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**CLINICAL STUDY PROTOCOL**  
**PROTOCOL NUMBER: 43USTH2201**

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## TITLE PAGE

**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**

**Clinical Trial Number (CTN): 43USTH2201**

### SPONSOR:

Q-Med AB, part of the Galderma Group  
 Seminariegatan 21  
 SE-752 28 Uppsala, Sweden  
 Telephone: +46 18 474 90 00

Galderma Research and Development, LLC  
 2001 Ross Avenue  
 Suite 1600  
 Dallas, Tx. 75201  
 United States  
 Telephone: +1 817 961 5000

### Statements of compliance

The study should be conducted in compliance with the clinical trial agreement, the Clinical Study Protocol (CSP), Good Clinical Practice (GCP), and applicable regional or national regulations. The international standard for clinical study of medical devices for human subjects, ISO14155:2020 should be followed. The International Conference on Harmonisation (ICH) guideline for GCP (E6 (R2)) should be followed as applicable for medical device. The study should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki<sup>1</sup>.

<sup>1</sup> <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>

## INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Details on all participating Investigators and the complete administrative structure of the study are found in the study files. Note that administrative changes are to be documented in the study files without requiring a Clinical Study Protocol (CSP) amendment.


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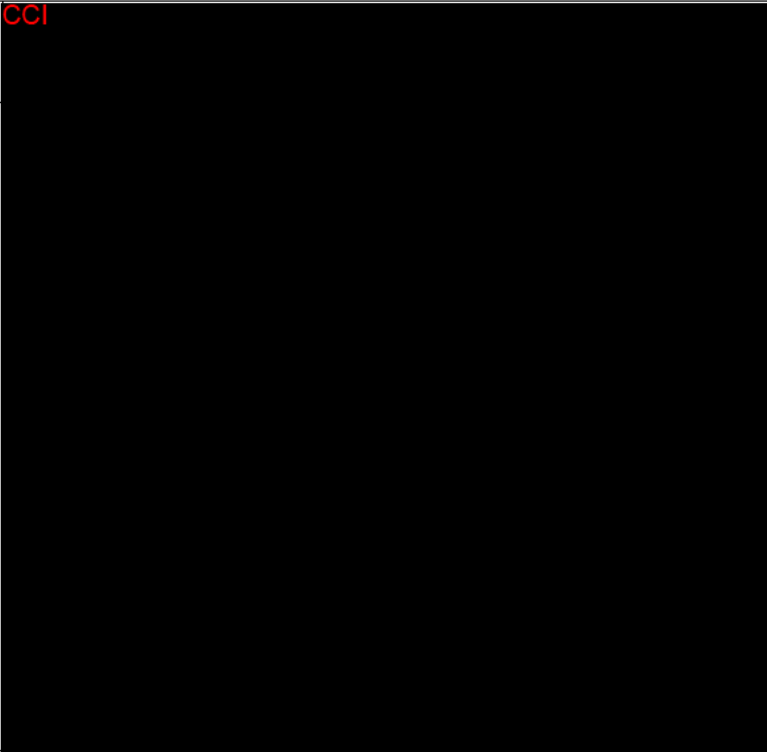



<div><div><div><div><div><div><span></span></div><div><div>GALDERMA</div></div></div><div><div><div><span></span></div></div></div><div><div><div>EST. 1991</div></div></div></div></div></div></div>		<div>Title</div> <div>43USTH2201, Clinical Study Protocol Restylane Contour Temples US</div>	<div>Doc id</div> <div>MA-52557</div>
	<div>CCI</div> <div></div> <div></div> <div>Before study start, a randomization list will be prepared under the supervision of a designated biostatistician from the Sponsor.</div> <div>CCI</div> <div></div> <div><u>General study safety stopping rules:</u> Enrollment and treatment in the study will be temporarily halted if a serious adverse event (SAE) occurs for the following:<ul style="list-style-type: none"><li>any unanticipated SAE which is possibly related to the study device or procedure including but not limited to a vascular embolic event that leads to skin necrosis, vision loss or stroke, damage to facial nerves which may result in facial paralysis or injury to internal facial structures.</li></ul>The SAE will be investigated by the Sponsor. If the Sponsor's investigation concludes the SAE:<ul style="list-style-type: none"><li>was unanticipated,</li><li>directly related to the investigational device or device injection procedure, and</li><li>presents an unreasonable risk to study subjects,</li></ul>the study will be terminated, and the Investigators notified. The Institutional Review Board (IRB) and Regulatory Authority (RA) will also be notified if the study is prematurely terminated due to safety concerns. If the SAE does not meet the above criteria, then enrollment in the study will continue provided all other safety criteria have been met.</div>		
Indication:	Correction of temple hollowing in subjects over the age of 21 years.		
Total Number of Subjects (Planned):	<div>CCI</div> <div></div> <div></div>		
Effectiveness Objectives and Endpoints:	<div>The primary objective of the study is to evaluate the effectiveness of <i>Restylane Contour</i> versus a no-treatment control in correction of temple hollowing by comparing GTVDS response rates.</div> <div><u>Primary endpoint:</u> Responder rate based on the Blinded Evaluators' live assessment of the GTVDS, at 3 months after baseline. <i>A responder is defined as a subject with at least 1 grade improvement from baseline in both temples concurrently on the GTVDS.</i></div> <div>The secondary objective is to further evaluate the effectiveness of <i>Restylane Contour</i> in correction of temple hollowing.</div>		

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	<div>Secondary endpoints:</div> <div><div>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%. <i>A responder is defined as a subject with at least 1 grade improvement from baseline in both temples concurrently on the GTVDS.</i></div><div>2. Responder rates, as assessed by the Blinded Evaluator at 6, 9 and 12 months after baseline for the treatment group. <i>A responder is defined as a subject with at least 1 grade improvement from baseline in both temples concurrently on the GTVDS.</i></div><div>3. Responder rates, as assessed by the Blinded Evaluator at 18 months after baseline for the Treatment group. <i>A responder is defined as a subject with at least 1 grade improvement from baseline in both temples concurrently on the GTVDS.</i></div></div> <div>CCI</div>
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<b>Safety Objective and Endpoints:</b>	
<b>Subgroup Analyses:</b>	<p>For consistency of the results of the primary effectiveness analysis, the primary endpoint will be evaluated across different subgroups:</p> <ul style="list-style-type: none"><li>• Study site</li><li>• Race</li><li>• Ethnicity</li><li>• Sex at birth</li><li>• Age (<math>\leq</math> median age vs <math>&gt;</math> median age)</li><li>• FST I-III and IV-VI</li><li>• Injection volume (<math>\leq</math> median total injection volume vs <math>&gt;</math> median total injection volume)</li></ul> <p>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.</p> <p>The consistency of AE data across different subgroups will also be evaluated. The following subgroup factors will be used:</p> <ul style="list-style-type: none"><li>• <b>CCI</b> </li><li>• Study site</li><li>• Race</li><li>• Ethnicity</li><li>• Sex at birth</li><li>• Age (<math>\leq</math> median age vs <math>&gt;</math> median age)</li><li>• FST I-III and FST IV-VI</li><li>• Injection volume (<math>\leq</math> median total injection volume vs <math>&gt;</math> median total injection volume)</li></ul>

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<div>Clinical Study Duration:</div>	<div>First subject first visit (FSFV) to last subject last visit (LSLV): Approximately C months.</div> <div>CCI</div> <div></div> <div><ul style="list-style-type: none"><li>Duration for each subject in the no-treatment Control group will be up to C months, including:</li></ul></div> <div>CCI</div> <div></div> <div>One month is defined as 4 weeks in the study and 4 weeks are defined as 28 days.</div>
<div>Inclusion Criteria:</div>	<div>CI</div> <div></div> <div>2. Males or non-pregnant, non-breastfeeding females, 22 years of age or older.</div> <div>CI</div> <div></div> <div>5. Intent to undergo treatment for correction of temple hollowing.</div> <div>CCI</div> <div></div>

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	<div><div><div>C</div><div>C</div><div>I</div></div><div></div></div>
<div>Exclusion Criteria:</div>	<div><div><div>1.</div><div>Known/previous allergy or hypersensitivity to any injectable hyaluronic acid (HA) gel or to gram positive bacterial proteins.</div></div><div><div>2.</div><div>Known/previous allergy or hypersensitivity to local anesthetics, e.g., lidocaine or other amide-type anesthetics or nerve blocking agents (if intended to be used for that subject).</div></div><div><div>3.</div><div>Previous or present severe or multiple allergies manifested by severe reactions, such as anaphylaxis or angioedema, or family history of these conditions.</div></div><div><div>4.</div><div>Previous facial surgery (e.g., facelift) above the level of the horizontal line from subnasale that in the Treating Investigator’s opinion could interfere with the study safety and/or effectiveness assessments.</div></div><div><div>5.</div><div>Any previous aesthetic procedures or implants:</div><div><div><div>C</div><div>C</div><div>I</div></div><div></div></div></div></div>

10. Recurrent temporal headaches such as temporal tendinitis migraine. Have a history of migraines or frequent headaches, as determined by the (Treating) Investigator, that could interfere with the study safety and/or effectiveness assessments.

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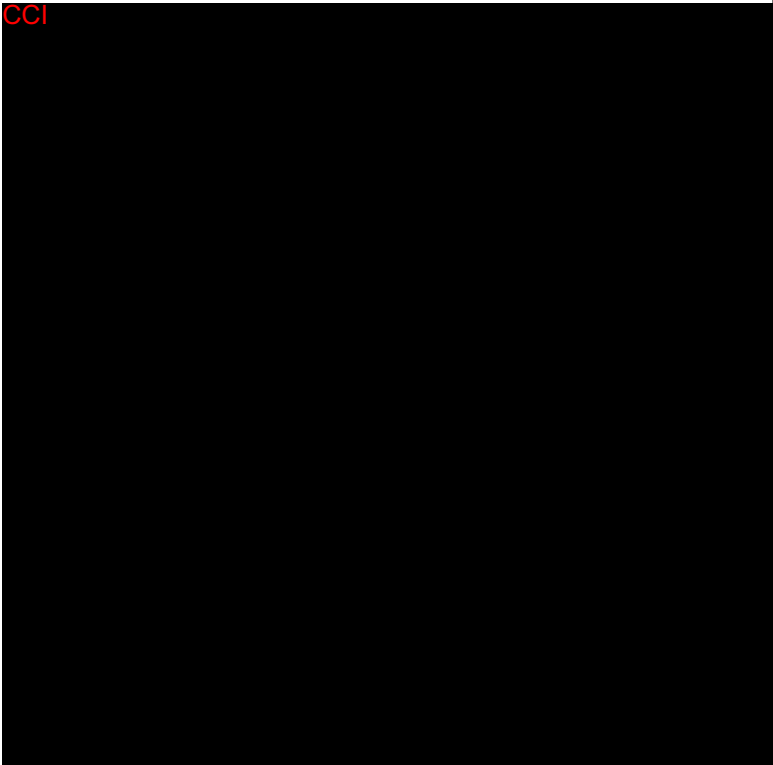
	<p>No-treatment Control group: CCI [REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>Aspiration is recommended prior to injection to verify that the needle is not intravascular. Intravascular injection into the superficial temporal artery should be avoided while injecting with a needle. When the injection is completed, the treated area may be gently molded or massaged for any irregularities.</p>
<b>Statistical Method:</b>	<p>A responder will be defined as a subject with at least 1 grade improvement from baseline (on both sides of the face) based on the GTVDS scale.</p> <p>The primary effectiveness analysis will be determined by using the Chi-Square Test for the intention to treat (ITT) analysis set.</p> <p>The study success criterion is defined so that:</p> <ol style="list-style-type: none"><li>At least one of these tests has to result in a p-value &lt;0.025, i.e., applying the Bonferroni correction, the overall study significance level is set to 0.05.</li><li>The corresponding two-sided 97.5% confidence interval (CI) around the responder rate at Month 3 (for needle and/or cannula) needs to be completely above 50%.</li></ol> <p>Percentage of responders as specified for the secondary endpoints will be analyzed in a similar manner.</p>

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	<p>For responder rates compared to reference standard responder rate of 50%, the exact p-value will be calculated using the binomial distribution and the test conducted at the 2.5% level of significance.</p> <p>Other secondary analyses will be performed using descriptive statistics as appropriate.</p> <p>Robustness of the results of the primary endpoint and AE analysis will be investigated across the subgroup analyses. Graphical presentation will be utilized in the subgroup analysis.</p>
<b>Sample Size:</b>	<p>Data on response rate on treatment of temporal hollows is limited.</p> <p>CCI</p> 
<b>Interim Analysis:</b>	Not applicable.

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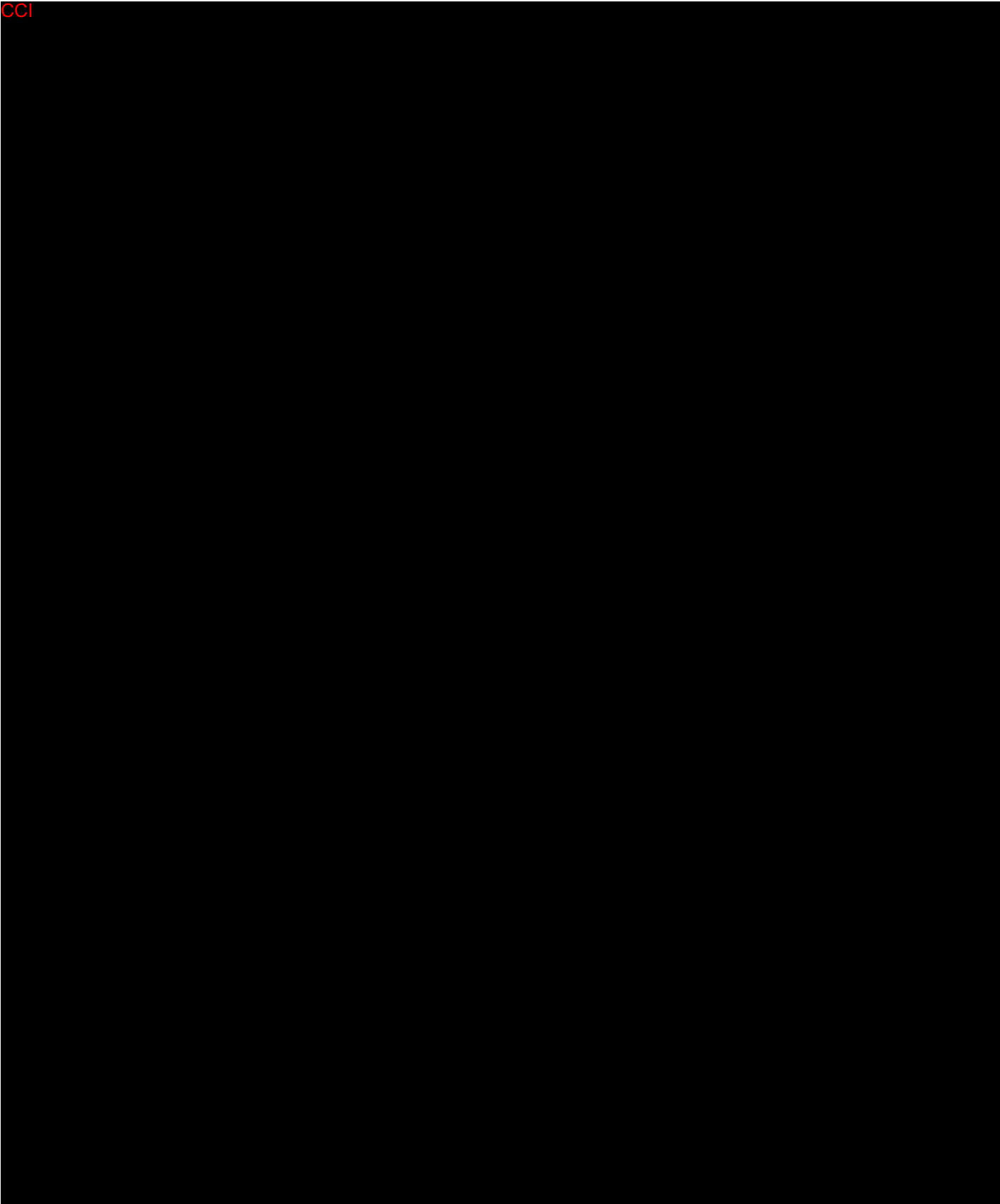
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CLINICAL STUDY FLOW CHART

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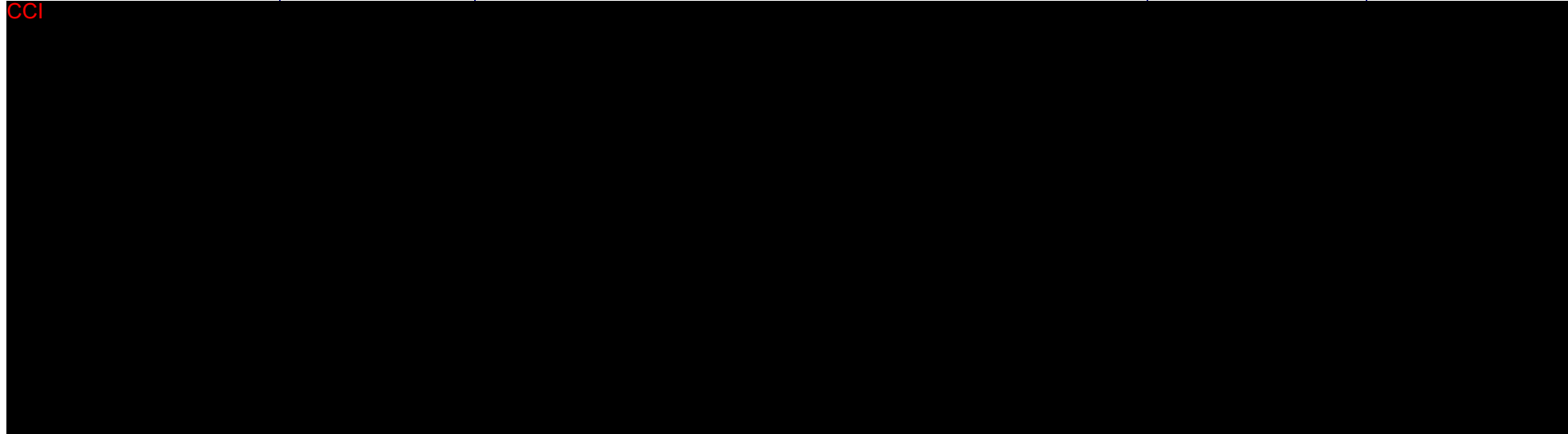
## SCHEDULE OF EVENTS

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ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
AESI	Adverse event of special interest
BDDE	1,4-butanediol diglycidylether
BOCF	Baseline observation carried forward
CaHA	Calcium hydroxylapatite
CFR	Code of Federal Regulations
CI	Confidence interval
CMC	Chemistry, manufacturing and control
CRO	Contract Research Organization
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTA	Clinical Trial Agreement
CTN	Clinical Trial Number
CV	Curriculum vitae
DMP	Data Management Plan
eCRF	Electronic case report form
EOS	End of study
FDA	Food and Drug Administration
FSFV	First subject first visit
FST	Fitzpatrick skin type
CCI	
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GLP	Good laboratory practice
GTVDS	Galderma Temple Volume Deficit Scale
HA	Hyaluronic acid/sodium hyaluronate
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonisation
IFU	Instructions for Use
IPR	Independent Photographic Reviewer
IRB	Institutional Review Board
ITT	Intention to treat
IUD	Intra uterine device
LSLV	Last subject last visit
MedDRA	Medical Dictionary for Regulatory Activities
MDR	Medical Devices Regulation
MI	Multiple imputation
n	Number of subjects
CCI	
NSAID	Non-steroidal anti-inflammatory drugs
PI	Principal Investigator

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PLLA	Poly-L-lactic acid
PMS	Post market surveillance
PT	Preferred term
RA	Regulatory Authority
ROPI	Report of Prior Investigations
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SDV	Source data verification
SOC	System organ class
CCI	
TC	Telephone call
Tx	Treatment
UADE	Unanticipated adverse device effect
UPT	Urine pregnancy test
UTW	Ultra-thin wall
WHO	World Health Organization

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



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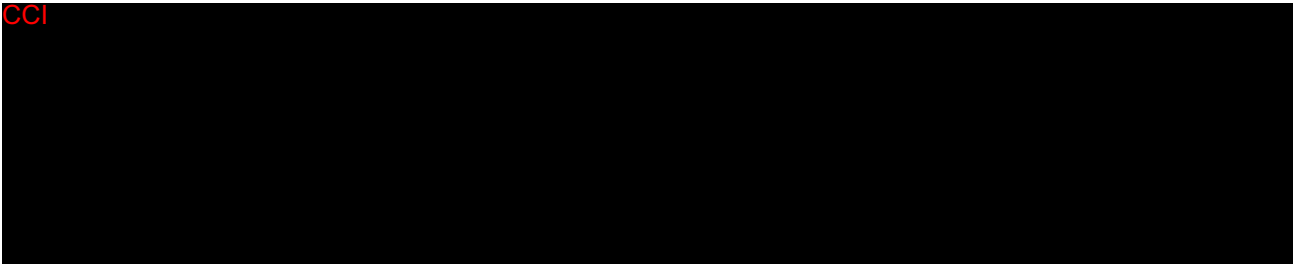


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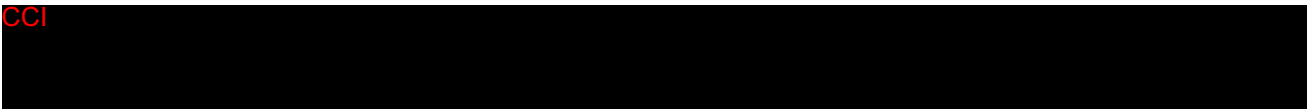



Figure 3 Definition of upper, middle and lower temple area.....53

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## 1. BACKGROUND INFORMATION

### 1.1 Medical background, indication and population description

The safety and effectiveness of *Restylane*<sup>®</sup> fillers are well known; the number of treatments performed with the *Restylane* range of products since first marketing approval has been estimated to over 40 million. *Restylane* was first approved for use on the US market in 2003, and other members of the *Restylane* family of products have been approved on the US market since then.

The *Restylane* family of products are transparent, viscous and sterile gels of sodium hyaluronate (HA) generated by *Streptococcus* species of bacteria, chemically cross-linked with BDDE (1,4-butanediol diglycidylether) and suspended in phosphate buffered saline (pH of 7) solution at a concentration of 20 mg/mL HA. Some of the products contain 0.3% lidocaine.

*Restylane Contour*<sup>2</sup> is manufactured by Q-Med AB, part of the Galderma group, located in Uppsala, Sweden.

In 2021, *Restylane Contour* received US marketing approval (P140029/S032) for use in cheek augmentation and correction of midface contour deficiencies in subjects over the age of 21 years.

This randomized and controlled clinical study is planned 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 Relevant previous data

#### 1.2.1 Non-clinical documentation


Biological evaluation of *Restylane Contour* has been performed according to EN ISO 10993 and the US Food and Drug Administration (FDA) guidance on use of ISO 10993. The ISO 10993-1 standard tests supporting biocompatibility were performed by good laboratory practice (GLP)-certified laboratories. The biological evaluation determined that *Restylane Contour* complies with the requirements in the EN ISO 10993 standard series and the FDA guidance on use of ISO 10993. According to the biological safety assessment, *Restylane Contour* should be safe to use for its intended purpose.

Further, *Restylane Contour* has been extensively tested and characterized by physical and chemical analysis in several chemistry, manufacturing and control (CMC) studies in accordance with ISO 10993. There are no changes in product manufacture or specifications, therefore, no additional animal or laboratory testing has been conducted.

#### 1.2.2 Clinical documentation

Please refer to the Report of Prior Investigations (ROPI) for a description of clinical studies completed in facial indications including the temple area with *Restylane* products, post-market reporting of the *Restylane* products in total as well as separately in the temple area, and available clinical data from publications with HA fillers in the temple area.

<sup>2</sup> *Restylane Volyme* outside of the US.

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Please also refer to the study specific Instructions for Use (IFU) for *Restylane Contour* that summarizes the expected AEs for this product along with precautions that can minimize these potential complications.


### 1.3 Risks and benefits

Hyaluronic acid (HA) has been safely used for many years in a variety of medical devices. *Restylane Contour* has been used extensively to augment the volume of facial tissues, notably for contouring, augmenting, and volumizing facial tissue in the midface, specifically cheek augmentation and correction of midface contour deficiencies. Results from clinical studies (Section 1.2.2) have confirmed that *Restylane Contour* is safe and well tolerated, with AEs typically comprising injection site reactions, such as swelling, erythema, bruising and tenderness. Results from these studies have also confirmed the effectiveness of *Restylane Contour*, with significant improvement in volume for all treated areas (including the temple), with high rates of subject satisfaction and a long-lasting treatment effect until 18 months after treatment.

