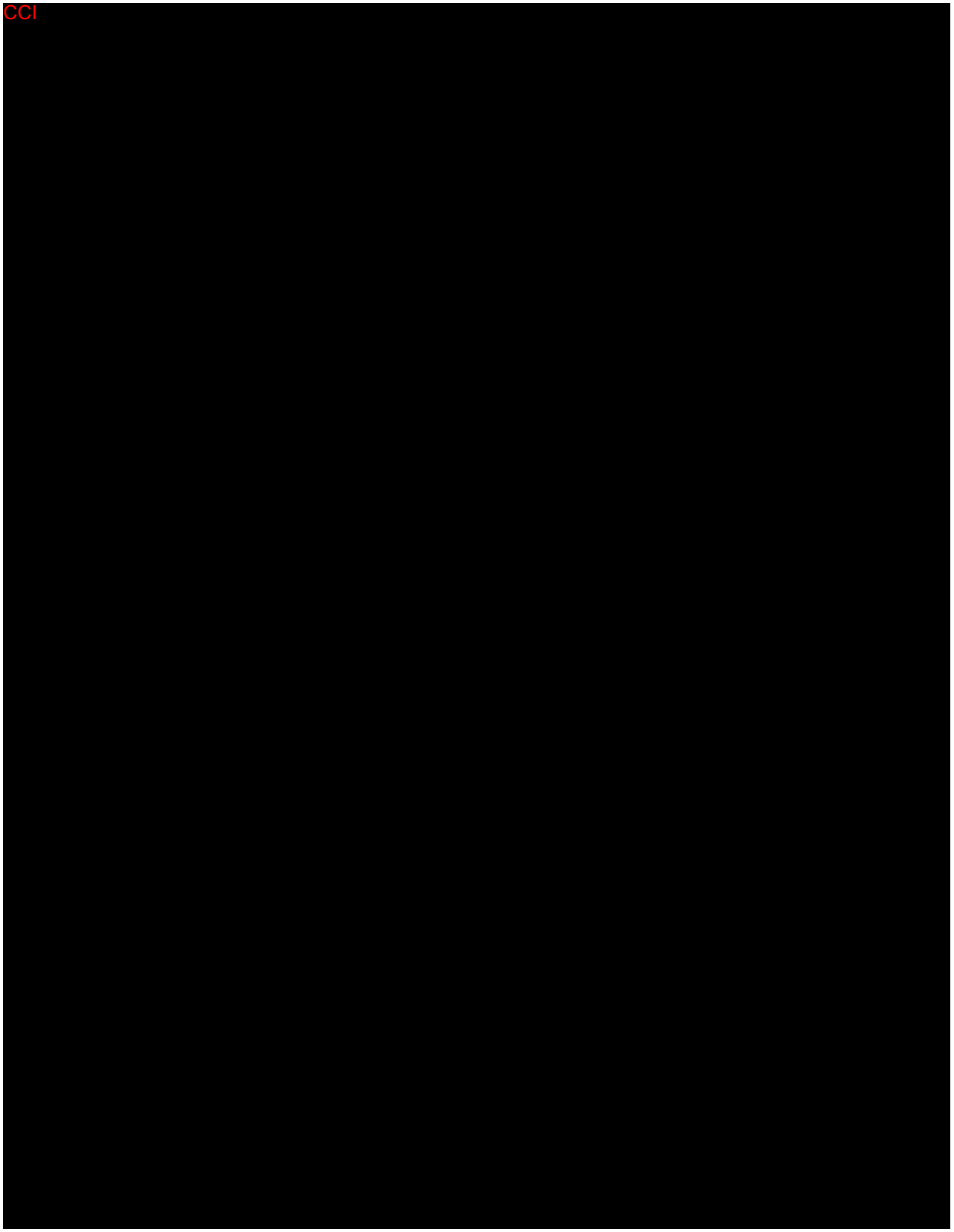

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