With regard to safety, data from post market surveillance (PMS) are consistent with reports from clinical studies and PMS-reported events from off-label use in the temple generally do not appear to differ, neither in type nor in intensity nor seriousness, from those reported after injections in other areas of the face with *Restylane* HA fillers. In study 29090 (1), conducted by the Sponsor, treatment of the temple with *Restylane Contour* was secondary to treatment of the cheekbones, nasolabial folds and jawline, and volume restoration was well sustained over 18 months with high patient satisfaction and good tolerability. Data from prospective and retrospective studies where the temple was treated with HA, demonstrated that HA-fillers used for treatment of temporal hollow volume deficit were generally well tolerated, however, visible veins on the temples may have seemed slightly dilated for two to three days after the injection. AEs typically reported comprised bruising, swelling, erythema, pain, tenderness and headache, which were generally mild to moderate in intensity, resolving quickly. Additional AEs reported after injection in the temporal area included transient jaw ache, chewing ache/discomfort, superficial vein prominence and muscle pain in the temporal area, which could be expected after injection in the temporal area. Rare single case reports of reversible alopecia with localized scalp necrosis (2), delayed foreign body granulomas in the orofacial region (3), or migration of HA filler (4), have been reported after HA filler treatment of the temple, however the outcome of these events was favorable. There is a potential theoretical risk of intracranial penetration when the deep injection technique is performed in perpendicular orientation to the bone surface, based on a single case report (5). Hence, profound knowledge of the temporal anatomy as well as the use of a gentle injection technique allowing periosteum contact, but no direct pressure on the bone, should be mandatory for physicians treating the temple.

In this study, superficial (subdermal) and supraperiosteal injection techniques for volumizing will be used, to increase the safety and to achieve better results (6). The subdermal layer is an optimal target for lifting and volumizing treatments with a stable and firm position of the subdermal temporal fat compartments, no major neurovascular structures are expected in this plane. Deep supraperiosteal injection technique is safer because the diameter of the arteries become smaller the further away from their emergence from the internal maxillary artery. A smaller arterial diameter of the anterior deep temporal artery might reduce the risk of intra-arterial product application in this location.

The most serious complication reported following facial cosmetic injections is visual impairment/loss including blindness, due to intravascular injection and retrograde embolization of the filler into the ophthalmic artery of the internal carotid. Chen et al. 2014 (7) reported cases of

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visual impairment/loss after intravascular injections with autologous fat in the temporal area, glabella, forehead, periorbital area, cheeks, and lips. Other cases of visual impairment/loss were reported after injection with bone collagen filler in the nose and after HA-fillers in the nose, periocular area, or the upper eyelid. The authors concluded that cosmetic facial injections could cause fundus artery occlusion. Thanasarnaksorn et al. 2018 (8) reviewed cases from October 2011 to December 2017, to identify cases of severe vision loss from cosmetic HA filler injections, and identified 6 patients treated with HA, whereof 1 treated in the temple, developed vision loss secondary to HA embolization in retinal or ophthalmic arteries.

In a literature search performed by Lee et al., 2020 (9) until July 2018, to identify reports on visual compromise after filler injections, there were no reports of blindness from injections into the temple and relatively few case reports involving forehead injections. Although blindness is a devastating complication, collectively these authors have reported that the risk of visual impairment or blindness is extremely low, in relation to the number of filler treatments performed worldwide.


To minimize the risk of intravascular complications, injection treatment with *Restylane Contour* in the temporal area should only be performed by physicians with a thorough knowledge of facial anatomy, topographically important blood vessels, critical venous structures, soft tissues and the skeletal structures of this area (10, 11, 12, 13, 14, 15, 16).

Furthermore, physicians must have a solid understanding of the depth and plane of injection, as well as knowledge of the signs and symptoms of vascular compromise and intravascular injection (8, 10, 11, 12). Physicians must also understand the volume deficiencies of this area and the lifting capacity of *Restylane Contour*. Before treatment, a detailed medical history must be taken from the subjects regarding previous treatments in the temporal area or other facial areas, also the subject must be informed about the potential risks involved with the treatment and when to contact the investigator in case of emerging symptoms. Strategies to prevent intravascular complications include a slow injection speed, under low pressure, with an injection volume not to exceed 3 mL per treatment site and the use of a gentle injection technique allowing periosteum contact, but no direct pressure on the bone (5, 10, 11). Injections with sharp needles are recommended to be preceded by aspiration. For the proposed new indication for *Restylane Contour*, “correction of temple hollowing”, treated subjects in this study will receive supraperiosteal injections using needle and superficial (subdermal) injections using needle or blunt cannula.

Additional information about expected AEs and anticipated risks are included in the study specific IFU and ROPI.

With regard to effectiveness, the benefits of treatment of the temporal area with HA have been documented in study 29090 (1) with the device in question by the Sponsor and in published literature (see the ROPI for more information). The effectiveness data presented in the publications reviewed are consistent with reported data from the Sponsor for facial indications and confirms that *Restylane Contour* is effective for augmentation of the temple area, with high subject and investigator satisfaction rates, with improvements in temple volume and with long-lasting results (until 24 months after treatment) (17). A further benefit is that pan-facial effects have been reported after treatment of the temple, with beneficial changes to the forehead as well as the medial and lateral midface and accentuation of the contour of the jawline, resulting in a more youthful shaped face.

In the literature reviewed, data from more than 495 subjects support the safety and effectiveness of HA in augmentation of the temple. In the majority of publications an average of 1 mL HA filler was

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administered per temple site per treatment, with injection into the suprapariosteal zone or subcutis most frequently reported and with injection performed most frequently using a 27G x ½” needle.

There is no reason to believe that injections of *Restylane Contour* into the suprapariosteal zone or subcutis in the temporal area should behave differently to injections with the currently approved use for the cheeks and midface. Potential hazards related to treatment of the facial temporal area are continuously assessed, evaluated, and managed in accordance with requirements in the ISO 14971 standard and established risk management procedures at Q-Med AB. To date, no unacceptable risks have been identified for the use of *Restylane Contour* for temple augmentation injected with either needle or cannula, by qualified and experienced physicians.

Data from existing published clinical studies, relevant literature and PMS have demonstrated a favorable benefit to risk ratio for HA filler treatments administered superficially (with cannula and needle) or deep (with a needle) in the temporal area. Safe administration approaches and injection sites/planes have been identified, based on recommendations in the literature and company experience and research. To date, HA injections in the temporal area have not revealed any unacceptable risks.

Under the recommended conditions identified in the benefit risk assessment it is concluded that there is reasonable assurance from a safety perspective for conducting a clinical trial in the US using *Restylane Contour* for correction of temple hollowing.

## 2. STUDY OBJECTIVES, ENDPOINTS AND HYPOTHESIS

### 2.1 Study objectives

#### 2.1.1 Primary objective and endpoint

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 GTVDS response rates.

#### Primary endpoint:

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 GTVDS.*

#### 2.1.2 Secondary objective and endpoints

The secondary objective is to further evaluate the effectiveness of *Restylane Contour* in correction of temple hollowing.

#### Secondary endpoints:

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.

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*A responder is defined as a subject with at least 1 grade improvement from baseline in both temples concurrently on the GTVDS.*

3. Responder rates, as assessed by the Blinded Evaluator at 18 months after baseline for the Treatment group.

*A responder is defined as a subject with at least 1 grade improvement from baseline in both temples concurrently on the GTVDS.*

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

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## 2.2 Appropriateness of measurements

The aim of the study is to evaluate the effectiveness and safety of *Restylane Contour* in correction of temple hollowing.

Primary effectiveness will be evaluated by comparing GTVDS response rates at 3 months (12 weeks) after baseline for the Treatment group and for the no-treatment Control group.

The GTVDS is a validated scale considered suitable to measure the treatment effect of temple volume restoration.

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In addition, subjects and investigators will assess their satisfaction with the treatment by use of

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Effectiveness evaluation in dermal filler clinical studies includes a combination of clinician-and subject-reported outcomes. As these are aesthetic devices and elective procedures, the incorporation of the subject perspective is critical to the study benefits associated with dermal fillers.

## 2.3 Clinical hypothesis

This study has been designed to evaluate the effectiveness of *Restylane Contour* versus a no-treatment control in correction of temple hollowing by comparing GTVDS response rates.

A responder is defined as a subject with at least 1 grade improvement from baseline on the GTVDS in both temples concurrently, based on the Blinded Evaluators' live assessment.

For the primary effectiveness endpoint, responder rate at 3 months after baseline, treatment with *Restylane Contour* is expected to be superior to no treatment.

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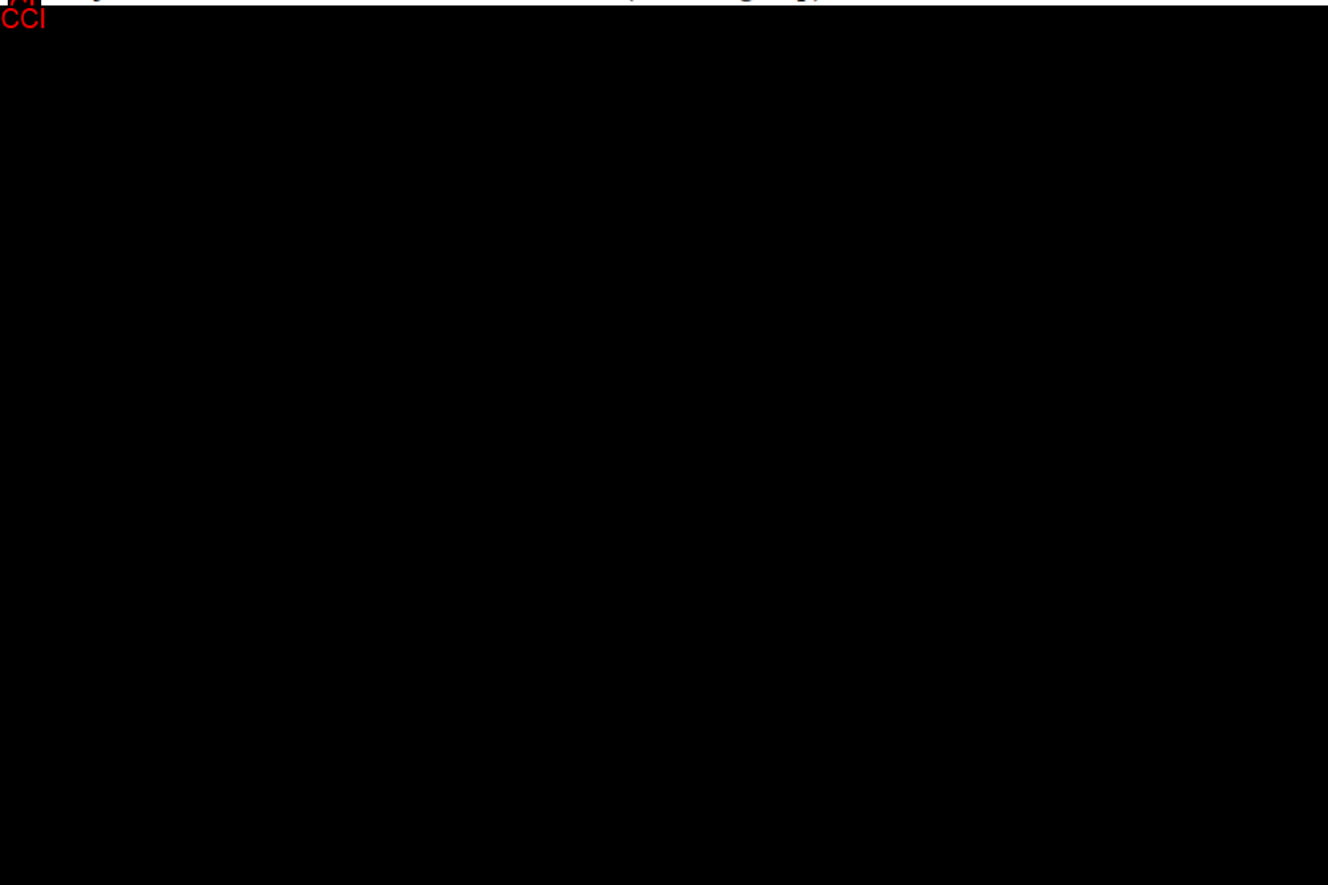
## 3. STUDY DESIGN

### 3.1 Overall design

This 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 [CCI] subjects is planned to be included in the study. At the baseline visit, approximately [CCI] subjects will be randomized to the *Restylane Contour* Treatment group and approximately [CCI] subjects will be randomized to no-treatment (Control group).



Investigator blinding will be accomplished by using [CCI]

[CCI] Safety assessments will be performed by non-blinded personnel.

Effectiveness and safety data will be collected for up to [CCI] after baseline. A subject will be involved in the study for up to [CCI] (Treatment group) or up to [CCI] (Control group), including a [CCI] screening period. [CCI]

[CCI]

Before study start, a randomization list will be prepared under the supervision of a designated biostatistician from the Sponsor.

[CCI]

The study visits are illustrated in the study flow chart (Figure 1) and the schedules of events (Table 1: Treatment group and Table 2: No-treatment Control group).

### 3.2 Study rationale and justification for design

The rationale of performing this study is to obtain evidence of safety and effectiveness of *Restylane Contour* for use in a new indication “correction of temple hollowing”.

There is no currently approved HA filler for the augmentation of the temple in the United States. Based on literature review, off-label use of HA fillers in the temporal region is occurring. The Sponsor determined it was important to conduct a study on temple augmentation with an HA filler in order to determine the safety profile and be able to potentially mitigate risks in this procedure through training on this new indication.

A study of the safety and effectiveness of *Restylane Contour* in the treatment of temporal hollows will establish whether aesthetic temple augmentation can be successfully achieved, with an acceptable safety profile.

By using a validated evaluation tool, the GTVDS assessed by the Blinded Evaluator and Investigator, the results of temple augmentation reported can be confirmed by accurate measurements. Objective evaluation of temple augmentation will enable Blinded Evaluator and Investigators to determine the degree to which treatment has improved the appearance of the temple compared to the no-treatment Control group.

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The study will also assure that *Restylane Contour* used in the temple will not impact the safety of the product in an ethnically diverse population. CCI

### 3.3 Number of subjects and study centers

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To minimize potential bias in the study results, 30 subjects will be the maximum allowed to be enrolled at any one study center.

### 3.4 Study duration

The total duration of the study is estimated to approximately CCI months.

Effectiveness and safety data will be collected for up to CCI


including a 21-day screening period.

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### 3.5 Procedures/reasons for subject discontinuation

An investigator may decide to discontinue a subject from the clinical study for safety reasons.

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Although the importance of completing the entire clinical study should be explained to the subject by the clinical study personnel, any subject is free to discontinue participation in this clinical study at any time and for whatever reason, specified or unspecified, and without any prejudice. No constraints are to be imposed on the subject, and when appropriate, a subject may be treated with other conventional therapy when clinically indicated.

When a subject does not complete the clinical study, he/she will be fully assessed if such assessment is possible. The procedures designated for the closest upcoming study visit should be completed for a subject discontinuing the clinical study and the appropriate electronic case report form (eCRF) should be completed.

All discontinuations and the reason for discontinuation are to be documented by the Investigator on the Study Exit form in the eCRF.

For discontinuation due to an adverse event (AE), the Adverse Event form in the eCRF is to be completed. The Investigator should also ensure that the subject receives suitable therapy for the AE.

A subject who has been randomized cannot be replaced by another subject if he/she discontinues the clinical study for any reason.

Pregnancies occurring during the screening period are considered as screening failures; they should be recorded as such in the eCRF, and no pregnancy form is to be completed.

In case of a pregnancy occurring after the baseline visit, the procedures described in Section 7.13.5 should be followed. The subject may remain in the study, but no invasive procedure should be conducted.

The Sponsor may also decide to prematurely terminate or suspend a subject's participation in the clinical study.

Potential reasons for discontinuation are defined below in the withdrawal criteria:

- **Medical reasons:** If the subject suffers from a medical condition and/or AE that, in the judgment of the Investigator makes it medically necessary to withdraw the subject. The specific rationale for Investigator-initiated withdrawal of a subject for medical reasons should document the specific condition for withdrawing the subject.
- **Withdrawal by Subject:** Includes consent withdrawal, subject relocation, schedule conflicts. A subject can withdraw their consent to participate in the study at their own request or be withdrawn from participation in the study at the request of their legally authorized representative at any time for any reason.
- **Lost to follow-up:** If a subject does not return for a scheduled visit, reasonable effort shall be made to contact that subject, confirm with three documented phone calls and a certified letter (delivery receipt requested) without answer before declaring the subject lost to follow-up.
- **Other:** This category is to be used for a subject who discontinues due to a reason other than as specified in the pre-defined categories above. The reason for discontinuation should be explained.

If the reason for discontinuation is “withdrawal by subject” or “other”, the subject will be questioned to rule out the possibility of an AE. If the AE led to discontinuation, then “Medical reason” should be chosen as the reason for discontinuation, rather than “withdrawal by subject” or “other”.

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If an AE which, according to the Investigator's assessment, is related to the use of the study product and is still ongoing at the time of the withdrawal, the Investigator shall follow-up the subject until the AE resolves, is assessed by the Investigator to be "chronic" or "stable" or subject is lost to follow-up. Follow-up information shall be reported on the AE follow-up form.

### 3.6 Suspension or premature termination

The Sponsor will suspend or terminate the study when so instructed by the Institutional Review Board (IRB) or Regulatory Authority (RA), or if it is judged that the subjects are subjected to unreasonable risks, or for valid scientific or administrative reasons, or for business reasons. The Sponsor shall submit a Clinical Study Report (CSR) within three months of an early termination or temporary halt.

The Sponsor may also decide to close a single study center due to unsatisfactory subject enrolment or non-compliance with the Clinical Study Protocol (CSP), Good Clinical Practice (GCP), or applicable regulatory requirements.

In the event of premature termination, the Sponsor will provide information on the handling of currently enrolled subjects who have not completed the study.

## 4. STUDY POPULATION

A total of 225 adult male and female subjects aged 22 years or older with the intent to undergo treatment for correction of temple hollowing is planned to be included in this study.

### 4.1 Clinical study population characteristics

#### 4.1.1 Inclusion criteria

The subjects must meet all the following criteria to be eligible for the study:

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2. Males or non-pregnant, non-breastfeeding females, 22 years of age or older.

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5. Intent to undergo treatment for correction of temple hollowing.

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4.1.2 Exclusion criteria

The presence of any of the following exclusion criteria excludes the subject from enrollment in the study:

1. Known/previous allergy or hypersensitivity to any injectable HA gel or to gram positive bacterial proteins.
2. Known/previous allergy or hypersensitivity to local anesthetics, e.g., lidocaine or other amide-type anesthetics or nerve blocking agents (if intended to be used for that subject).
3. Previous or present severe or multiple allergies manifested by severe reactions, such as anaphylaxis or angioedema, or family history of these conditions.
4. Previous facial surgery (e.g., facelift) above the level of the horizontal line from subnasale that in the Treating Investigator’s opinion could interfere with the study safety and/or effectiveness assessments.
5. Any previous aesthetic procedures or implants:

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10. Recurrent temporal headaches such as temporal tendinitis migraine. Have a history of migraines or frequent headaches, as determined by the (Treating) Investigator, that could interfere with the study safety and/or effectiveness assessments.

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## 4.2 Medical history

The history of relevant surgical events and medical conditions, including any prior dermatological procedures or implants, should be documented in the eCRF, using medical terminology.

## 4.3 Previous and concomitant therapies

### 4.3.1 Definition

Previous 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 (Section 4.1), 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.


### 4.3.2 Categories

Previous and concomitant therapies are to be recorded on the appropriate form in the eCRF.

Concomitant therapies are to be recorded, reviewed, and updated at each visit, including telephone calls.

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Any new concomitant therapy or modification of an existing therapy may be linked to an AE. A corresponding AE form must be completed in the eCRF to account for the change in therapy, except in some cases such as therapy used for prophylaxis or dose modification for a chronic condition.

#### 4.3.3 Authorized concomitant therapies

Unless listed in prohibited concomitant therapies (Section 4.3.4), all therapies are authorized.


#### 4.3.4 Prohibited concomitant therapies

The following therapies are prohibited during the study because they may interfere with the effectiveness and/or safety assessment of the study product and/or injection procedure:

- Medications that have the potential to prolong bleeding times such as anticoagulants or inhibitors of platelet aggregation (e.g., warfarin, clopidogrel, aspirin, NSAIDs), Omega 3 or Vitamin E should not be used within 2 weeks (i.e., 14 days) before any treatment to avoid increased bruising or bleeding at injection sites.

Omega 3 and Vitamin E are acceptable only as part of a standard multivitamin formulation. COX-2 inhibitors are allowed.

- The study product contains lidocaine, but additional local anesthesia may be used. Lidocaine should however be used with caution in subjects receiving other local anesthetics or agents structurally related to amide-type anesthetics, e.g., certain antiarrhythmics, as the systemic toxic effects can be additive.
- Concomitant treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g., monoclonal antibodies, antiviral treatment for hepatitis) is prohibited.
- Systemic steroids (except intranasal/inhaled steroids) or prescription topical steroids (near or on the area to be treated).
- Topical (facial) prescription retinoids above the level of the horizontal line from subnasale or systemic retinoids.
- Energy based aesthetic procedures (e.g., laser, intense pulsed light, radiofrequency and ultrasound) above the level of the horizontal line from subnasale.
- Mechanical (e.g., dermabrasion, needling) or chemical aesthetic procedures (e.g., chemical peel) above the level of the horizontal line from subnasale.
- Treatment with cryotherapy above the level of the horizontal line from subnasale.
- Lipolytic injections in the face above the level of the horizontal line from subnasale.
- Neurotoxin treatment above the level of the horizontal line from subnasale.
- Facial treatment with absorbable or temporary dermal fillers (e.g., collagen, HA products, CaHA, PLLA products, etc.)
- Treatments with any permanent filler or implant, lifting threads, or autologous fat in the face or neck.
- Tattoo or piercing in the area of treatment interfering with the study injections and/or study assessment.

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- Planned aesthetic facial plastic surgery (e.g., facelift, rhinoplasty, facial liposuction etc.), sinus surgery or oral surgery including dental implants, tooth extractions, orthodontia are prohibited.
- Participation in any other clinical study during this study is prohibited.

If a prohibited therapy becomes a necessary treatment for the safety or best interest of the subject, the Sponsor's Medical Expert should be notified, time permitting, to discuss possible alternatives prior to administration of a prohibited therapy.

If a subject receives prohibited therapy during the clinical study, the Sponsor should be notified to discuss the pertinence and the modalities for the subject to continue in the clinical study.

#### 4.4 Documentation and recording instructions

##### 4.4.1 Subject identification number

Prior to any study procedures being conducted, the subject must sign the informed consent form (ICF). Each subject who has signed the ICF will be assigned a subject identification number that will be allocated in ascending order within each center.

A screen failure is a subject who signed the ICF but never enrolled (i.e., was randomized and/or received treatment) in the study. For screen failures, the subject source documents should indicate which assessments have been made and the reason why the subject was determined to be a screen failure. A screen failure should not be re-entered in the study. A subject is considered enrolled when they have signed the ICF and are randomized and/or treated.

For the duration of the clinical study, each subject will be identified using the subject identification number for all documentation and discussion. A Subject Identification Log is required to be kept in the Investigator file.

### 5. STUDY INTERVENTION

#### 5.1 Description of the investigational device

##### 5.1.1 Investigational device

The investigational device (i.e., the study product) is *Restylane® Contour*, manufactured by Q-Med AB, part of the Galderma group, located in Uppsala, Sweden.

*Restylane® Contour* is a sterile, biodegradable, viscoelastic, non-pyrogenic, clear, colorless, and homogeneous HA gel. The product has a HA concentration of 20 mg/mL in phosphate buffered saline at pH 7 and contains 3 mg/mL lidocaine hydrochloride.

During manufacturing, cross-links are introduced into the HA molecule by use of BDDE. This is to obtain the desired physical form; a gel network, that gives the gel its residence time in the body. *Restylane Contour* is produced using the XpresHAN™ Technology.

Lidocaine is included in the formulation to reduce local pain associated with the injection. The addition of lidocaine has been shown to substantially reduce pain experienced by subjects in clinical trials.

##### 5.1.2 Reference product

Not applicable since subjects in the no-treatment Control group are randomized to no treatment.

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### 5.1.3 Additional products and materials

Topical or local anesthesia may be used at the discretion of the treating Investigator before the treatment. If used, the anesthesia shall be supplied by the study center. Type of anesthesia, administration route, product name, and quantity used must be recorded in the eCRF.

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Urine pregnancy tests will also be provided to each study center for testing of all females of childbearing potential, at screening, baseline, and prior to treatment at optional touch-up for the Treatment group and at 3 months (12 weeks) optional treatment for the no-treatment Control group.

## 5.2 **Packaging and labelling**

*Restylane Contour* is supplied in a sealed blister package containing a syringe with 1 mL sterile gel

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Labelling will be performed according to United States Code of Federal Regulations (CFR) 21 CFR 812.5: Labelling of investigational devices. The carton will be labeled with the lot number as well as expiration date and the Clinical Trial Number (CTN) and the following:

"CAUTION - Investigational Device. Limited by US Law to Investigational Use."

## 5.3 **Instructions for use and administration**

Detailed information regarding the injection procedure, pre- and post-treatment care and subjects' instructions are provided in the study specific IFU for *Restylane Contour*.

Please also refer to the ROPI for *Restylane Contour* for a description of performed clinical studies, PMS data on reported AEs, and published data related to injections of HA in the temple area.

### 5.3.1 Treatment procedure

The study product is reserved for use by Treating Investigators who are experienced in temple area procedures. Treating Investigators will be trained on the use of the study product.

Before treatment the subject will be informed about the expected post-treatment events that should be recorded in the CCI and potential risks involved with the treatment and when to contact the Investigator in case of emerging symptoms.

### 5.3.2 Pre-treatment procedure

It is necessary to counsel the subject and discuss the appropriate indication, risks, benefits and expected responses to the *Restylane Contour* treatment.

- Advise the subject of the necessary precautions before commencing the procedure.

Prior to treatment, the patient's medical history should be obtained, and the subject should be fully appraised of the indications, contraindications, warnings, precautions, treatment responses, adverse

reactions, and method of administration. Subjects also should be advised that supplemental “touch-up” implantations may be required to achieve and maintain the desired level of correction.

Prohibited concomitant medication use should be checked before any treatment is given (see Section 4.3.4).

For subjects who have experienced medically important AEs during initial treatment, a decision for touch-up should take into consideration the cause and severity of previous reactions.

Move any hair in the proximity of the temple before treatment, e.g., by using a headband or cap, to obtain complete visual field of the area to be treated.

Any makeup in the temple area should be removed. It is important to thoroughly cleanse the face with an antiseptic preparation that extends below and beside the temple area.

*Restylane Contour* contains lidocaine, but an ice pack can be applied on the site for a short period, or additional topical or local injection may be used to further reduce pain on injection. If additional topical, local injection anesthetic, or ice is used, the area should be cleaned after anesthetic is removed.

Subjects will be asked to:

- Avoid heat (sunbathing, sauna, steam baths, etc.) or extreme temperatures until any signs of local inflammation have disappeared.
- Avoid touching or shaving the treated area and not to apply any creams or cosmetics in the treated area before the skin has healed completely in order to prevent infections or elicit an inflammatory reaction.
- Abstain from prohibited medications, treatments and procedures (see Section 4.3.4).
- Advised not to massage or apply pressure to the treated area for a few days following the injection.
- Contact the study center if common injection-related reactions such as bruising, redness, pain, tenderness, lumps/bumps, itching, swelling at the injection site, have not diminished within two weeks or if they get worse.
- Contact the study site if they have signs of infection and/or inflammation such as pain, tenderness, heat, redness, swelling, small lumps that contain pus or yellowish fluid, and fever. These symptoms can occur within days or several weeks after treatment.

### 5.3.3 Treatment regimen (dose and interval)

*Restylane Contour* will be administered by needle and cannula injections in the temple area. CCI

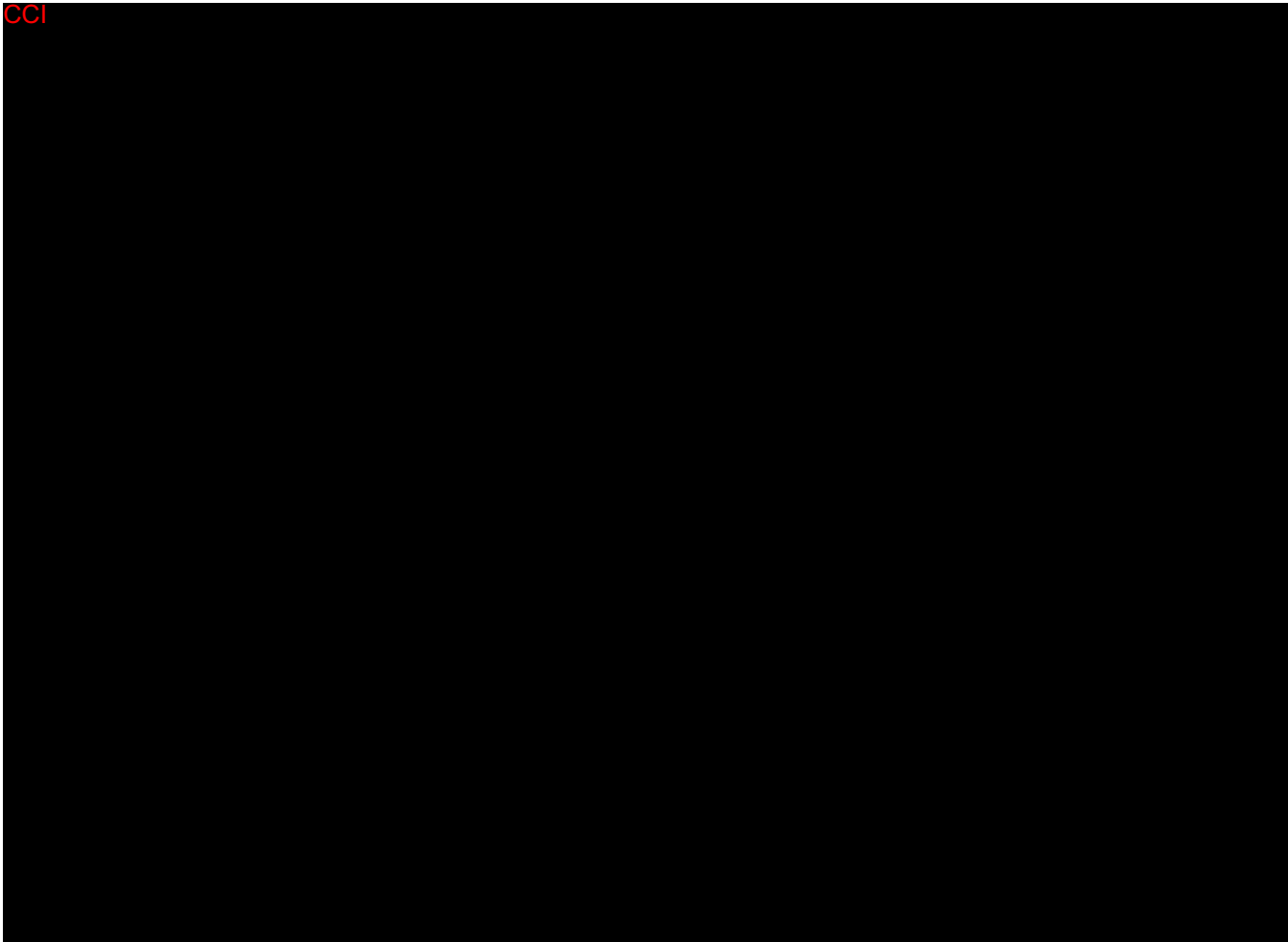
Subjects randomized to the Treatment group will be administered at baseline (Day 1) and if deemed necessary at optional touch-up after 1 month (4 weeks).

Subjects randomized to the no-treatment Control group will be offered optional treatment at 3 months (12 weeks) after baseline.

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5.3.4 Post-treatment care

When the injection is completed, the treated area may be gently molded or massaged for any irregularities.

5.3.5 Recording instructions

The following information for the injection should be recorded in the eCRF:

- Date and time of completed injection
- Lot number
- Number of syringes used
- Volume of study product used per right and left temple

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[Redacted]

- Injection method and depth of injection
- Additional local or topical anesthesia used

## 5.4 Supplies management

### 5.4.1 Product accountability

The study product *Restylane Contour* will be released to the Investigator or his/her authorized designee after study approvals have been received from the FDA and IRB, and the Clinical Trial Agreement (CTA) has been signed by all parties.

The Investigator must ensure that the study products are kept in a secure location (separated from commercial inventory) with access limited to those authorized by the Investigator.

The study products must be traceable from the manufacturer to their use in subjects until return or disposal. It is therefore important that the Investigator maintain accurate product accountability records, i.e., documentation of the physical location of all study products, deliveries, and return of study products between the Sponsor and the Investigator, and documentation of administration of product to the subject.

Any malfunctioning study product should be reported as described in Section 7.13.4.

Products deliberately or accidentally destroyed during shipment or at a study center should be accounted for and documented. Used syringes, needles, cannulas and any unused material must be discarded immediately after the treatment session and must not be reused due to risk for contamination of the unused material and the associated risks including infections according to standard procedures at the study center. Disposal of hazardous material, i.e., syringes, needles and cannulas must conform to applicable laws and regulations. The study products must not be used outside the study.

### 5.4.2 Storage of study product

*Restylane Contour* should be stored at a temperature of up to 25°C/77°F, protected from sunlight and freezing. Refrigeration is not required.

Detailed product information is provided in the study specific IFU.

### 5.4.3 Dispensing and return

The treatment will be administered by the Treating Investigator at the study center and be documented in the accountability records.

When the study is completed, all unused or expired study products at each study center should be returned to the Sponsor representative for destruction, or to be destroyed locally at the study center if documented as agreed with Sponsor.

### 5.4.4 Treatment compliance

The study product will be administered by the Treating Investigator at the study centers and the administration will be recorded in the eCRF.

## 5.5 Randomization

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At least **C** subjects will be FST IV-VI.

Before starting the study, a computer-generated randomization list will be prepared under the supervision of a designated biostatistician from the Sponsor.

The randomization will be stratified by 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.

Randomization will be performed using an Interactive Response System by assigning each subject to treatment with *Restylane Contour* (Treatment group) or to no treatment (Control group) according to the randomization list. Randomization numbers will be allocated in ascending sequential order to each subject.

## 5.6 Blinding

The Treating Investigator will not be blinded to study treatments.

A Blinded Evaluator, to whom randomization and treatment are concealed, will conduct the blinded assessments. As much as possible the same Blinding Evaluator should assess a particular subject throughout the study.

The Blinded Evaluator is not allowed to be present during the injections or to discuss treatments with the Treating Investigator or subjects. All documents with information regarding study products and randomization assignment should be kept in a separate binder not available to the Blinded Evaluator.

Safety assessment will be performed by non-blinded personnel.

### 5.6.1 Verification of blinding

Not applicable as the Treating Investigator is not blinded to treatment.

The Blinded Evaluator is not allowed to be present during the injections or to discuss treatments with the Treating Investigator or subjects. All documents with information regarding study products and randomization assignment should be kept in a separate binder not available to the Blinded Evaluator.

### 5.6.2 Emergency unblinding

Not applicable as the Treating Investigator is not blinded to treatment.

## 5.7 Post-trial provisions

In time, the study product will be degraded in the body and additional treatments will be necessary to maintain the aesthetic result.

After the final study visit the Sponsor will not supply any more treatments to the subjects, even if the result does not persist.

## 6. EFFECTIVENESS ASSESSMENTS

The methods for collecting effectiveness data are described in the following sections.

To minimize inter-observer variability, every effort should be made to ensure that preferably the same individual who made the initial baseline determinations completes all corresponding follow-up evaluations.

Assessments should be performed according to the time points indicated in the schedules of events (Table 1 and Table 2) and recorded in the eCRF.

### 6.1 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

Site personnel will be thoroughly trained in the photographic equipment and techniques before study start.

Camera equipment will be provided by the Sponsor, or their designee and standardized photographs shall be achieved. Further details regarding photography procedure will be specified in a separate user guide.

### 6.2 Independent Photographic Reviewer assessment of improvement

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

CCI

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

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An improved subject is defined as CCI

### 6.3 Galderma Temple Volume Deficit Scale

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

The Treating Investigator will perform GTVDS assessment:

- At screening and baseline for all subjects

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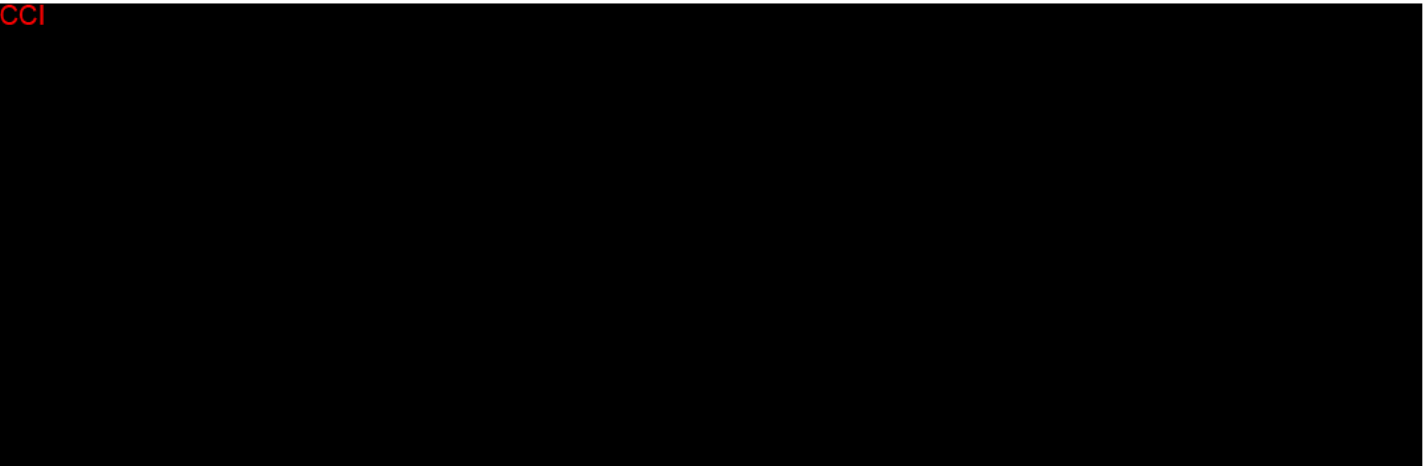
The Blinded Evaluator will perform GTVDS assessment:

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Figure 2 Galderma Temple Volume Deficit Scale (GTVDS)

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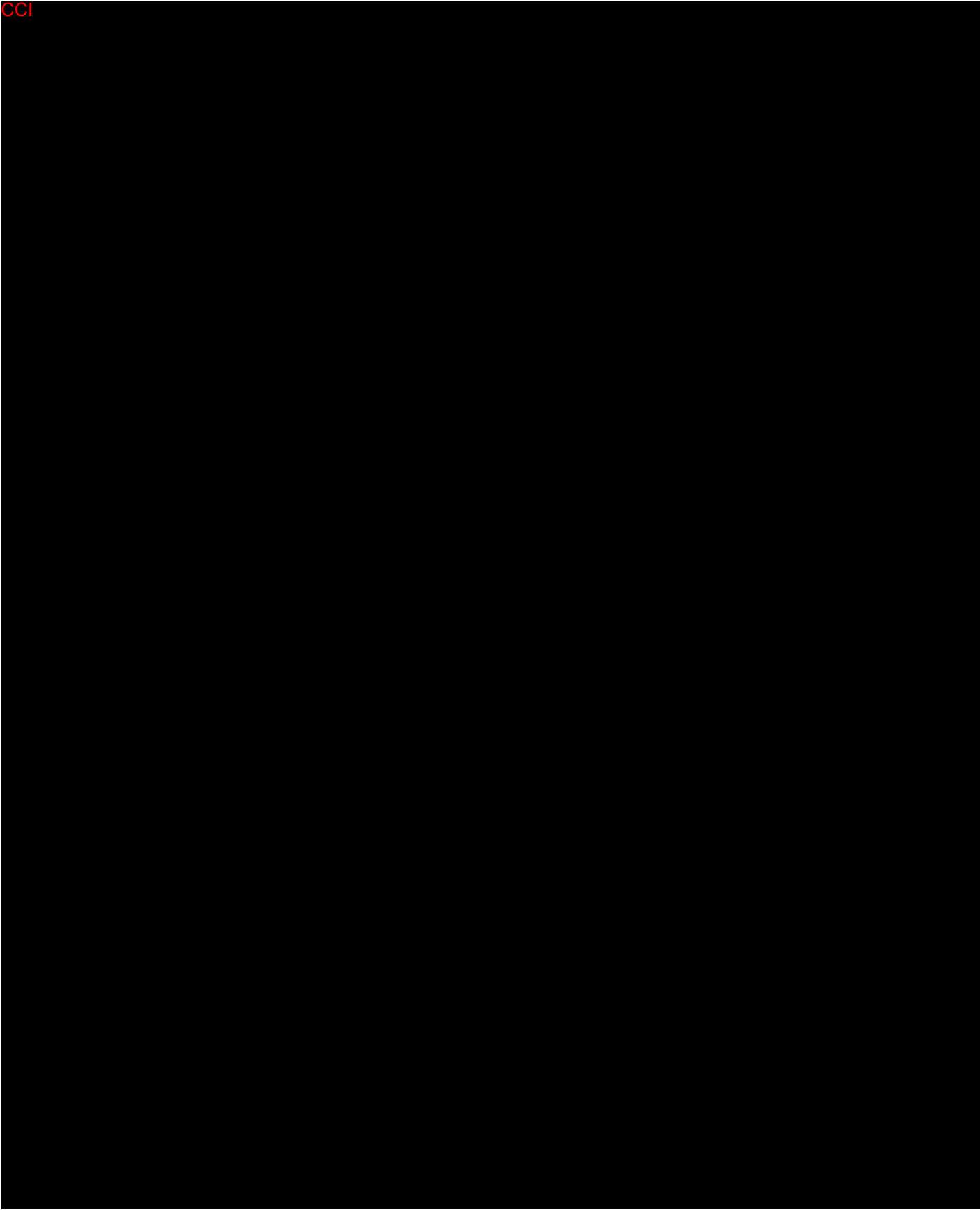
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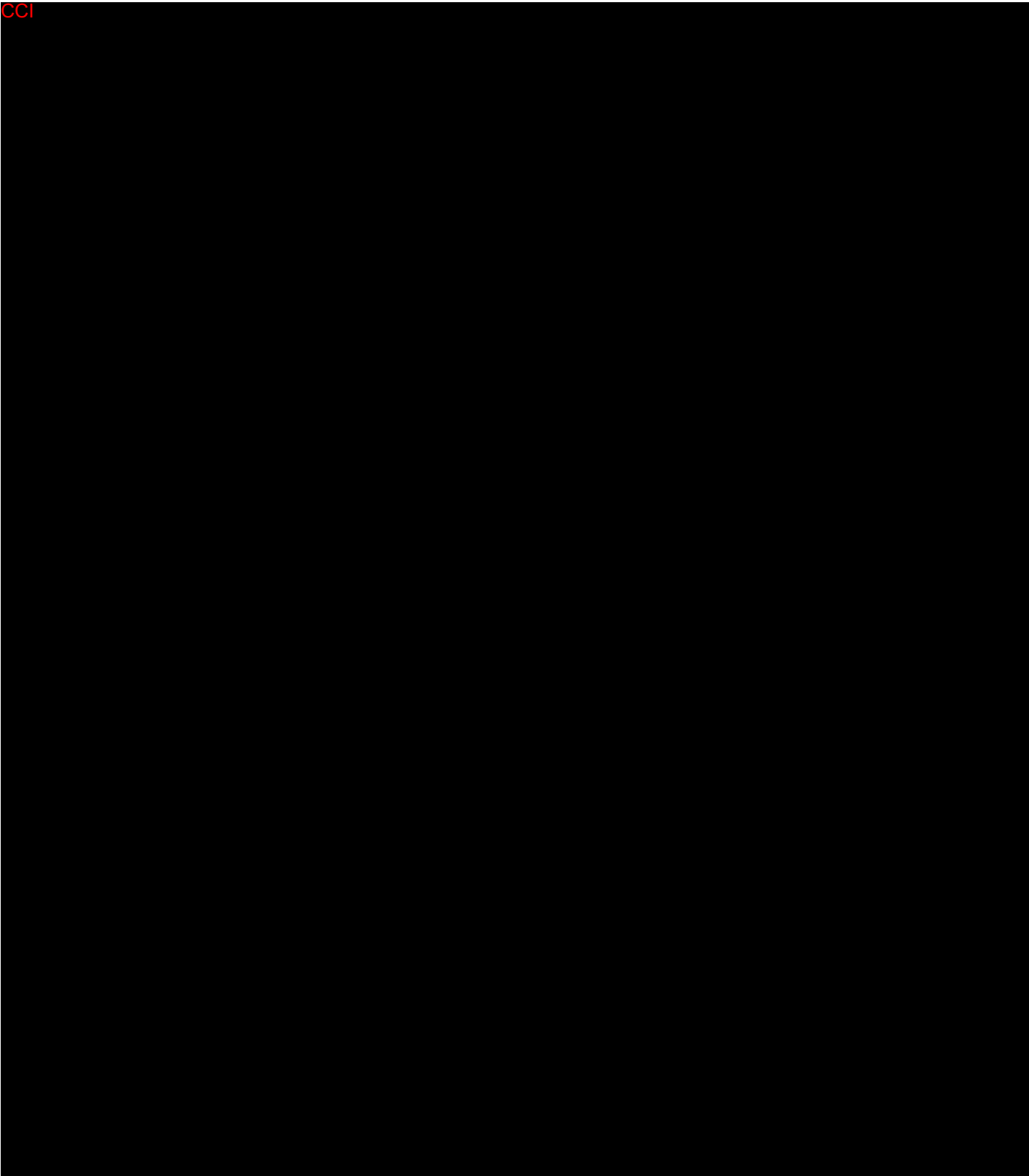


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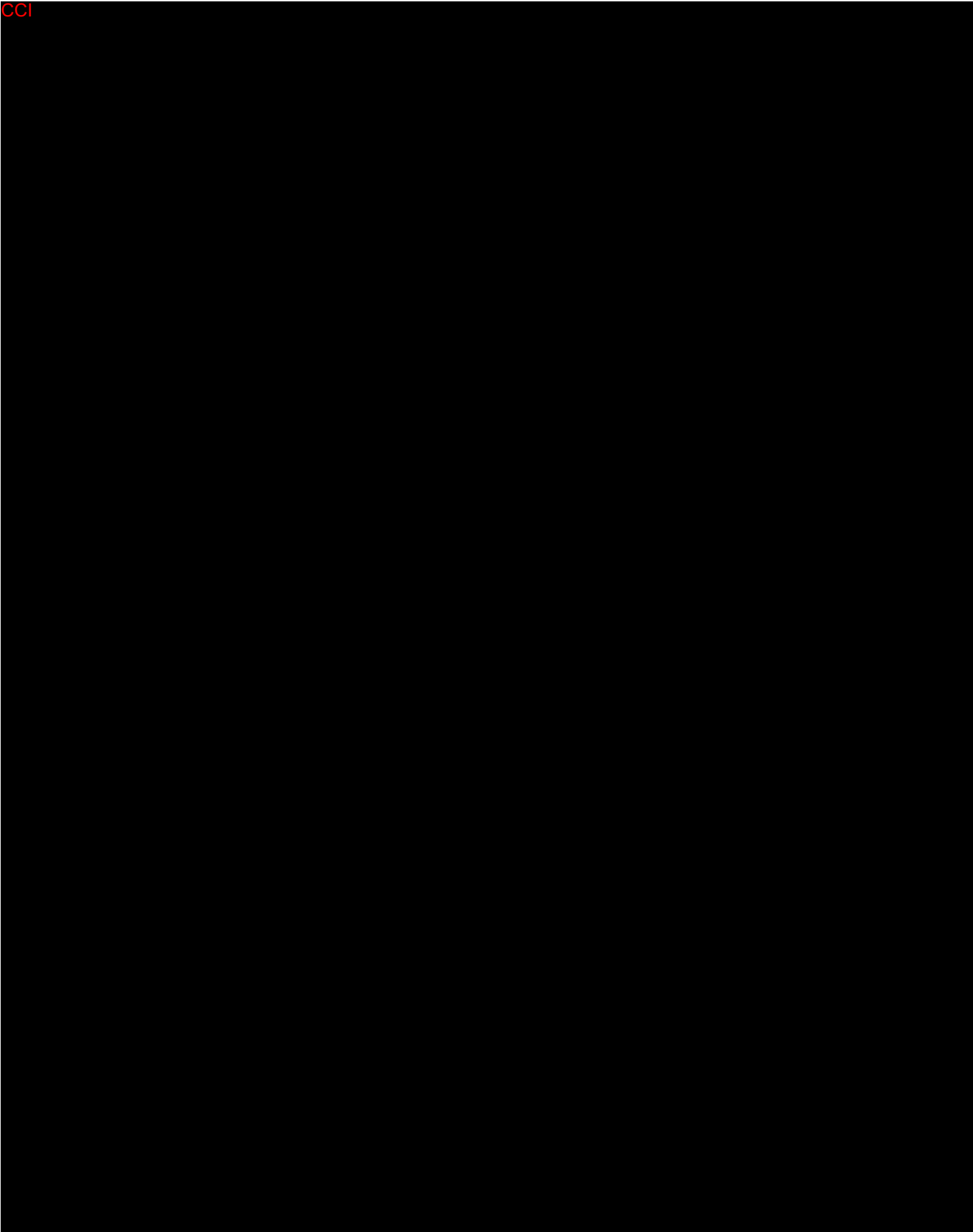
**7. SAFETY ASSESSMENTS**

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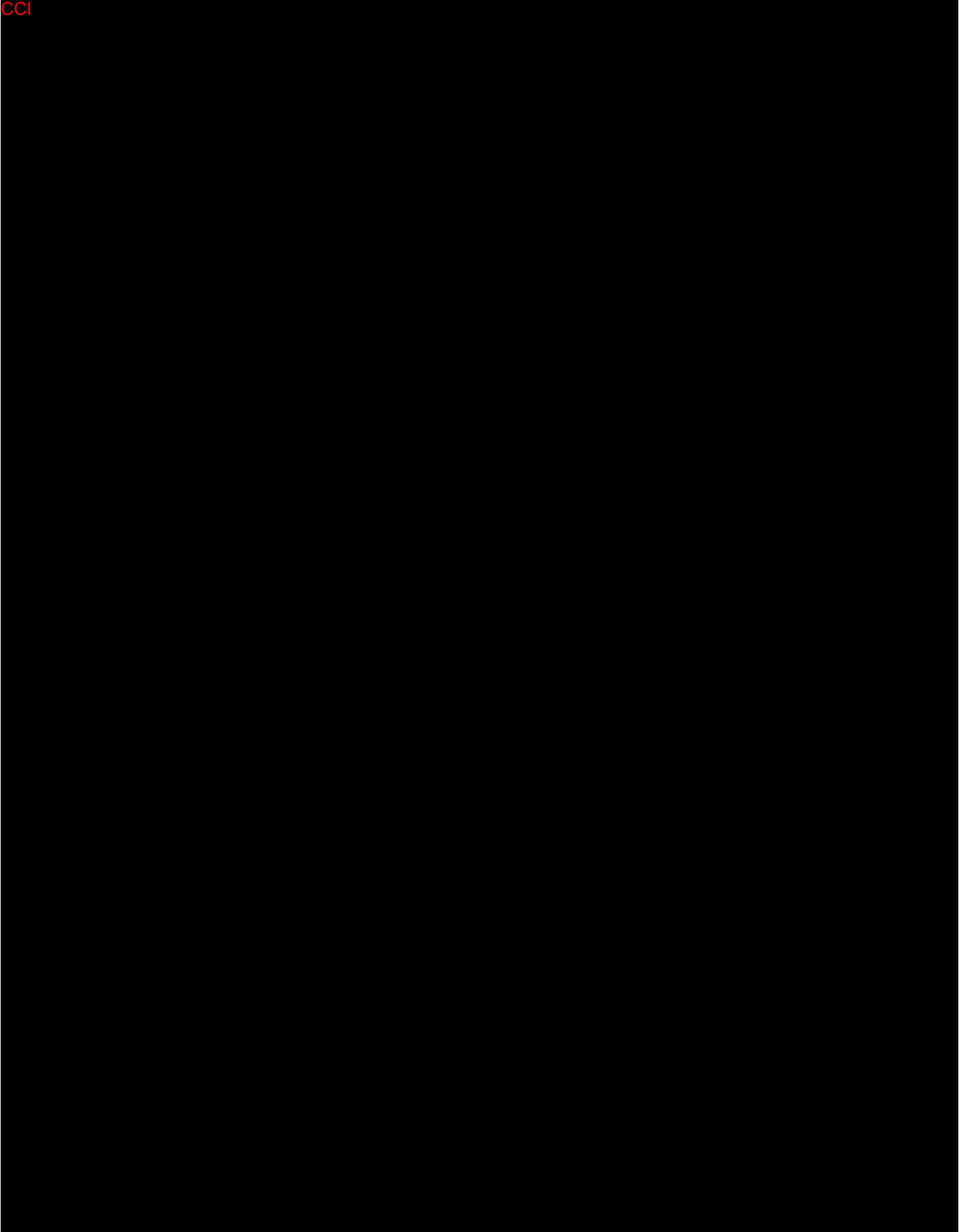
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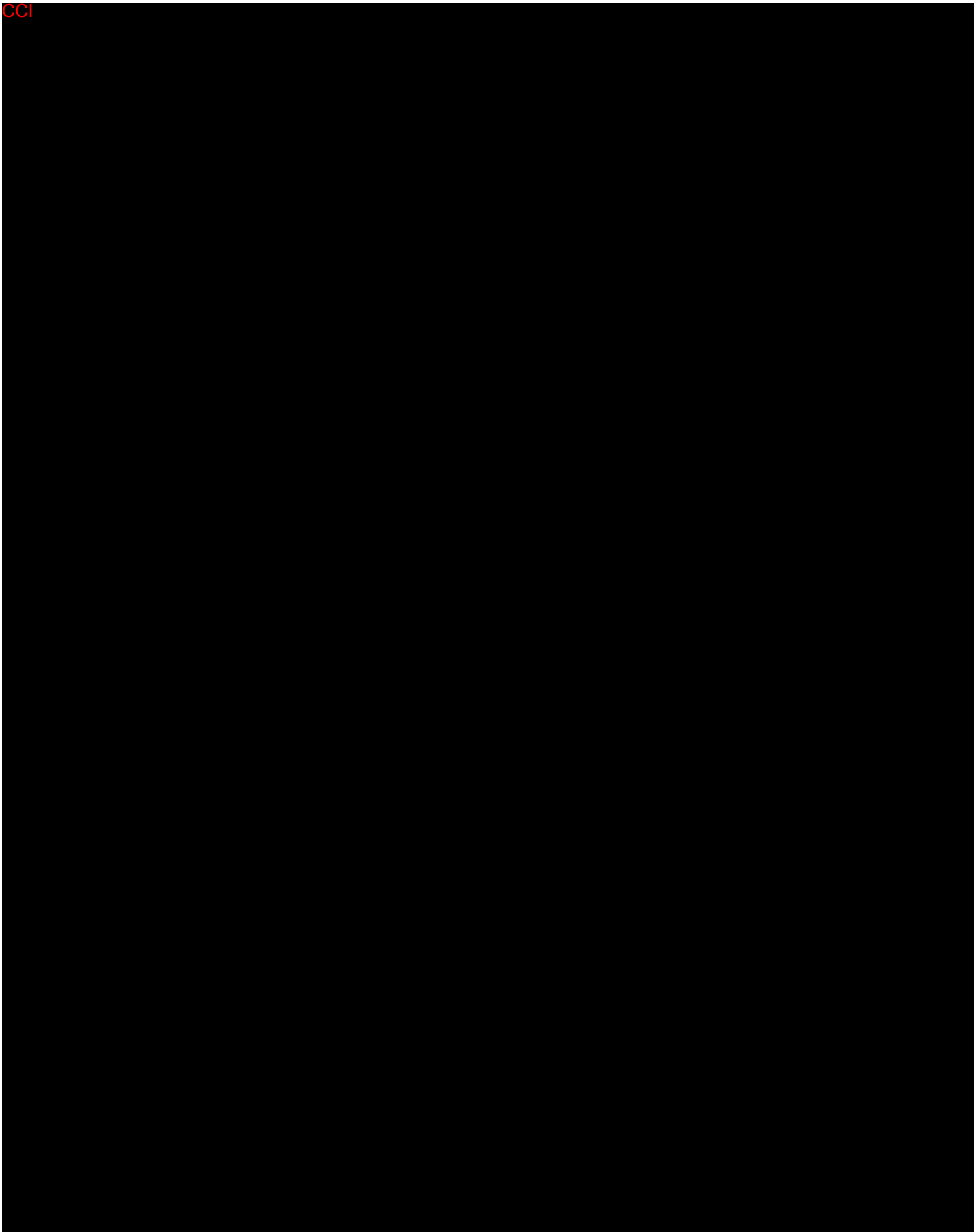


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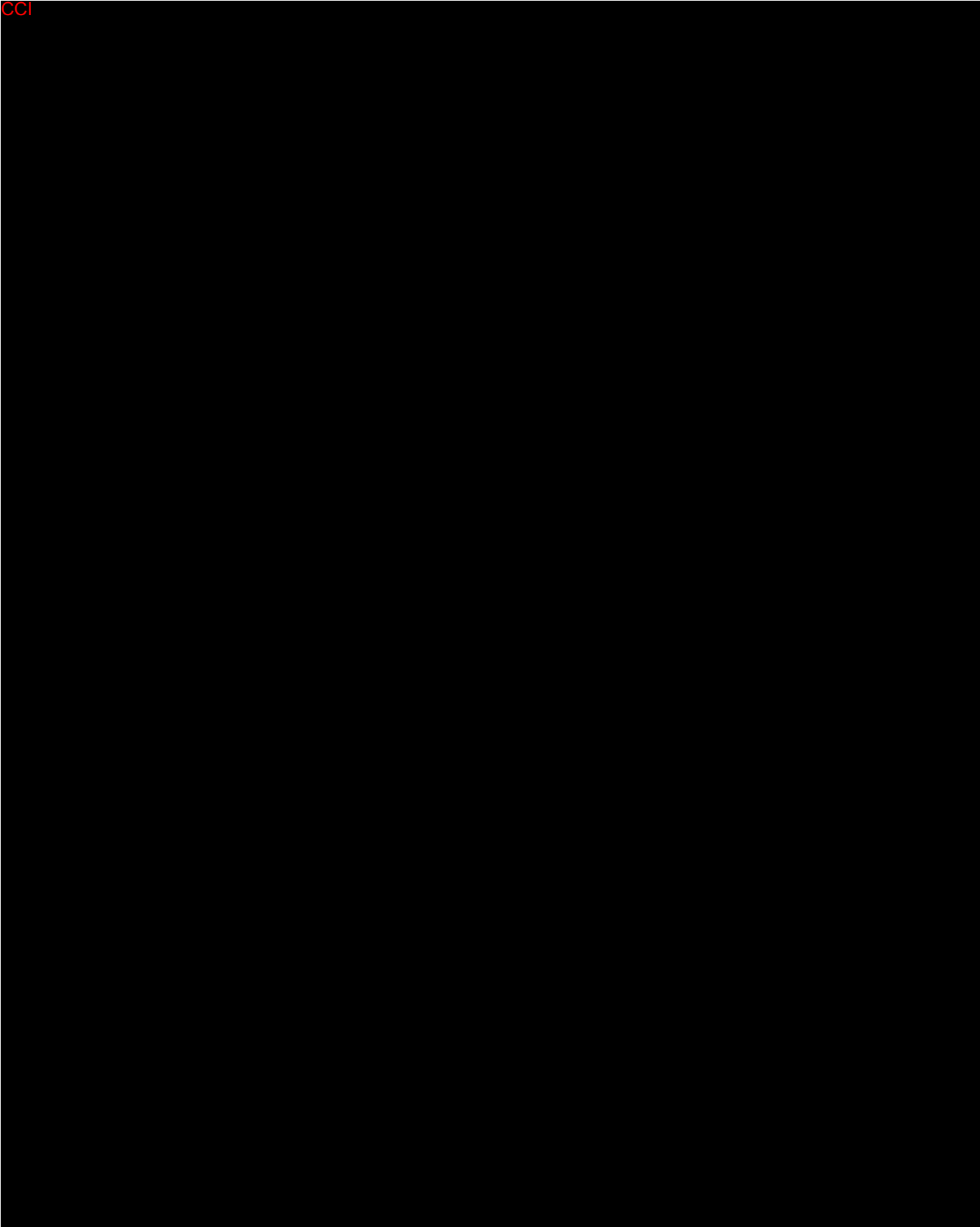


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## 7.8 Pregnancy testing

For all women of childbearing potential, including those currently using contraception, a UPT is required prior to receiving any study treatment (at screening, baseline, and optional touch-up for the Treatment group and at 3 months optional treatment for the Control group). The test result must be negative for the subject to receive any treatment with the study product. The test result will be documented in the subject's file and eCRF.

## 7.9 Adverse events


The definition of an AE (Medical Devices Regulation [MDR] article 2[57]): An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons<sup>3</sup>, in the context of a clinical investigation, whether or not related to the Investigational device.

This definition includes:

- events related to the investigational product or the reference product

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<sup>3</sup> For users or other persons, this definition is restricted to events related to the investigational product.

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- b) events related to the procedures involved
- c) events that are anticipated as well as unanticipated

The AE reporting on each subject shall 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 shall continue during each follow-up visit (including telephone contacts and extra visits between planned visits) until the last scheduled visit in the study.

All AEs, non-serious as well as serious AEs (SAEs), are to be reported as AE in the eCRF.

A request for additional information from the Sponsor/Contract Research Organization (CRO) Medical Expert(s) for non-serious AEs, should be collected and answered using the Adverse Event Clarification Form.

#### 7.9.1 Anticipated adverse events

Information regarding anticipated AEs for *Restylane Contour* is included in the study specific IFU.

Further, the ROPI for *Restylane Contour* includes information from clinical studies in the temple area with *Restylane Contour* and similar products, spontaneously reported cumulative post-market reporting, and available clinical data from publications with HA fillers in the midface area.

#### 7.9.2 Unanticipated adverse device effect

An unanticipated adverse device effect (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, intensity, or degree of incidence in the protocol/investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (see FDA regulation CFR 812.3 [s]).

The UADEs should be reported to the CRO and IRB/FDA in accordance with Section 7.13.3.

#### 7.9.3 Assessment of intensity

Intensity will be recorded for each reported AE. The following definitions of intensity are to be used:

**Mild:** Awareness of symptoms or signs, but easily tolerated (acceptable)

**Moderate:** Enough discomfort to interfere with usual activity (disturbing)

**Severe:** Incapacity to work or to do usual activity (unacceptable)

If the intensity changes within one day, the maximum intensity of the AE during that day shall be recorded.


#### 7.9.4 Assessment of causality

Each AE shall be assessed by the Investigator for causal relationship with the study product and its use (the injection procedure) and for seriousness (Yes or No) of the event.

A two-point scale (Yes or No response) shall be used for the causality assessments. The Investigators shall be asked to indicate a response to each of the following questions in the eCRF:

- “Do you consider that there is a reasonable possibility that the event may have been caused by the study product?”, and

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- “Do you consider that there is a reasonable possibility that the event may have been caused by the study product injection procedure?”

If any of these questions is answered Yes, the AE is considered related.

Each AE will also be assessed for causal relationship and seriousness by the Sponsor, in order to fulfil regulatory requirements.

In addition, each SAE will be classified by both the Investigator and Sponsor separately, according to four different levels of causality:

1. **Not related:** Relationship to the device, comparator or procedures can be excluded when:
  - the event has no temporal relationship with the use of the investigational device, or the procedures related to investigational device;
  - the SAE does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
  - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the SAE;
  - the event involves a body-site or an organ that cannot be affected by the device or procedure;
  - the SAE can be attributed to another cause (e.g., an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment or other risk factors);
  - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable.

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the SAE.

2. **Possible:** The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
3. **Probable:** The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.
4. **Causal relationship:** the SAE is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:
  - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
  - the event has a temporal relationship with investigational device use/application or procedures;
  - the event involves a body-site or organ that
    - the investigational device or procedures are applied to;

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- the investigational device or procedures have an effect on;
- the SAE follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the SAE (when clinically feasible);
- other possible causes (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable.

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the SAE.

#### 7.9.5 Action taken

The action taken (none, medication treatment, non-pharmacological treatment, or other procedures/tests, subject withdrawn) for an AE should be recorded in the eCRF.

The study related medical care provided to the subjects during the study is the responsibility of an appropriately qualified medical doctor (i.e., the Principal Investigator [PI]) or, where appropriate any other person entitled by national law to provide the relevant subject care.

#### 7.9.6 Follow-up of adverse events

##### 7.9.6.1 Follow-up of unresolved events ongoing at termination of the study

All serious as well as non-serious AEs with a probable, possible or causal relationship to the study product or treatment procedure and ongoing at study end/or ongoing when a subject terminates the study participation early/or ongoing if the study is temporarily halted, shall be followed up after the subject's participation in the study is over.

Such events shall be followed-up until resolved, assessed as chronic or stable, or subject is lost to follow-up. Final outcome after the end of the study shall be reported on the AE Follow-up form.

Other AEs will be monitored until the last visit if they have not resolved or reached a stable condition.

##### 7.9.6.2 Follow-up of events occurring after subject termination of the study

All AEs with a causal relationship to the study product or treatment procedure that the Investigator becomes aware of, serious as well as non-serious, with onset after the study termination (subject's last study visit) shall be reported to the Sponsor by email to:

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The Investigator shall follow the subject until the event is resolved.

#### 7.9.7 Documentation and recording instructions

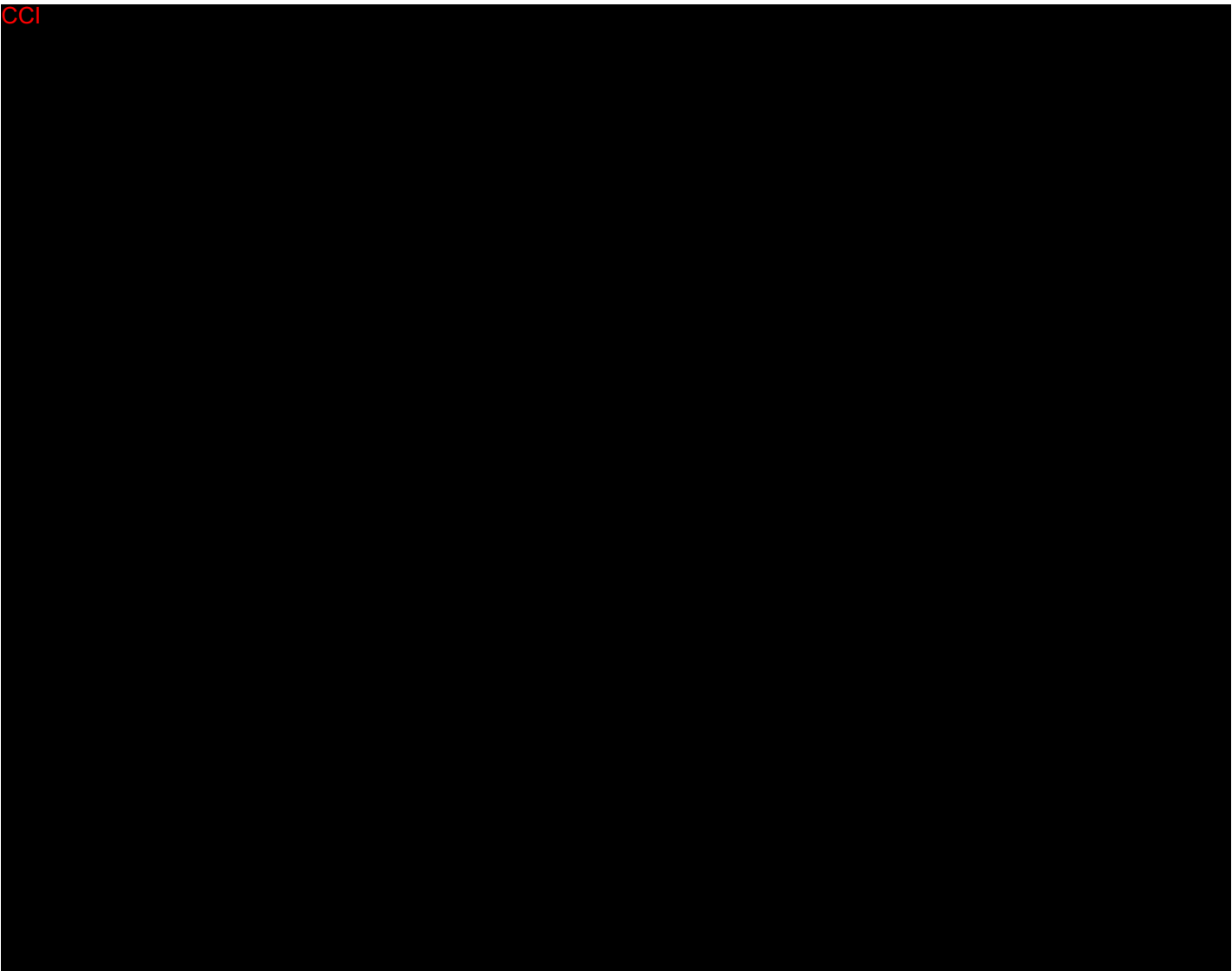
Investigators, or other study center personnel, shall record all AEs in the eCRF, including:

- a) Event term (recorded in standard medical terminology and avoiding abbreviations)

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- b) Affected area
  - c) Start date (first day with symptoms)
  - d) Stop date (last day with symptoms)
  - e) Intensity (mild, moderate, or severe, according to definition in Section 7.9.3)
  - f) Seriousness (serious or not serious, according to definition in Section 7.11)
  - g) Relationship to study product or study product injection procedure (According to definition in Section 7.9.4)
  - h) Action taken (none, medication treatment, non-pharmacological treatment, or other procedures/tests, subject withdrawn)
  - i) Outcome of the AE (ongoing, resolved, resolved with sequelae, death) at the end of the study)
- The AE form/module in the eCRF must be signed and dated by the Investigator.



### 7.11 Serious adverse event

The definition of a SAE (MDR article 2[58]). A SAE is any AE that:

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- a) led to death,
- b) led to serious deterioration in the health of the subject, that either resulted in
  - 1. a life-threatening<sup>4</sup> illness or injury, or
  - 2. a permanent impairment of a body structure or body function, or
  - 3. hospitalization or prolonged hospitalization<sup>5</sup>, or
  - 4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
  - 5. chronic disease
- c) led to fetal distress, fetal death, or a congenital physical or mental impairment or birth defect

In cases of doubt, whether an AE fulfils a serious criterion or not, there should be a predisposition to report as a SAE rather than not report as such. When an AE is related to a device deficiency, including technical device malfunction, the AE shall be recorded on the AE form/module in the eCRF, and the technical complaint shall be reported separately on the clinical study complaint form.

Also see SAE reporting procedures in Section 7.13.2.

## 7.12 Device deficiencies

A device deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety<sup>6</sup>, or performance.

Note: Device deficiencies include malfunctions, user errors or inadequate information supplied by the manufacturer.

Also see device deficiency reporting procedures in Section 7.13.4.

## 7.13 Safety reporting procedures and timelines

Safety evaluations for this study include an interview of the subjects at each visit to obtain information about any medical occurrence that meets the definition of an AE. Each subject should be questioned about AEs at each study visit following the baseline visit. An event that occurs after the subject signs the ICF but before enrollment (i.e., randomized and/or treated) will be recorded in the subject's medical history. The question about AEs should be asked: "Since your last clinical visit have you had any health problems?"

Information on AEs can also be obtained from signs and symptoms detected during each examination by the Investigator or designee, which should include visual inspection of the treatment area or from a laboratory test, subject diaries, or spontaneous reports from the subjects or their relatives.

<sup>4</sup> The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (Source: ICH-E2A clinical safety data management: definitions and standards for expedited reporting).

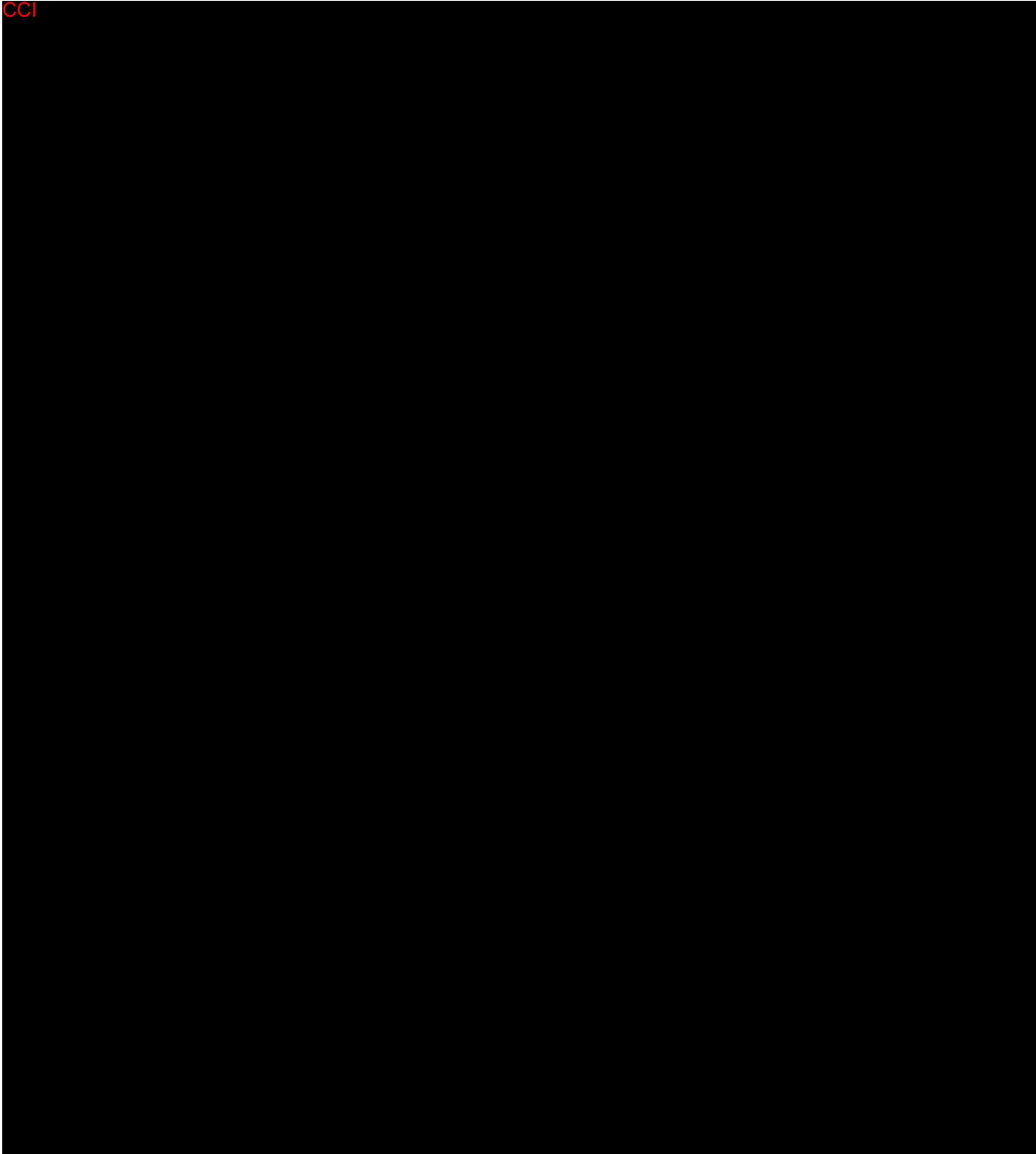
<sup>5</sup> Planned hospitalization for a pre-existing condition, or a procedure required by the CSP, without serious deterioration in health, is not considered a SAE (Source: ISO14155:2011).


<sup>6</sup> Inadequacy of device safety refers to properties of the device which could have or have led to an AE.

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The AEs must be documented in the source document and eCRF without regard for cause or relation to investigational product. If in the process of the interview, additional information regarding medical history or pre-planned medical or surgical procedures is revealed, it must be documented in the source document(s) and eCRF.

It is the responsibility of the Investigator to determine intensity of the AE and relatedness of the event to the study product.



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### 7.13.2 Reporting of serious adverse events

The Investigator shall **report any SAE** (see Section 7.11) to the CRO **immediately but not later than 24 hours of awareness of the event**. This initial report can be made via e-mail or submitted via the eCRF.

In case of difficulty to obtain all the required information within 24 hours, an initial report can be submitted, with the following information as a minimum, irrespective of whether some of it is regarded as preliminary:

- Subject identification (age, gender, initials, subject number)
- AE description
- Date when AE occurred
- Name of PI
- Name of study product

Follow-up information and data missing in the initial SAE reporting shall be gathered as soon as possible and reported to the CRO immediately but not later than 24 hours of awareness of the new data. Complete and adequate information on each SAE is required. All attempts to obtain this information, including dates for follow-up activities, must be documented by the Investigator.

Supporting documentation to be provided with the SAE report:


- Concomitant therapies form/list
- AE form/list
- Medical history form/list
- Any other relevant supporting documentation (e.g., hospital notes, death certificate, autopsy reports etc.)
- Study treatment records from eCRF pages including information for: date and time of injection, lot number, number of syringes and volume used, needle or cannula used per treatment area, injection technique and depth of injection, additional local or topical anesthesia used.

**E-mail** (preferred) for SAE reporting:

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**E-fax** number for SAE reporting:

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The SAE form must be signed and dated by the Investigator. If the initial 24-hour SAE report does not contain full information or if it is made without using the SAE form the fully completed and signed SAE form shall be e-mailed to the Sponsor. A copy of the fully completed SAE form shall be kept at the study center. The Blinded Evaluator should perform live effectiveness assessments only and not discuss the treatment or any potential AE with the subject.

In addition, the PI shall report SAEs to the responsible IRB without undue delay. The PI is responsible for checking what reporting procedures are applicable for his/her IRB regarding SAEs and final report of the outcome of the study and to comply with such reporting procedures during the study period.

The Sponsor is responsible for reporting to the RA, if applicable and according to national regulations.

### 7.13.3 Reporting of unanticipated adverse device effects

An Investigator shall prepare and submit a complete and accurate report to the CRO for contact details see Section 7.13.2, and to the reviewing IRB on a suspected UADE as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect, in accordance with FDA regulation CFR 812.150.

Upon receipt of the report, the Sponsor will review the information provided, assess the event, and, if deemed reportable, report to FDA within timelines specified in FDA regulation CFR 812.150.

### 7.13.4 Reporting of device deficiencies

When a device deficiency is discovered, Part A of the Clinical Study Complaint Form shall be completed by the Investigator. The type of complaint shall be described and injury to the subject or user or unintended exposure to the study product shall be reported as applicable. If an injury has occurred, an AE or an SAE form shall be completed as applicable (refer to Sections 7.9 and Section 7.13.2). If no SAE was experienced as a result of the device deficiency, the Investigator shall assess whether or not the device deficiency could have led to an SAE if:

- Suitable action had not been taken,
- Intervention had not been made or,
- Circumstances had been less fortunate

In Part B of the Clinical Study Complaint Form the CRO will make the same assessment.

The Investigator shall provide the completed Clinical Study Complaint Form to the CRO.

**E-mail** for device deficiencies reporting:

CCI

**Fax** number for device deficiencies reporting:

A device deficiency that led to a SAE and any device deficiency that could have led to a SAE shall be reported to the Sponsor/CRO within 24 hours after the Investigator's awareness (for contact information, see Section 7.13.2).

If the Investigator or the Sponsor assesses that the device deficiency could have led to a SAE, the Sponsor is responsible for reporting the device deficiency to RA and the PI is responsible for reporting it to the IRB.

The deficient study product shall be kept by the study center until the Sponsor has confirmed whether the product shall be returned to Sponsor for further study or if it can be destroyed at the study center.

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### 7.13.5 Pregnancy

Pregnancy itself is not regarded as an AE.

If there is a pregnancy during the study period, the subject must be withdrawn from any following study treatment but should continue to be followed within the study and the outcome of pregnancy must be reported even if the delivery occurs after study completion.

A pregnancy confirmed during the study period must be reported by the Investigator on a Pregnancy Report Form immediately upon acknowledge and be submitted to the CRO according to contact details specified in Section 7.13.2. The report can be prospective or retrospective. Follow-up shall be conducted to obtain outcome information on all prospective reports.

Cases that led to fetal distress, fetal death or a congenital abnormality or birth defect are to be regarded as SAEs and shall be reported on the Exposure *in utero* Report Form to the Sponsor immediately but no later than 24 hours after the Investigator's awareness. These events shall be handled as SAEs during data processing. Other complications during the pregnancy that are related to the pregnant woman and fulfils any serious criteria, such as pre-eclampsia requiring hospitalization, shall be reported, and handled as SAEs. Elective abortions without complications shall not be reported as AEs.

### 7.14 Stopping rules

Enrollment and treatment in the study will be temporarily halted if a SAE occurs for the following:

- any unanticipated SAE which is possibly related to the study device or procedure including but not limited to a CCI

The SAE will be investigated by the Sponsor. If the Sponsor's investigation concludes the SAE:

- was unanticipated,
- directly related to the investigational device or device injection procedure, and
- presents an unreasonable risk to study subjects,

the study will be terminated, and the Investigators notified. The IRB and RA will also be notified if the study is prematurely terminated due to safety concerns.

If the SAE does not meet the above criteria, then enrollment in the study will continue provided all other safety criteria have been met.

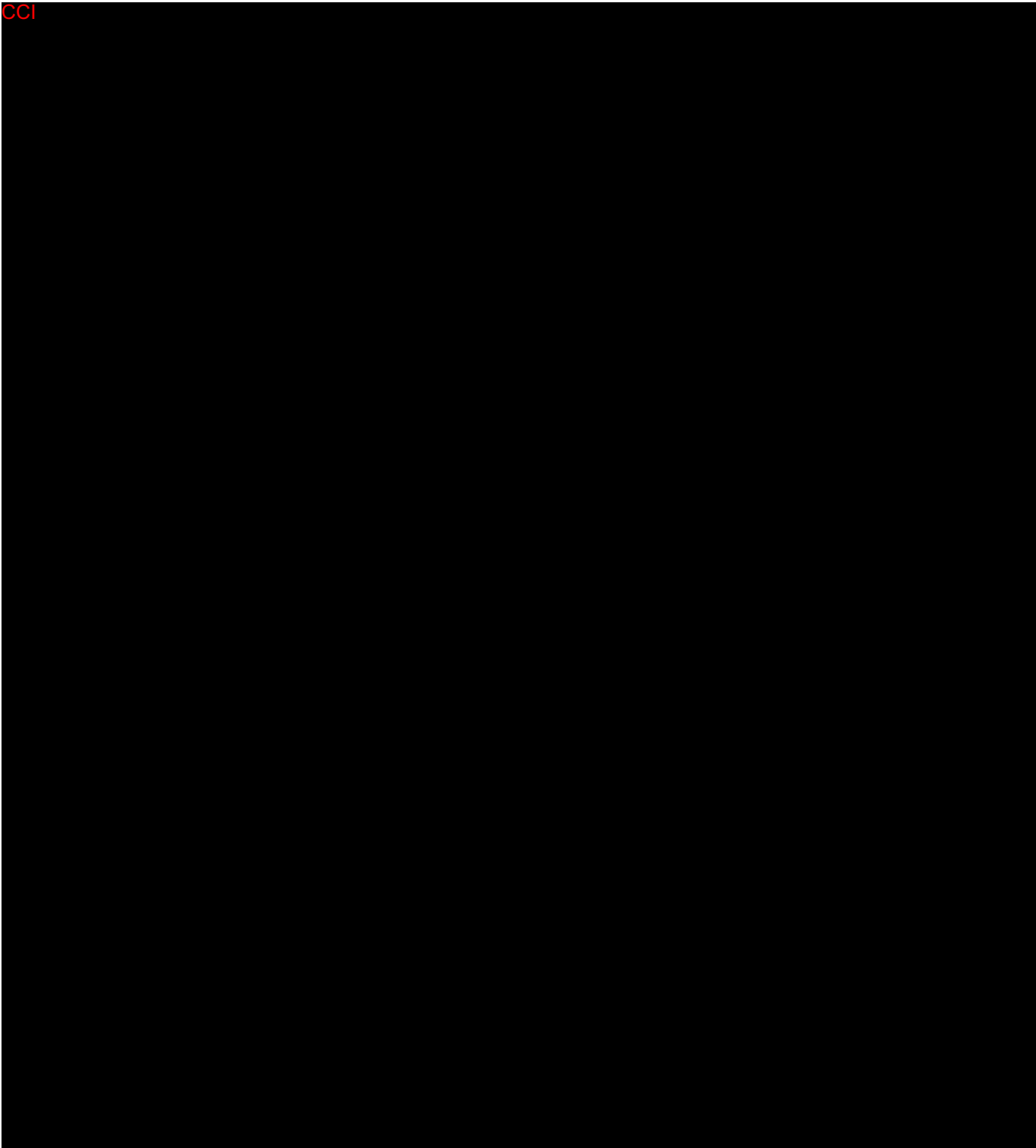
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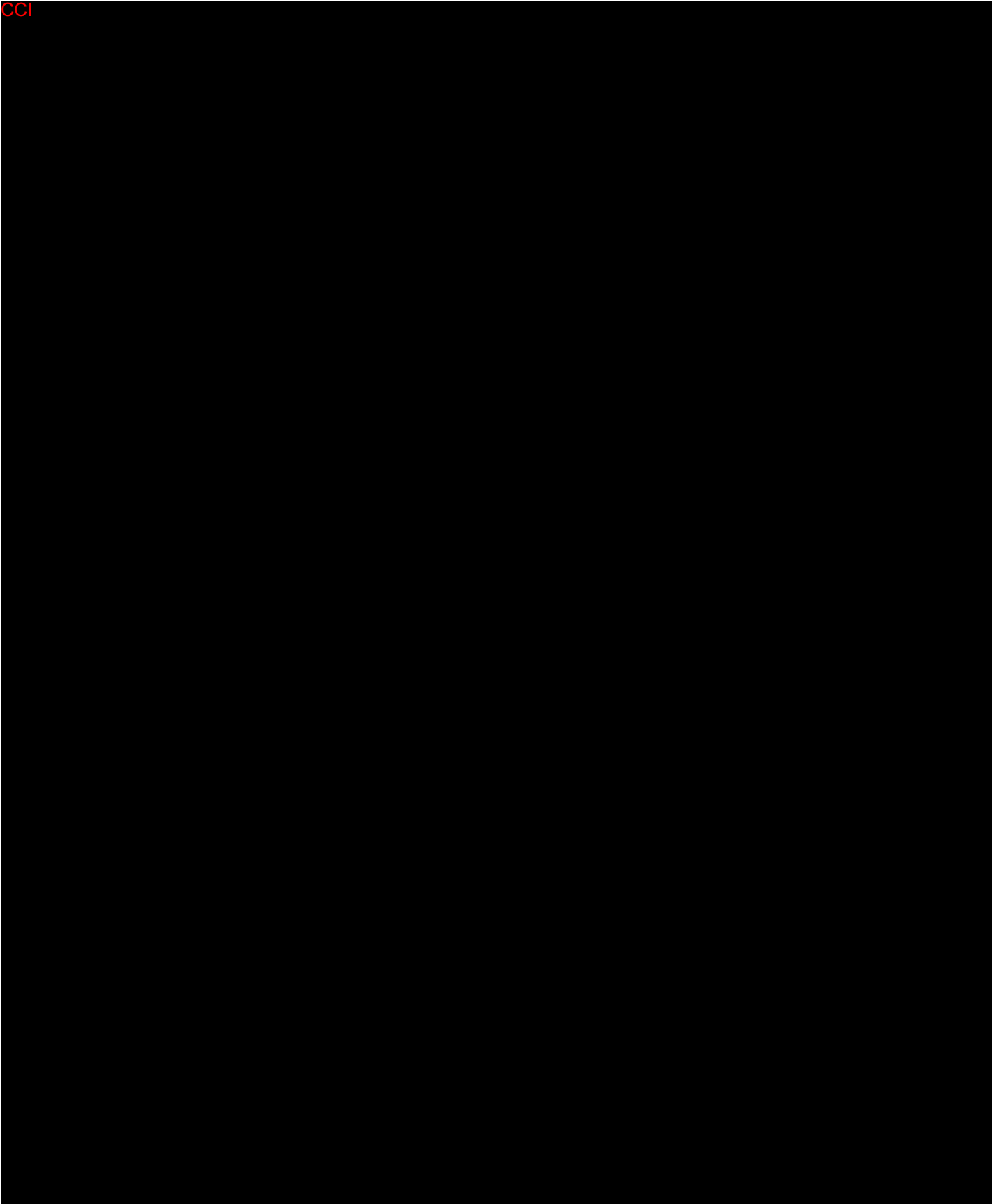
<sup>7</sup> The screening and baseline visits can be combined.

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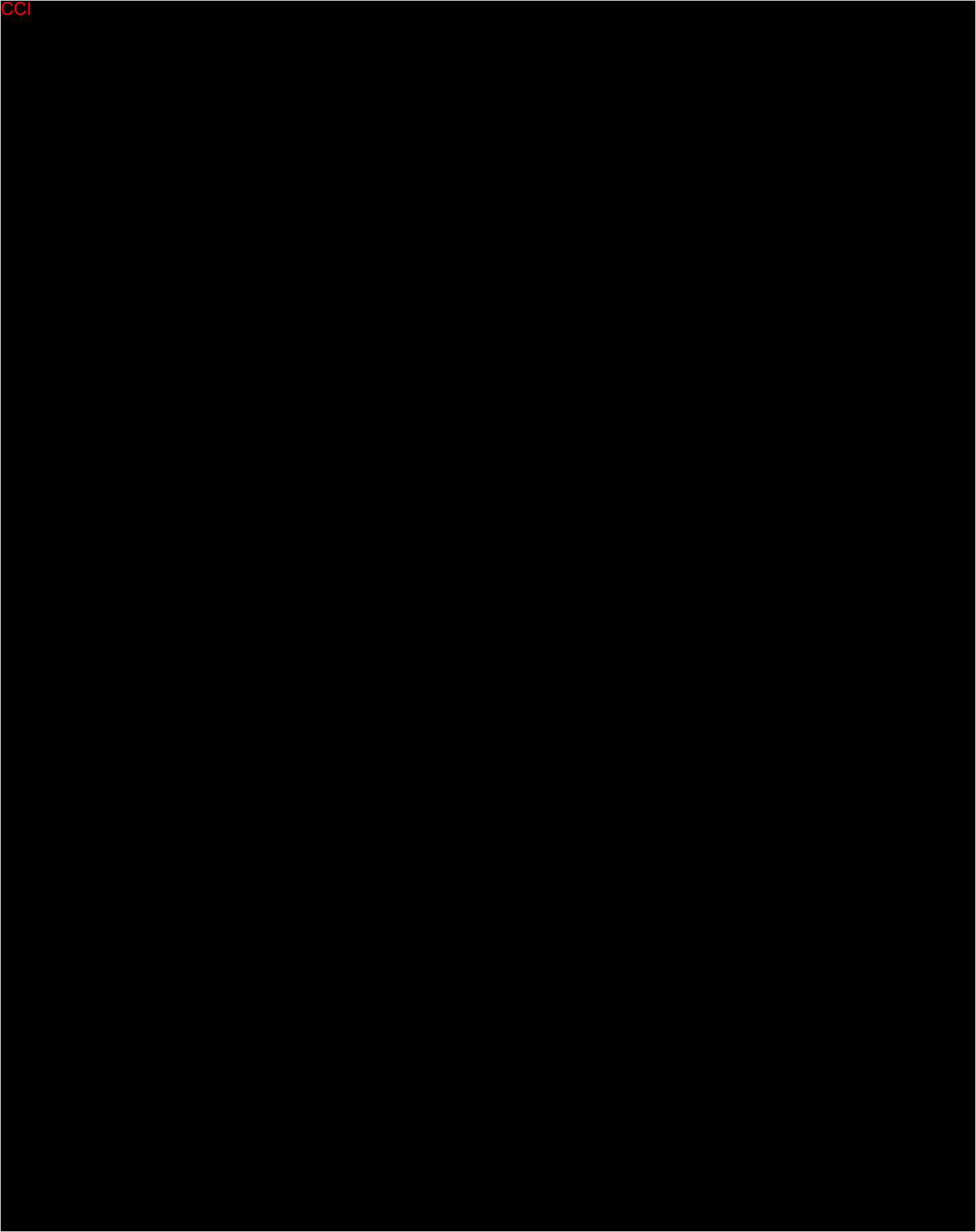


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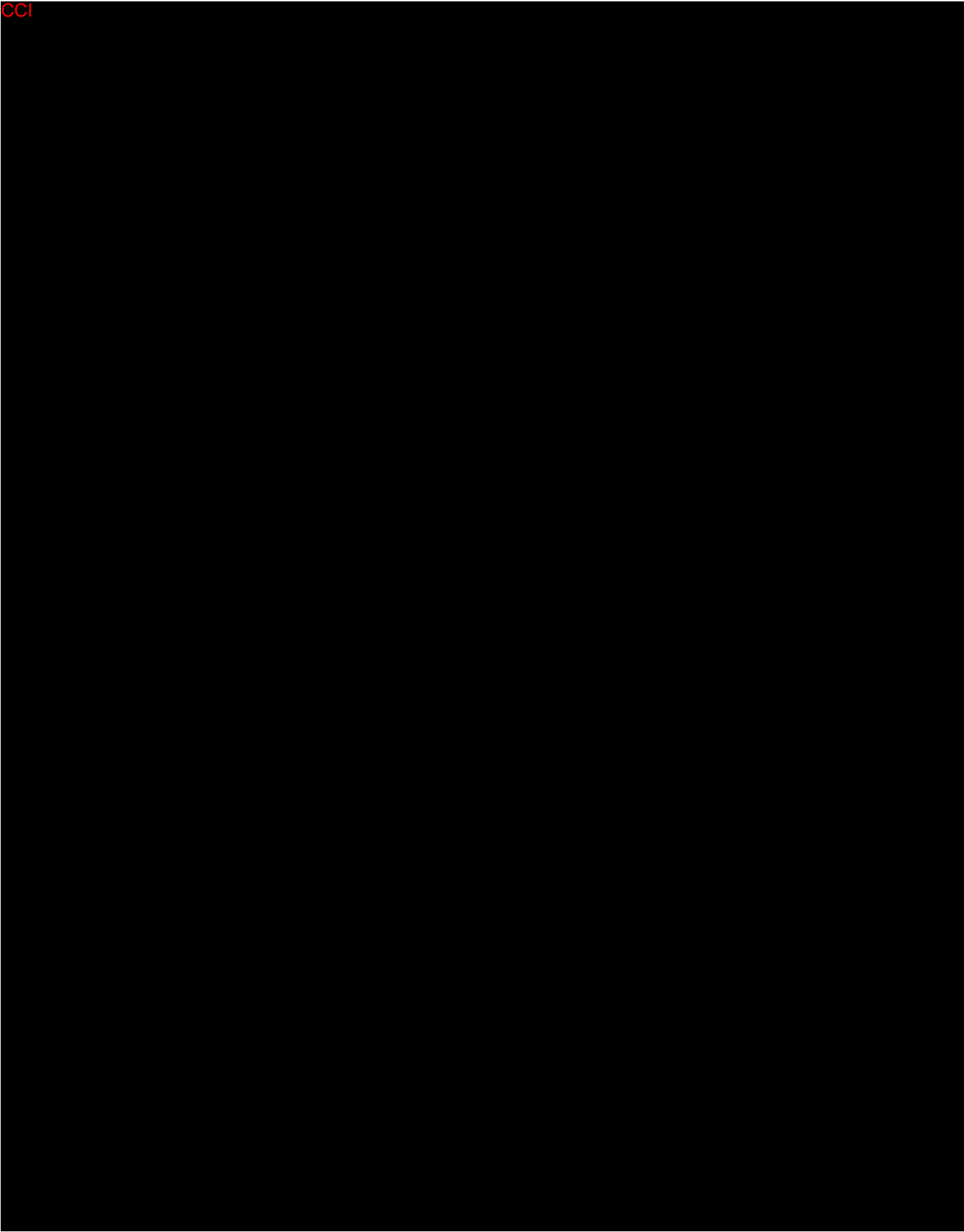


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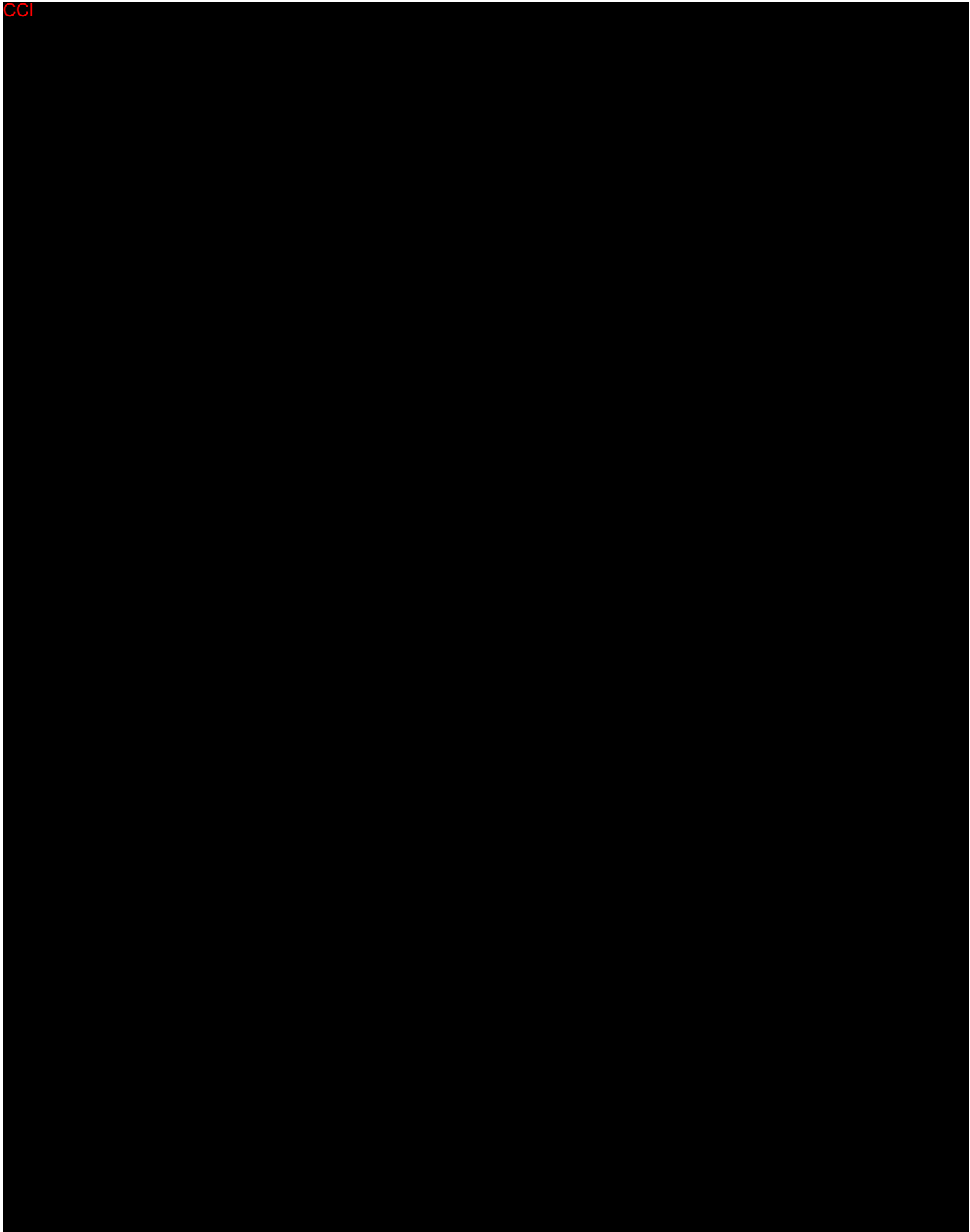
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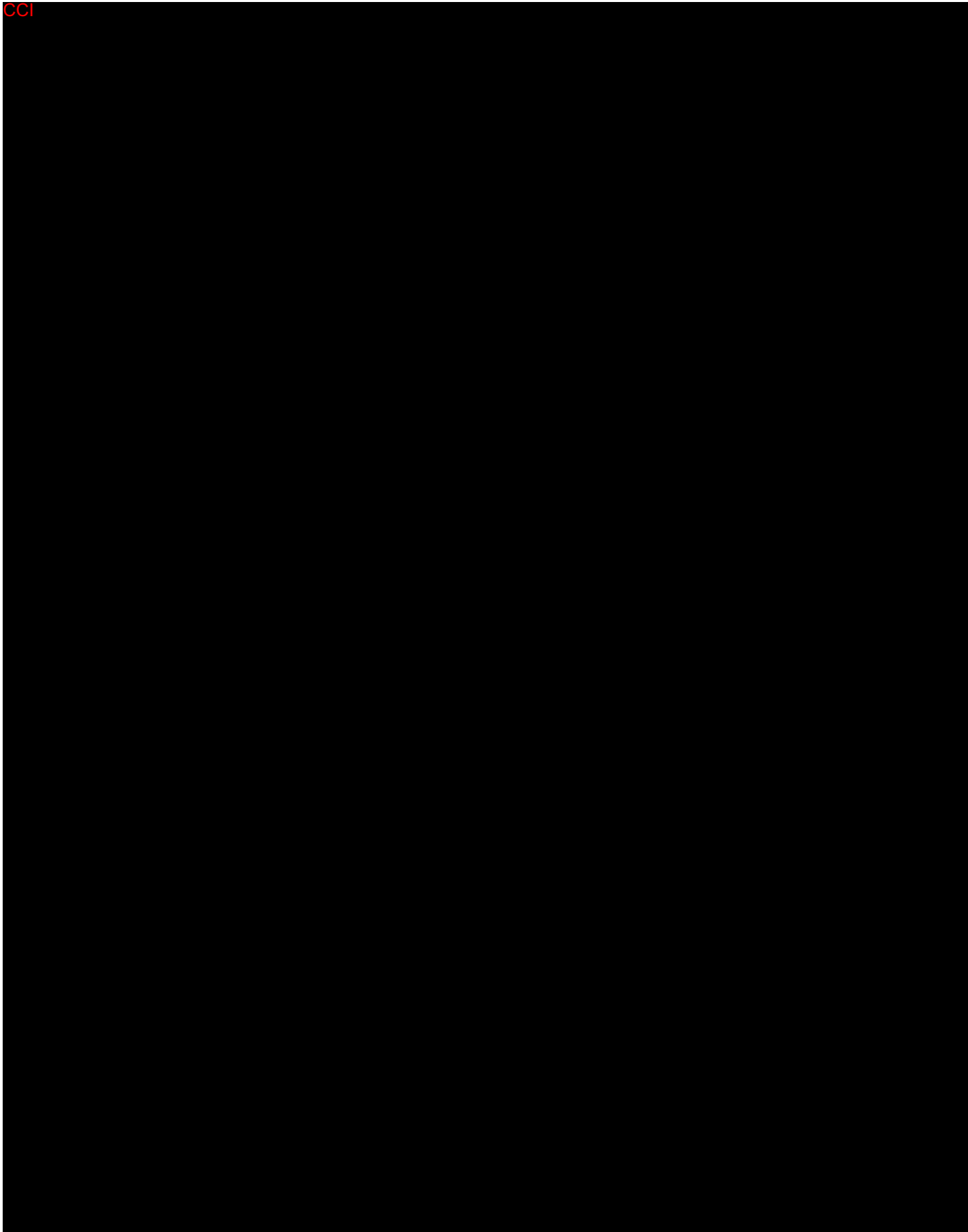
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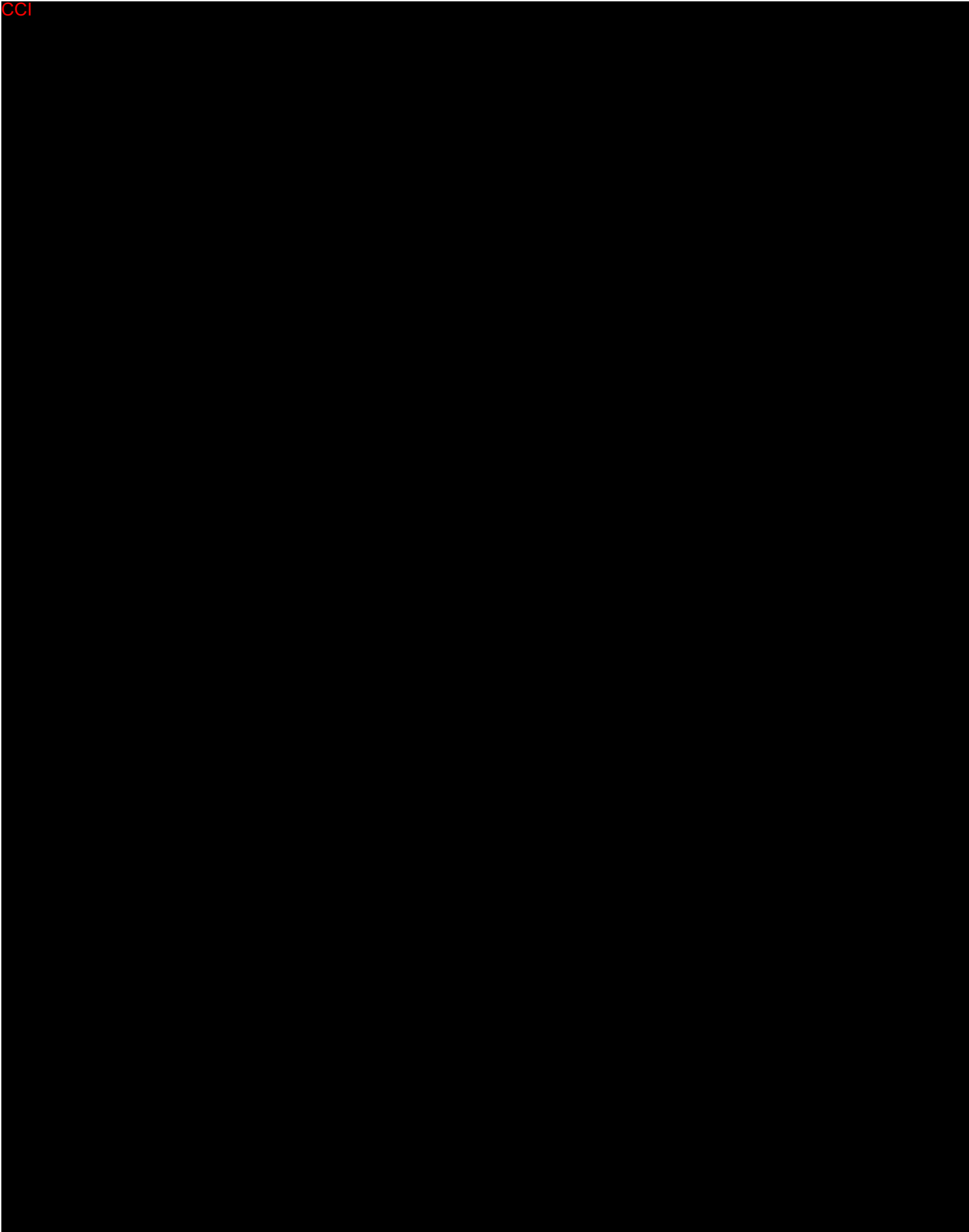
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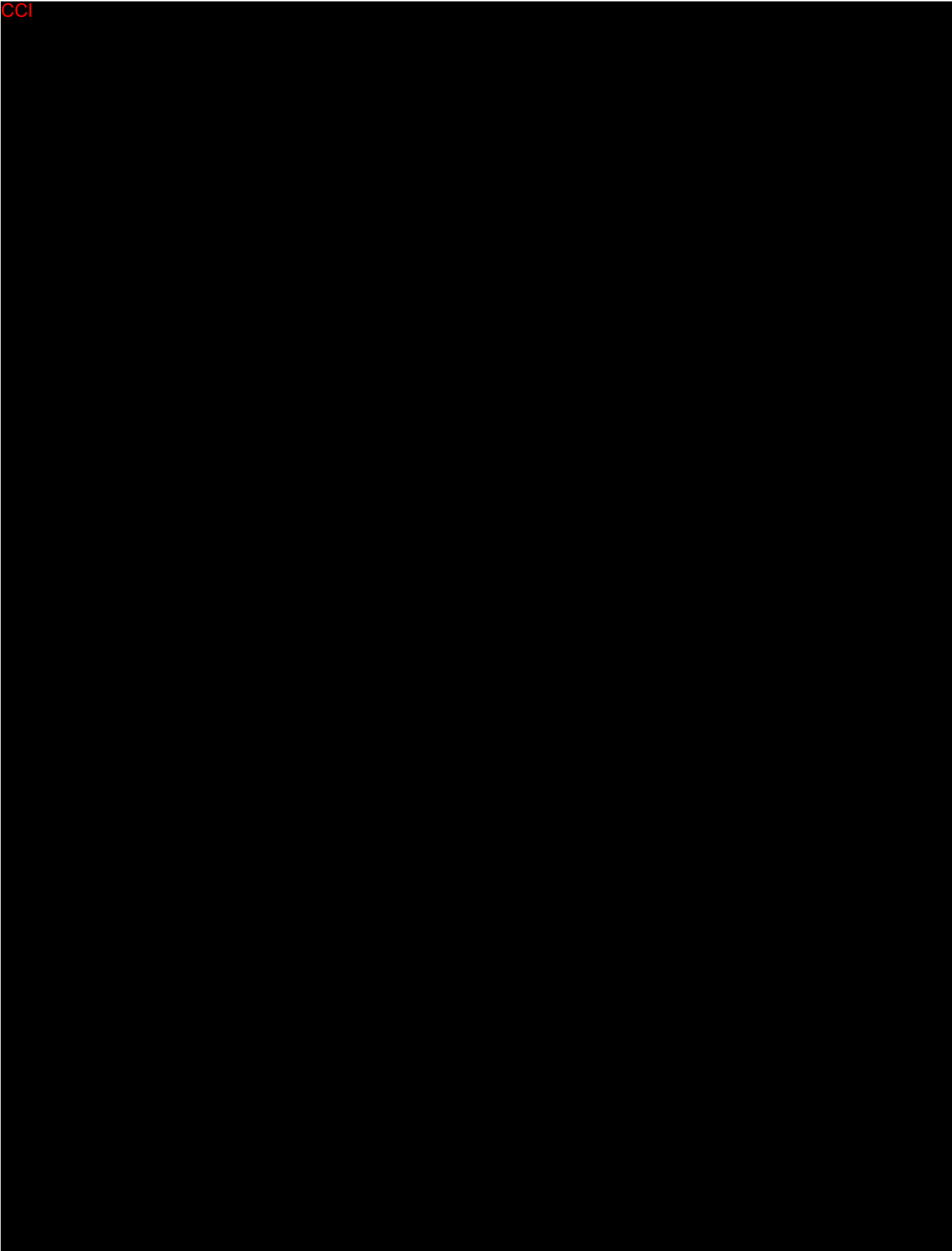
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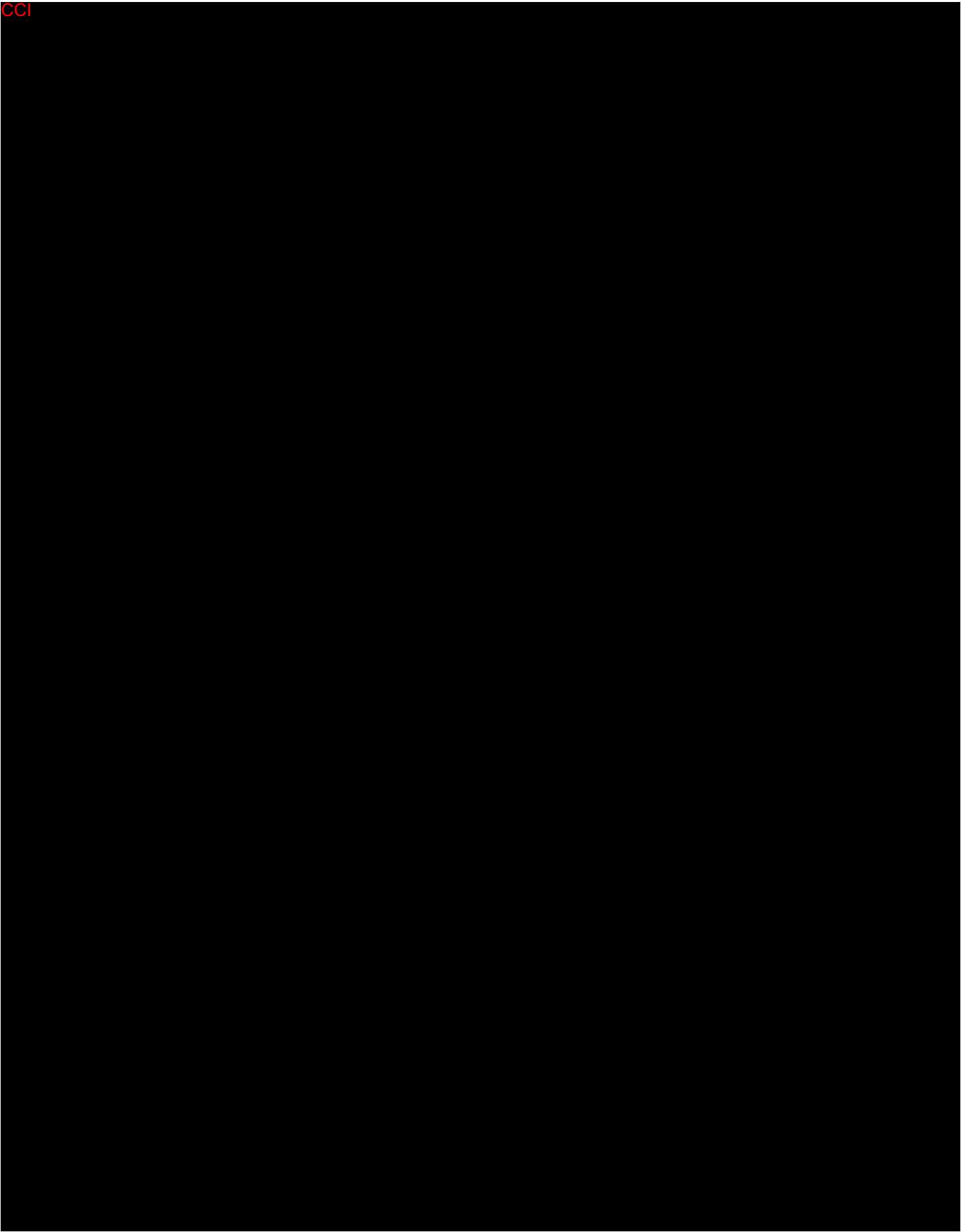
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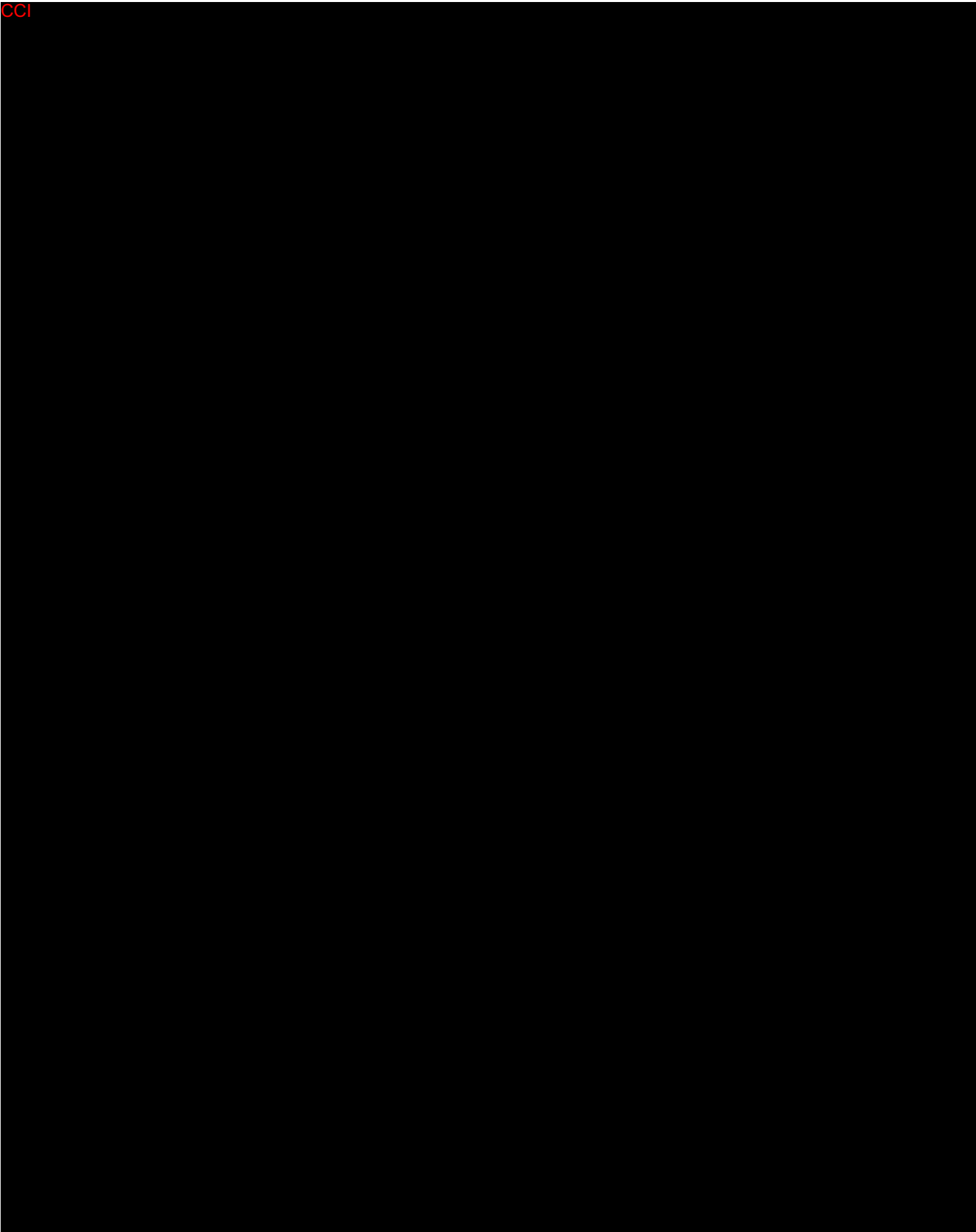


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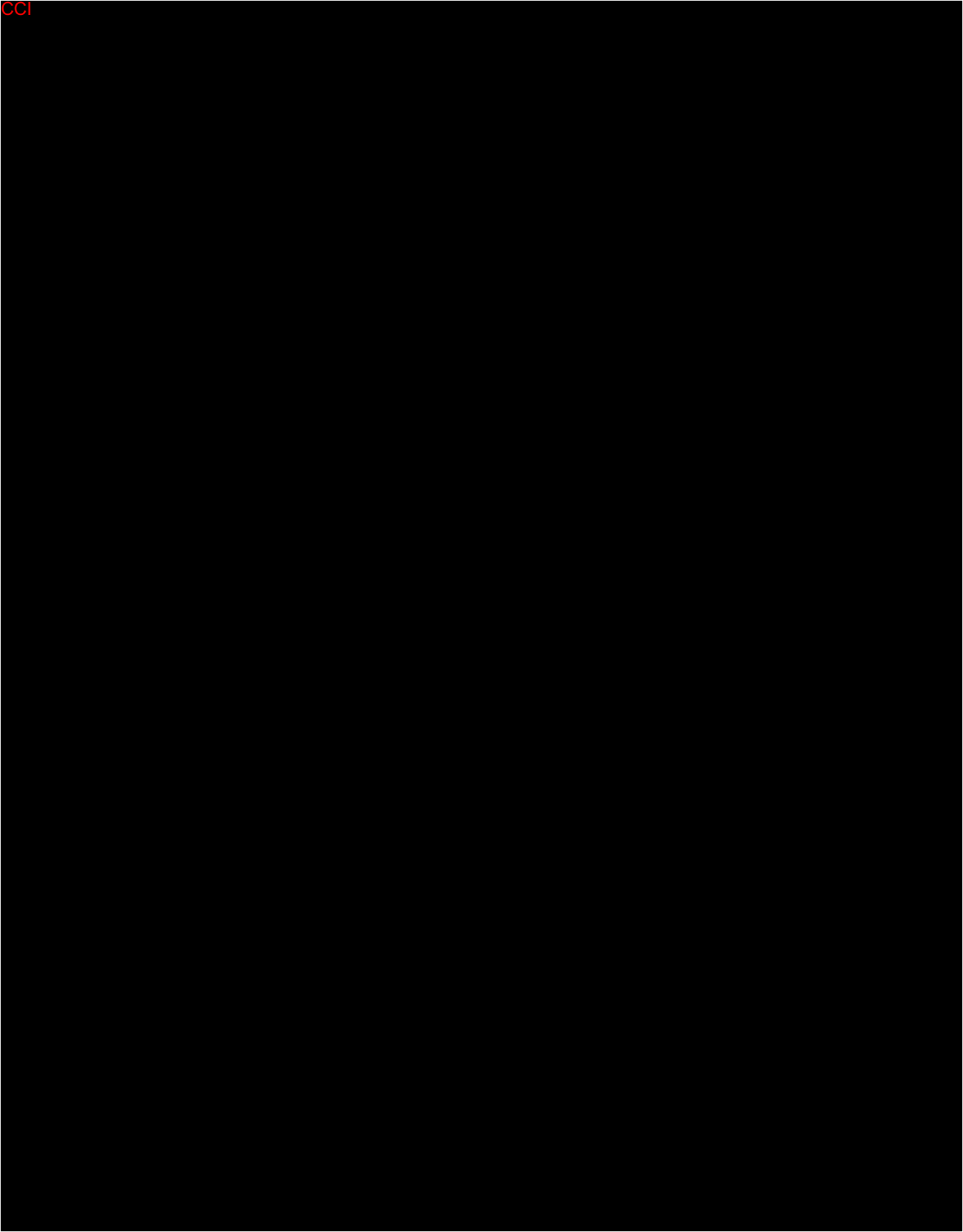


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## 9. STATISTICAL DESIGN AND ANALYSIS

### 9.1 General

A comprehensive Statistical Analysis Plan (SAP) with detailed description of all statistical analyses will be developed before database lock.

All study data will be listed in subject data listings.

All statistical analyses, including summary tables and data listings, will be performed using SAS. Confidence intervals (CIs) will be two-tailed and constructed at a confidence level of 95% unless otherwise specified. Statistical tests will be performed at a significance level of 5%, and p-values will be two-sided, unless otherwise specified.

Continuous endpoints will be summarized using descriptive statistics, e.g., number of subjects (n), mean, median, standard deviation (SD), minimum and maximum values. Categorical endpoints will be presented in frequency tables with number and percentage of observations for each level.

### 9.2 Analysis populations

The following analysis populations will be defined:

#### Intention to treat (ITT):

Includes all subjects who are randomized and will be analyzed according to the randomization scheme.

#### Per protocol (PP):

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.

#### Safety:

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 ITT population will be the primary population for all effectiveness analyses. If the PP population contains less than 90% of the subjects in the ITT, a sensitivity analysis of the primary effectiveness endpoint will be performed based on the PP population.

The safety analysis will be performed on the safety population.

The disposition of subjects will be presented in tables and/or figures as appropriate. The number of screened, randomized, treated, completed, and withdrawn subjects will be presented, as well as number of subjects in each analysis population set.

### 9.3 Demographics, baseline assessments, and subject characteristics

Demographic endpoints, baseline assessments, and subject characteristics will be presented based on the ITT analysis set using descriptive statistics by treatment, as appropriate.

## 9.4 Effectiveness analysis

### 9.4.1 Primary effectiveness analysis

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

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The proportion of responders will be compared between *Restylane Contour* group (Treatment group) and the Control group using a CCI

The test will be two-sided and performed on the CCI significance level.

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The test will be two-sided and performed on the CCI significance level.

The study success criterion is defined so that:

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### 9.4.2 Secondary effectiveness analysis

For responder rates, based on the GTVDS as assessed by the Blinded Evaluator at Month 3 after baseline for the Treatment group, compared to a reference standard responder rate of 50% the exact p-value will be calculated using the binomial distribution and the test 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.

Responder rates (defined as at least 1 grade improvement from baseline in both temples concurrently) based on the GTVDS, as assessed by the Blinded Evaluator at 6, 9, 12 and 18 months after baseline for the Treatment group will be analyzed in the same way as the primary effectiveness endpoint.

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.

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## 9.5 Safety analysis

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All AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC), preferred term (PT) and treatment.

A summary of all AEs will be provided, which will include:

- number of subjects with at least one AE and number of events (in total as well as SAEs)
- number of subjects with at least one related AE and number of events (in total as well as SAEs)
- number of subjects with at least one unrelated AE and number of events (in total as well as SAEs)
- number of subjects who did not have an AE

The number of subjects with AEs related to study product or injection procedure as well as the number of events will be summarized by SOC, PT and maximum intensity.

In addition, for related AEs the number of days to onset and the duration of event will be summarized by SOC and PT using mean, SD, min, max and median. Action taken for related AEs will also be summarized.

The SAEs will be listed. Related AEs with onset >21 days after most recent treatment will be listed.

Non-related AEs will be summarized by SOC, PT and intensity.

To evaluate consistency of AEs across different subgroups, AEs will also be summarized by subgroups defined as described below.

Safety analysis will be descriptive only.

## 9.6 Subgroup analyses

### 9.6.1 Effectiveness

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

- Study site
- Race
- Ethnicity
- Sex at birth
- Age ( $\leq$  median age vs  $>$  median age)
- FST I-III and IV-VI
- Injection volume ( $\leq$  median total injection volume vs  $>$  median total injection volume)

Poolability analysis will be performed to assess the consistency of the results between sites.

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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.

### 9.6.2 Safety

The consistency of AE data across different subgroups will be evaluated. The following subgroup factors will be used:

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- Study site
- Race
- Ethnicity
- Sex at birth
- Age ( $\leq$  median age vs  $>$  median age)
- FST **CCI**
- Injection volume ( $\leq$  median total injection volume vs  $>$  median total injection volume)

### 9.7 Handling of missing data

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

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. The following covariates will be included in the imputation model: treatment group and baseline Blinded Evaluator's GTVDS right/left.

Impact of missing data on the primary endpoint will be evaluated by performing sensitivity analyses in the ITT set, based on the baseline observation carried forward (BOCF) method, the observed cases, and a tipping point method.

All other effectiveness endpoints will be evaluated based on the observed cases in ITT.

Descriptive statistics of all safety data will be performed on observed cases in the Safety population.

### 9.8 Interim analysis

Not applicable.

### 9.9 Independent data monitoring committee

Not applicable.

### 9.10 Withdrawals and deviations

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

Subjects with protocol deviations will be listed individually, including subject number and observed deviation. Depending on the seriousness of the deviation, subject might be excluded from the PP population, which shall be documented prior to database lock.

Deviations from the SAP will be documented in the CSR.

### 9.11 Sample size

Data on response rate on treatment of temporal hollows is limited. Using a 4-point scale with responder estimated as one grade improvement, a responder level of 70% is usually estimated in the active group and a maximum of 35% responders in the no-treatment group after 3 months. Subjects start at grade 2 or 3 at the GTVDS at baseline.

A total sample size of CCI subjects is planned to be included in this study; approximately CCI subjects will be randomized to treatment with *Restylane Contour* (CCI) and approximately CCI subjects will be randomized to no-treatment.

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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..

## 10. ETHICS AND GENERAL CLINICAL STUDY CONDUCT

### 10.1 Ethical considerations

#### 10.1.1 Statement of ethical compliance

The study shall be conducted in compliance with the CTA, the CSP, GCP, and applicable regional or national regulations.


The study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (1964, and its amendments in force at the initiation of the study) insofar as such revisions are consistent with US treaty obligations and in accordance with US law.

The study shall follow the international standard for clinical study of medical devices for human subjects, ISO 14155:2020 or later updates as applicable for US regulations, and the International Conference on Harmonisation (ICH) guideline for GCP (E6[R2]) as applicable for medical device.

The study related medical care provided to the subjects during the study is the responsibility of an appropriately qualified medical doctor (i.e., the PI and delegated Investigators) or, where appropriate any other person entitled by national law to provide the relevant subject care.

#### 10.1.2 Application to independent Institutional Review Boards and/or Regulatory Authorities

It is the responsibility of the PI to obtain approval of the CSP and any CSP amendment(s) from the IRB. The study shall not begin until the required favorable opinion from the IRB has been obtained. The PI shall file all correspondence with the IRB in the Investigator file and copies of IRB approvals

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shall be forwarded to the Sponsor. Any additional requirements imposed by the IRB or RA shall be followed.

The study requires application for approval from the FDA. The study will not be started until the Sponsor has received written approval or until the statutory waiting period from the appropriate authority has elapsed. The Sponsor will provide the PI with a copy of the relevant document.

The collection, access to, processing, and transfer of protected health information or sensitive personal data shall be carried out in accordance with applicable rules and regulations.

## 10.2 Subject information and consent

The PI or his/her authorized designee must always use the IRB-approved subject information and ICF and it must not be changed without prior discussion with the Sponsor and approval from the applicable IRB.

It is the responsibility of the PI or his/her authorized designee to give each subject prior to inclusion in the study, full and adequate verbal and written information regarding all aspects of the clinical study that are relevant to the subject's decision to participate throughout the study, e.g., explain the purpose and procedures of the study, the duration and number of expected participants, possible risks involved, and the opinion of the IRB. The subject shall be informed that the participation is confidential and voluntary and that the subject has the right to withdraw from the study at any time, without any consequences to his/her future medical care, treatment, or benefits to which the subject is otherwise entitled. The information shall be provided in a language clearly and fully understandable to the subject. The subject shall be given sufficient time to read and understand the ICF and to consider participation in the study. Before any study-related activities are performed, the ICF shall be personally signed and dated by the subject and the PI or his/her authorized designee responsible for conducting the informed consent process. The consent includes information that data will be collected, recorded, processed, and may be transferred to other countries. The data will not contain any information that can be used to identify any subject.

Photographs collected during the study will be analyzed and stored in a database by the Sponsor and its representatives in order to evaluate the effect of the treatment in the study. The subjects will be recognizable on the photographs, but their names will not be disclosed.


All signed ICFs shall be filed in the Investigator file. The subject shall be provided with a copy of the signed and dated ICF and any other written information.

The Investigator shall ensure that important new information is provided to new and existing subjects throughout the study. The subject should be informed that a description of this study, as well as results of the study once completed and reported, will be available on <http://www.ClinicalTrials.gov>. This website can be searched at any time. The website will not include information that can identify the subject.

## 10.3 Personnel training

It is the responsibility of the PI to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study, including detailed knowledge of and training in all procedures to be followed. All Investigators and other responsible persons shall be listed together with their function in the study on the Signature and Delegation Log.

The product is reserved for use by the PI or his/her authorized designee in accordance with local legislation, trained in the appropriate aseptic injection techniques and expected to follow the

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recommendations in the study specific IFU. Additional training for treatment with the study product in the temples will be provided by the Sponsor.

#### 10.4 Data management and documentation

Data management based on GCP refers to the activities defined to achieve safe routines to enter clinical data information into a database, efficiently and avoiding errors. The data management routine includes procedures for database set-up and management, data entry and verification, data validation, and documentation of the performed activities including information of discrepancies in the process. The data management process will be described in detail in the Data Management Plan (DMP).

The database, the data entry screens, and program will be designed in accordance with the CSP and the eCRF Specification. Data validation will be performed by computerized logical checks and manual review.

Drugs and events will be coded in accordance with World Health Organization (WHO) Drug and MedDRA dictionaries as specified in the DMP. Safety data (SAE and if applicable AESIs) in the clinical database will be reconciled against the data in the safety database.

When all efforts have been made to ensure that the data recorded in the eCRFs and entered in the database is as correct and complete as possible, the clinical database will be locked. Study data will be transferred to SAS datasets, which thereafter will be write-protected. Statistical analyses will be generated in SAS using data from the locked datasets.

##### 10.4.1 Data entry and collection

A 21 CFR Part 11-compliant electronic data capture application will be used to collect, modify, maintain, archive, retrieve, and transmit study data. An eCRF is required and should be completed electronically for each screen failure as well as enrolled subjects.


The eCRF includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Study data should be entered directly from the source documents, which are to be defined at each study center before inclusion of the first subject.

Authorized study center personnel designated by the PI should complete data collection. Appropriate training and security measures should be completed with all authorized investigation study center personnel prior to the study being initiated and any data being entered into the system for any subject.

The study data is the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate RA, without written permission from the Sponsor. At the end of the study, electronic data are kept at the Sponsor and a copy (provided by the vendor) at the study center as part of the Investigator file.

Any delegation of collection of data should be specified in the Signature and Delegation Log.

All data shall be entered in English. The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs shall be completed as soon as possible during or after the subject's visit. The subject's identity must always remain confidential, i.e., the name and address of the subjects must not be registered in the eCRFs or in the database. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable or unknown, the Investigator shall indicate this in the eCRF. The Investigator shall electronically sign off the study

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data. By signing, the Investigator takes responsibility for the accuracy, completeness, and legibility of the data reported to the Sponsor in the eCRF.

The monitor shall review the eCRFs and evaluate them for completeness and consistency. Each eCRF shall be compared with the respective source documents to ensure that there are no discrepancies between critical data. All entries, corrections, and alterations shall be made by the PI or his/her authorized designee. The monitor cannot enter data in the eCRFs. Once study data have been submitted to the central server via the eCRF, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who made the change, together with time and date will be logged. Roles and rights of the study center personnel responsible for entering study data into the eCRF shall be determined in advance. If discrepant data is detected during review of the data, either by the Sponsor or by its representatives, the responsible data manager or monitor shall raise a query in the electronic data capture application. The query shall state the question or data to be changed and shall be resolved in the system by the PI or his/her authorized designee. The appropriate study center personnel shall answer the queries in the eCRF. This will be audit trailed by the electronic data capture application meaning that the name of study center personnel, time, and date is logged.

The eCRF records will be automatically appended with the identification of the creator, by means of their unique UserID. Specified records shall be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique UserID and password; date and time stamps will be added automatically at time of electronic signature. If an entry in an eCRF requires change, the correction shall be made in accordance with the relevant software procedures.

All changes will be fully recorded in a protected audit trail and a reason for the change shall be stated. Once all data have been entered, verified, and validated, the database will be locked.

#### 10.4.2 Source documentation

Source documents are all documents used by the Investigator or study center that relate to the subject's medical history, that verifies the existence of the subject, the inclusion and exclusion criteria, and all records covering the subject's participation in the study. They include laboratory notes, memoranda, material dispensing records, subject files, etc.


The PI is responsible for maintaining source documents. These should be made available for inspection by the monitor at each monitoring visit. The Investigator must submit a completed eCRF for each subject for whom signed informed consent has been collected. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the CTN and subject number. Any personal information, including name, should be removed, or rendered illegible to preserve individual confidentiality.

#### 10.4.3 Protection of personal data

The study shall include collection and processing of personal data as specified in the Regulation European Union (EU) 2016/679 (General Data Protection Regulation, GDPR) and the regulation EU 2017/745 (MDR) on the protection of individuals with regard to the processing of personal data. For the purposes of the study, Sponsor will be considered the data controller, and the Institution/the Investigational site and the PI will both be considered data processors.

All processing of personal data must be carried out in accordance with national legislation concerning the protection of personal data. The Institution/Investigational site and the PI are responsible for complying with all requirements pursuant to national legislation in which the

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Institution and the Investigator are located. The Sponsor will ensure that all requirements for data processing are fulfilled.

The Investigator understands that clinical studies conducted under an IDE are exempt from the study subject identifier confidentiality provisions of the HIPAA, and the study subject should be made aware of this exception in the informed consent. The Institution/Investigational site and PI are jointly responsible for providing sufficient information to all subjects to enable them to give their informed consent not only to the participation in the investigation, but also to the processing of Personal Data. Such information includes information regarding the purposes of the processing, the length of time during which Personal Data will be stored, the right of access to stored Personal Data and the right to correction or purging of incorrect or obsolete Personal Data. A subject may also withdraw his or her consent at any time.

If a subject decides to terminate the study prematurely, data collected before withdrawal of consent will be used in the evaluation of the study, however no new data may be collected.

Authorized representatives from the Sponsor, CRO or a RA may visit the study center to perform audits/inspections, including source data verification (SDV), i.e., comparing data in the subjects' medical records and the eCRF. Data and information shall be handled strictly confidential.

#### 10.4.4 Archiving/record keeping

The PI/Institution/Investigational site should permit study-related monitoring, audits, IRB review, and RA inspections and should provide direct access to the source data/medical record including the identity of all participating subjects (sufficient information to link records, i.e., eCRF, medical records, original signed ICFs and detailed records of study product accountability). The records should be retained by the PI as required by local legislation and international guidelines. Any transfer of responsibility for storage of the records should be documented and the Sponsor should be informed in writing.

The Sponsor should verify that each subject has consented in writing to direct access to the original medical record/source data (by the use of written subject information and signed informed consent). The data recorded in the eCRFs will be checked for consistency with the source documents/medical record by the monitor during monitoring (SDV). In order to be able to perform SDV, information about each subject's participation in the study has to be detailed in the medical records.


All records pertaining to the conduct of the study, including signed eCRFs, ICFs, study product accountability records, source documents, and other study documentation must be retained for as long as is specified in the CTA. Measures should be taken to prevent accidental or premature destruction of these documents (e.g., protection against damage and unauthorized access, preferably by storage in a fire-proof cabinet).

It is the PI's responsibility to inform the Sponsor in writing if the Investigator file is moved or if the responsibility for the documents is transferred to someone else.

### 10.5 Protocol deviations

The PI and delegees are not allowed to deviate from the CSP and no up-front waivers from the CSP will be issued. Any CSP deviation shall be documented appropriately, verified, discussed, and collected by the monitor and appropriate actions will be taken.

Under emergency circumstances, deviations from the CSP to protect the rights, safety and well-being of the subjects may proceed without prior approval of the Sponsor and the IRB and RA. Such

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deviations should be documented and reported to the IRB and RA as soon as possible. Deviations will be reviewed to determine the need to amend the CSP or to terminate the study.

The PI is responsible for promptly reporting any deviations from the CSP that affects the rights, safety or well-being of the subject or the scientific integrity of the study, including those which occur under emergency circumstances, to the Sponsor (within 24 hours following detection) as well as the IRB if required by national regulations.

## 10.6 Clinical Study Report

After completion of the study a CSR will be compiled. A summary of the study results will be published on a public database, <http://www.ClinicalTrials.gov>.

## 10.7 Quality control / quality assurance

### 10.7.1 Clinical Monitoring

On-site monitoring of the study will be arranged by the Sponsor according to GCP guidelines to verify that the rights and well-being of the subjects are protected, the reported data are accurate, complete, verifiable from source documents, and that the conduct of the study complies with the approved CSP, subsequent amendment(s), GCP and the applicable regulatory requirements.

Specific details about monitoring in the study will be outlined in a separate Monitoring Plan.

### 10.7.2 Audits/inspections

The study center may be subject to quality assurance audit by the Sponsor as well as inspection by appropriate RA. It is important that the PI and other relevant study center personnel are available during the monitoring visits, possible audits, and inspections, and that sufficient time is devoted to the monitoring process.

Each participating member of the study center team shall provide a curriculum vitae (CV) or equivalent that demonstrates their qualifications to conduct the study.

## 10.8 Protocol amendments

The PI and other study center personnel involved in the study must not implement any changes to the CSP without agreement with the Sponsor and prior review and documented approval from the IRB and RA, if applicable, except where necessary to eliminate an immediate hazard to the subjects. All changes to the final CSP must be documented in a dated and version-controlled written protocol amendment.

### 10.8.1 Amendments

This is the first protocol amendment.

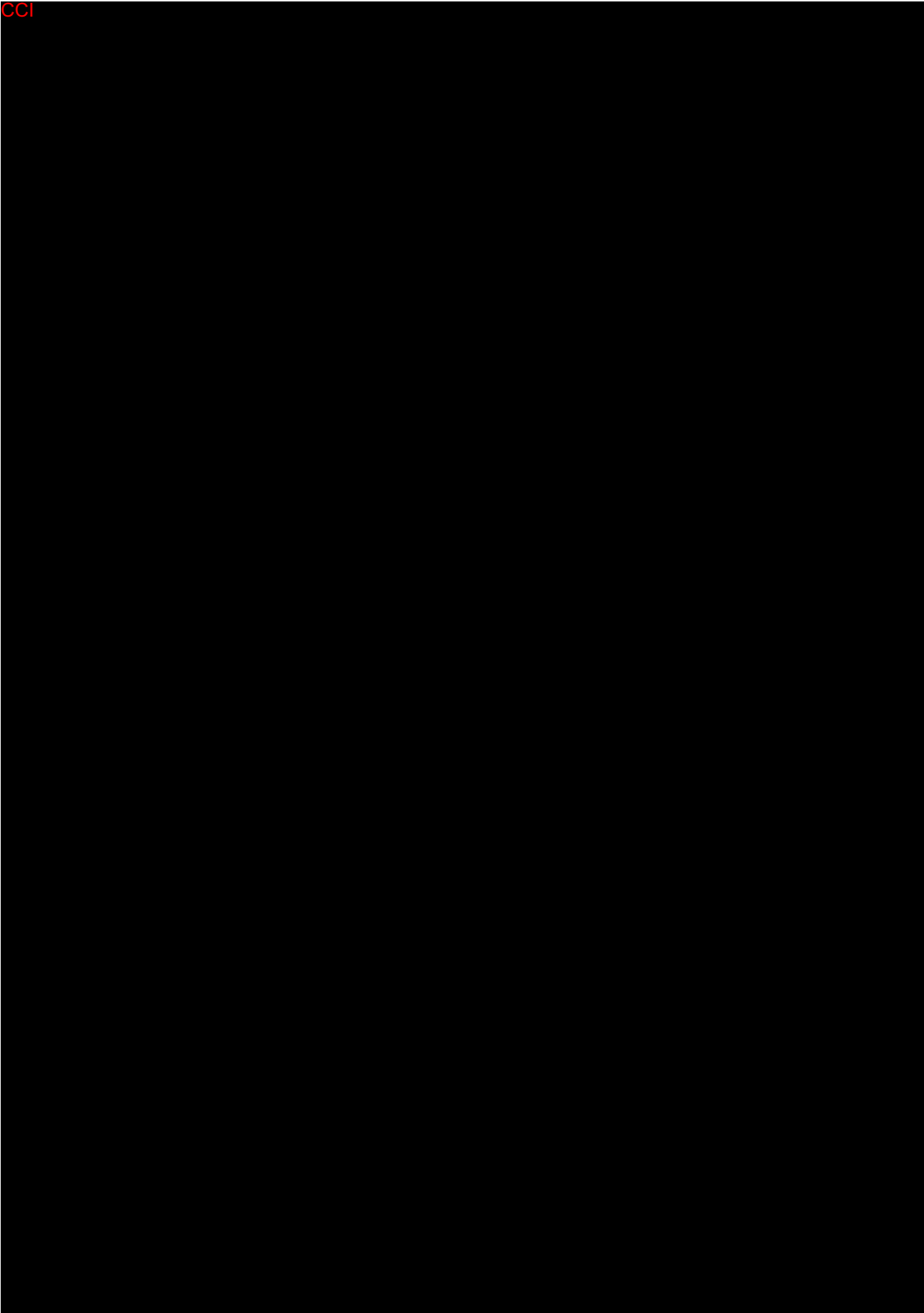
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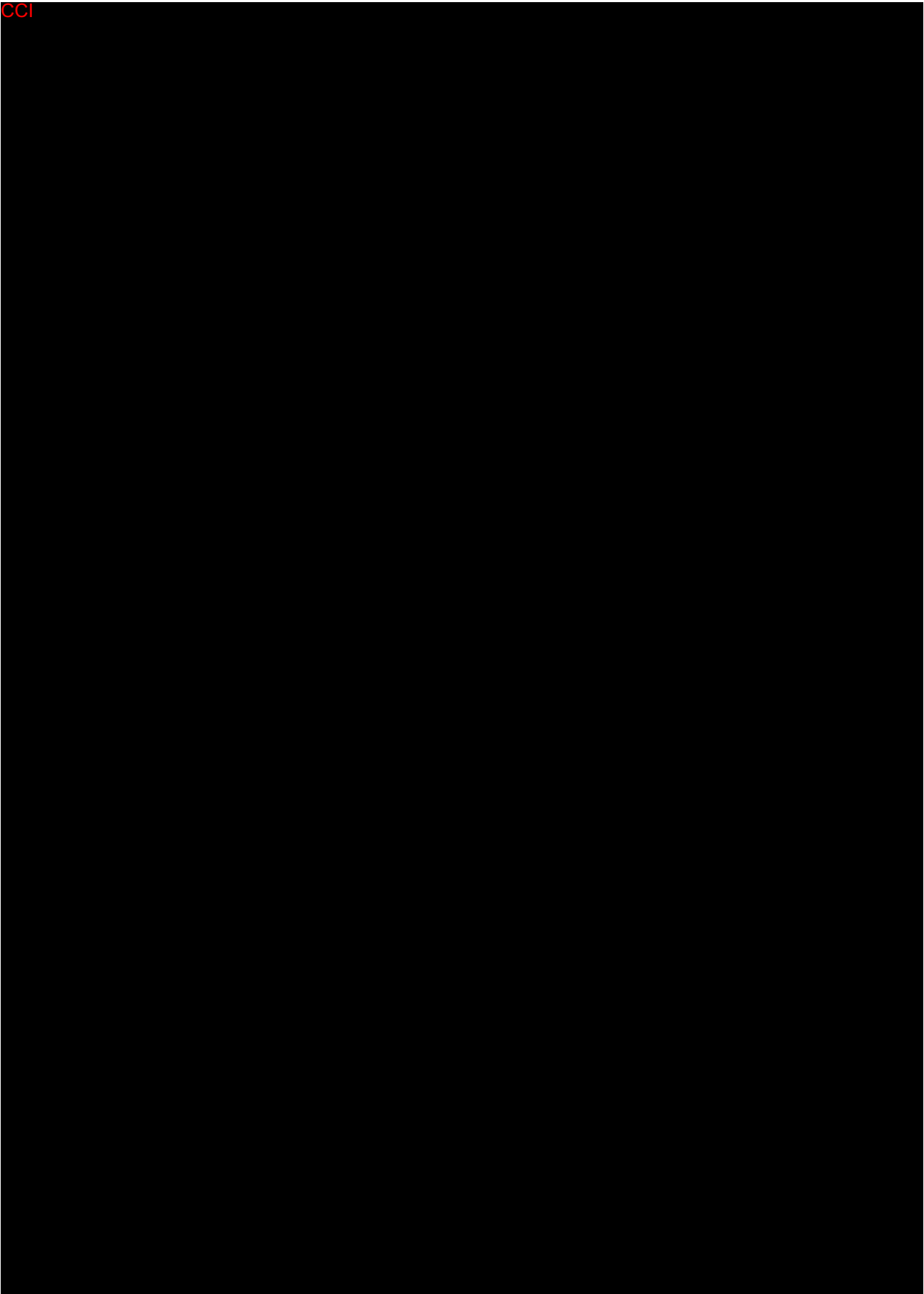
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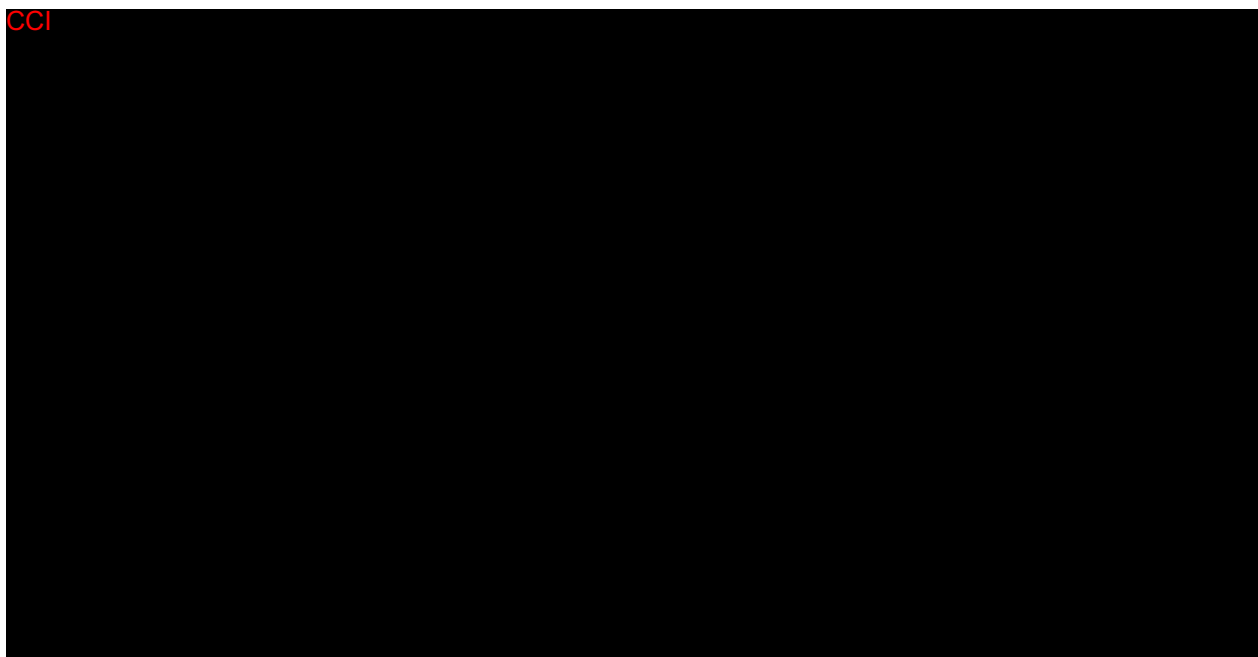
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## 10.9 Financing, indemnification and insurance

This is a study fully sponsored by Galderma Research and Development, LLC and Q-Med AB, part of the Galderma Group. The CTA between Sponsor (or the CRO) and Investigational sites outlines the compensation and payment terms of the study. The CTA must be signed before the first subject is screened in the study. If there are differences between the CTA and the CSP regarding certain rights and obligations, the CTA is the prevailing document.

The Sponsor's obligations in this clinical study are covered by Galderma Research and Development, LLC's global general liability program. An insurance certificate will be provided upon request. The Institution/Investigational sites/PI are obligated to maintain insurance coverage for their obligations in the clinical study according to the CTA.

## 10.10 Publication policy

The PI's, the Institution's/Investigational site's, and Galderma Research and Development, LLC's/Q-Med AB's obligations regarding intellectual property rights, confidentiality, and publications are described in detail in the CTA.

The aim is to submit the results of this study for publication in the public database (<http://www.ClinicalTrials.gov>) and to a medical journal for a first joint publication of the results.


Everyone who is to be listed as an author of the results of this multicenter study shall have made a substantial, direct, intellectual contribution to the work. Authorship will be based on (1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and (2) drafting the work or revising it critically for important intellectual content; and (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved<sup>8</sup>. Conditions 1, 2, 3, and 4 must all be met in order to be designated as author. Those who do not meet all four criteria will be acknowledged.

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<sup>8</sup> Defining the role of authors and contributors, compiled by the International Committee of Medical Journal Editors (ICMJE) (<http://www.icmje.org>).

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Among the authors that fulfil the above-mentioned criteria, one author will be appointed by Galderma Research and Development, LLC/Q-Med AB to take primary responsibility for the overall work as primary author.

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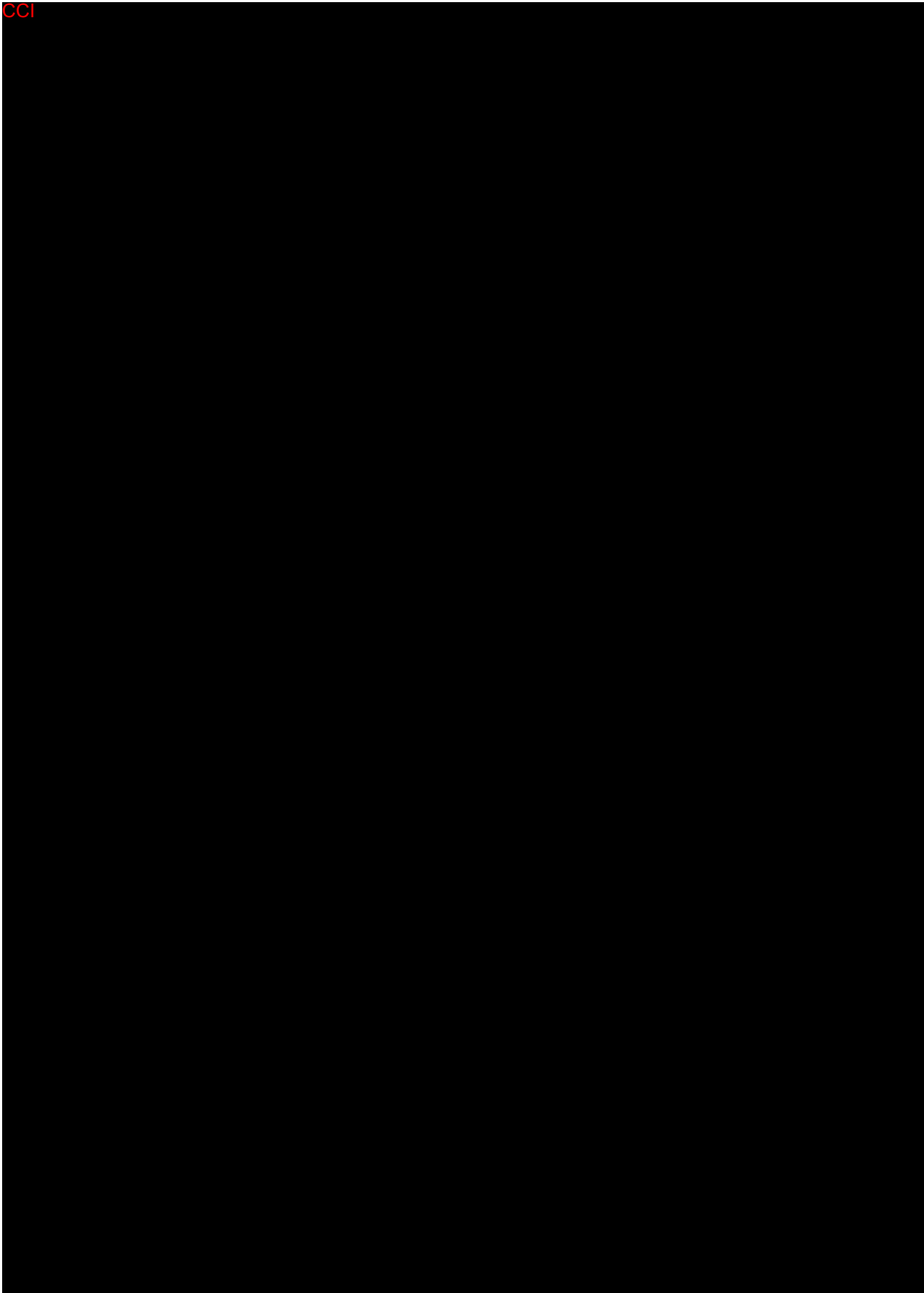
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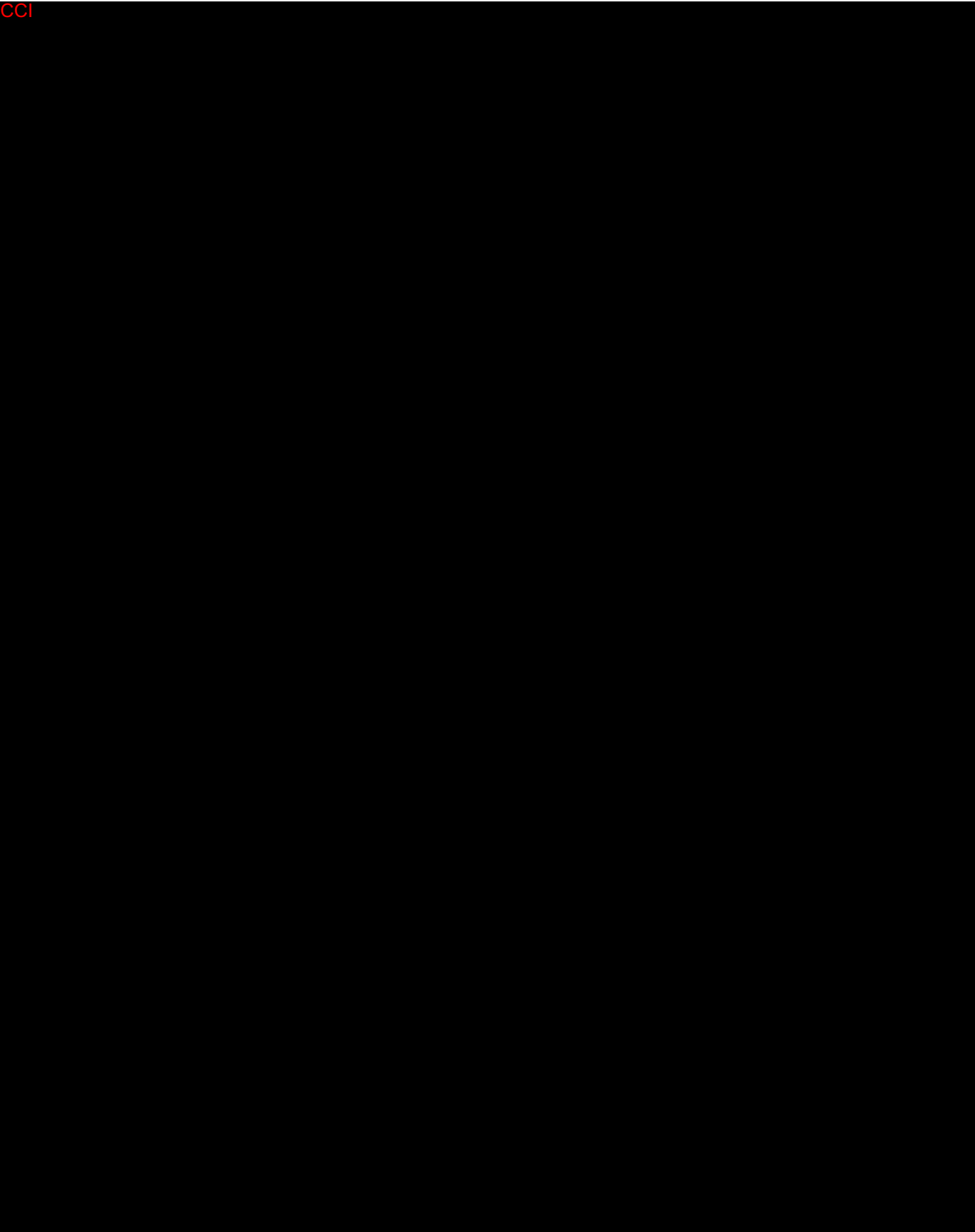


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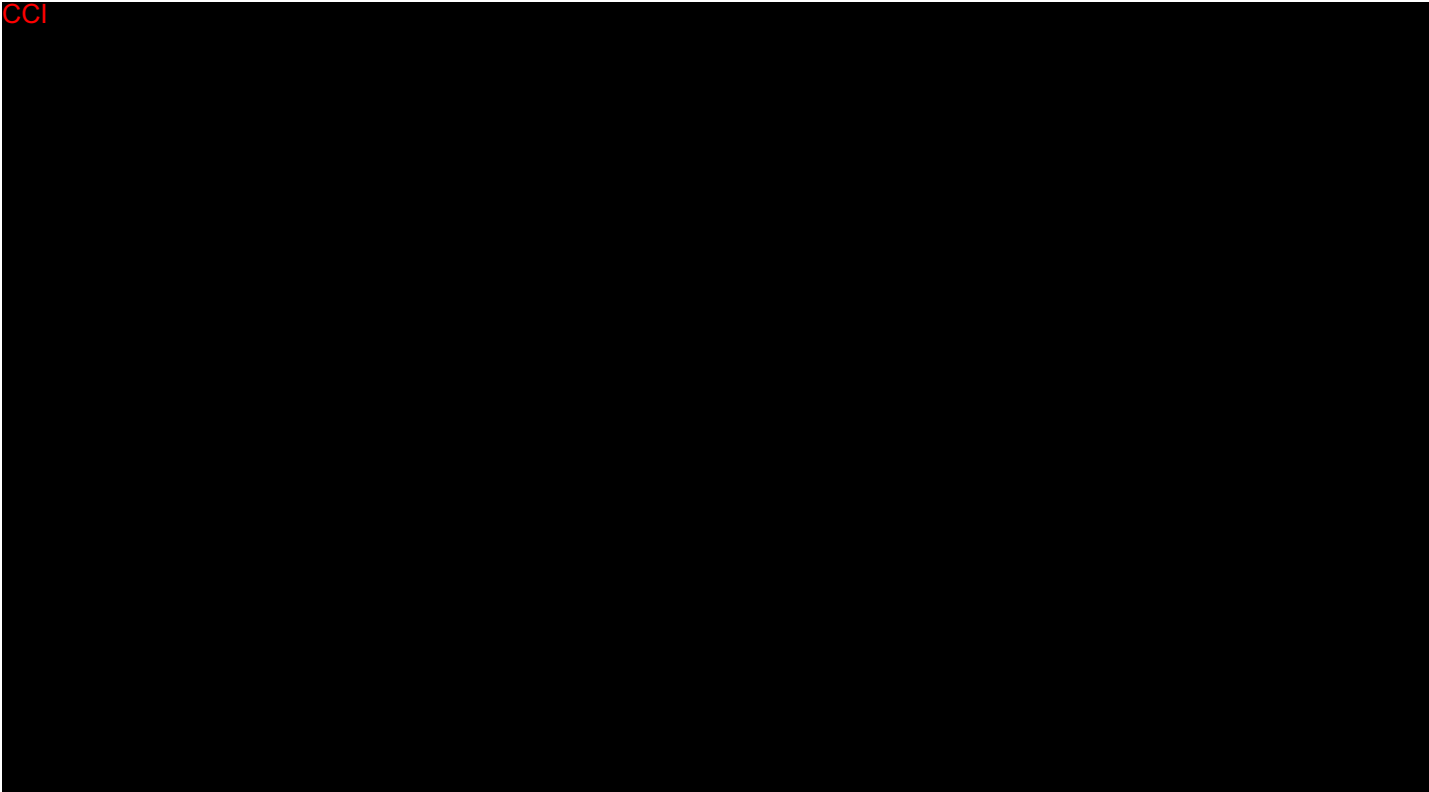


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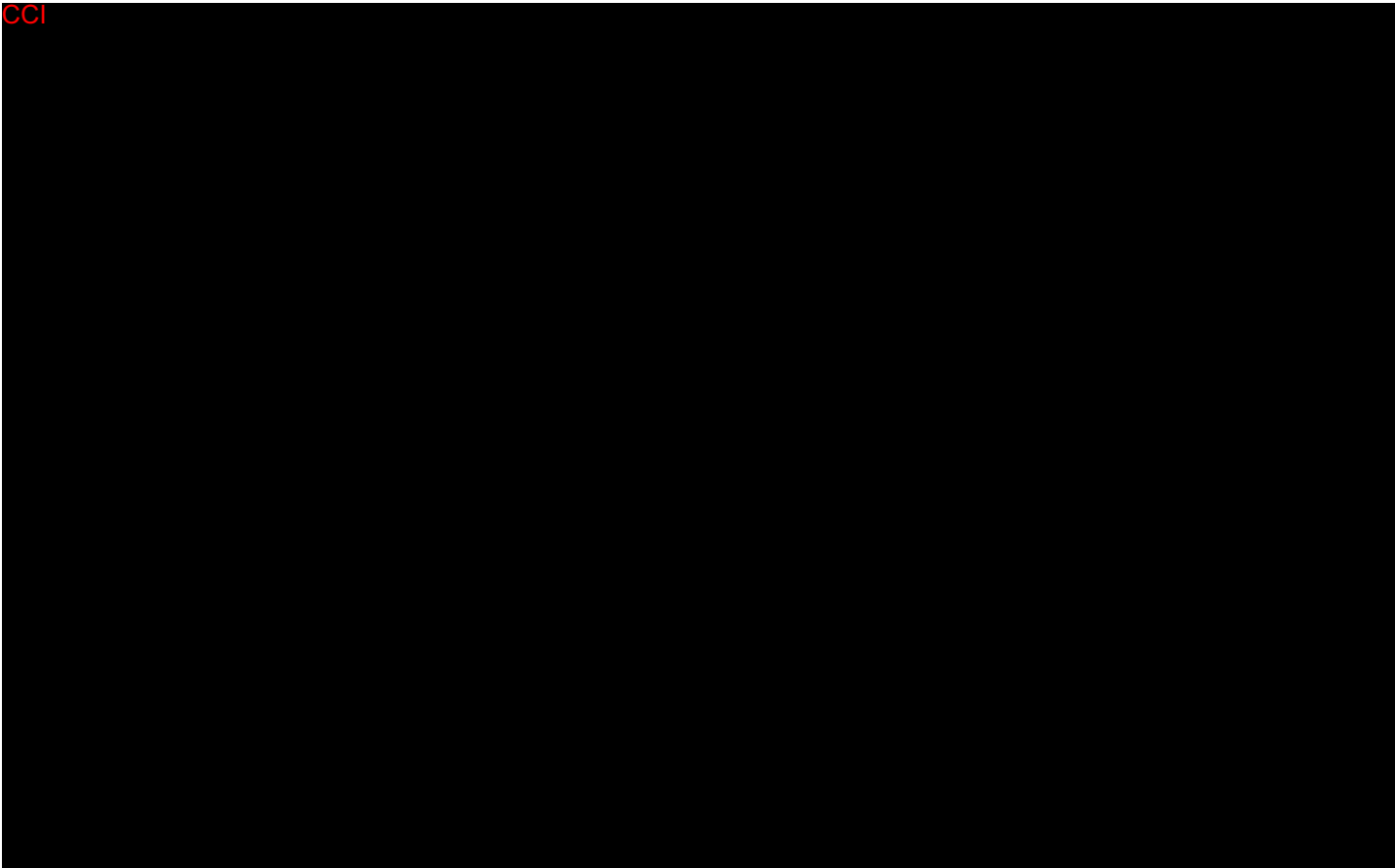
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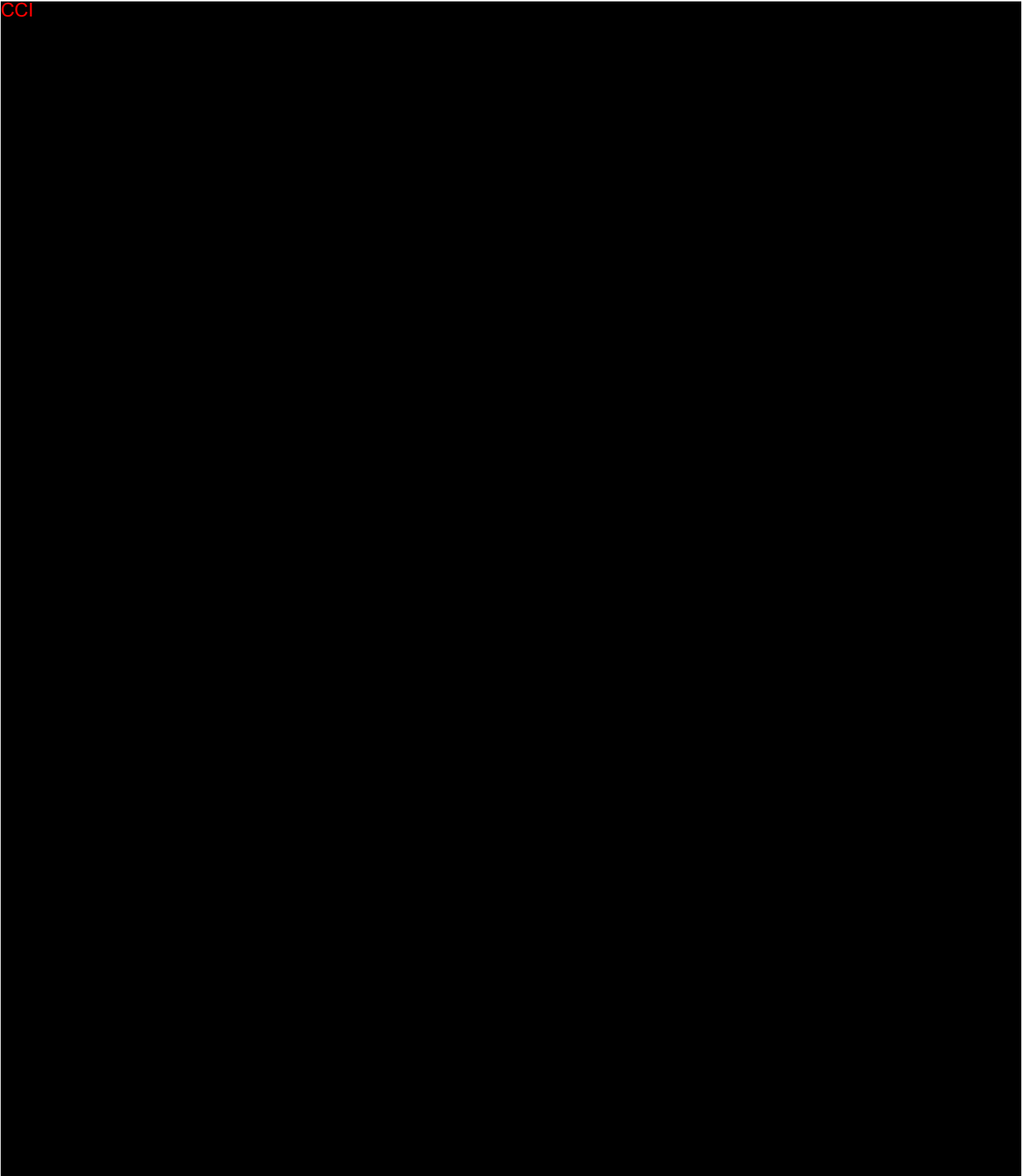
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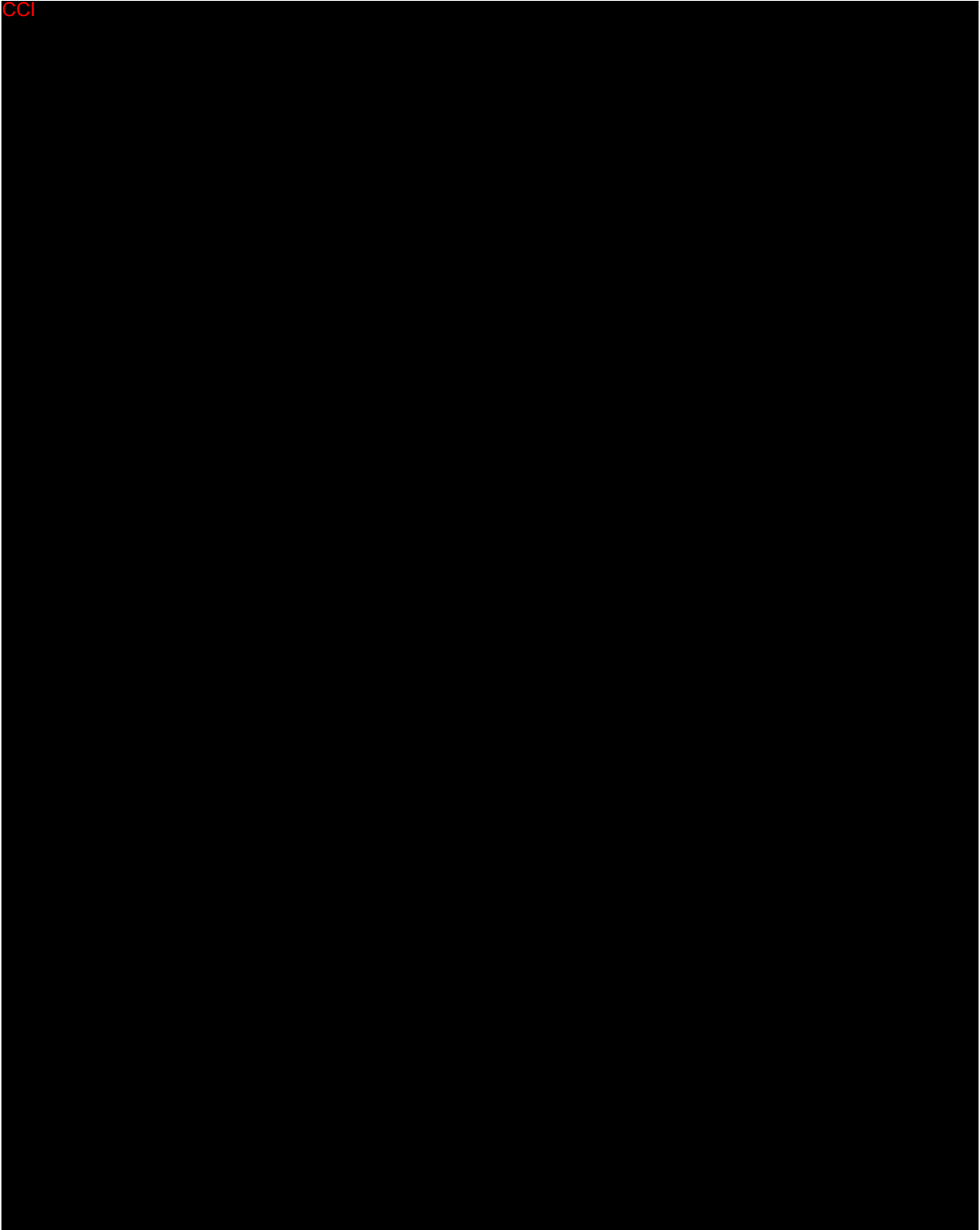


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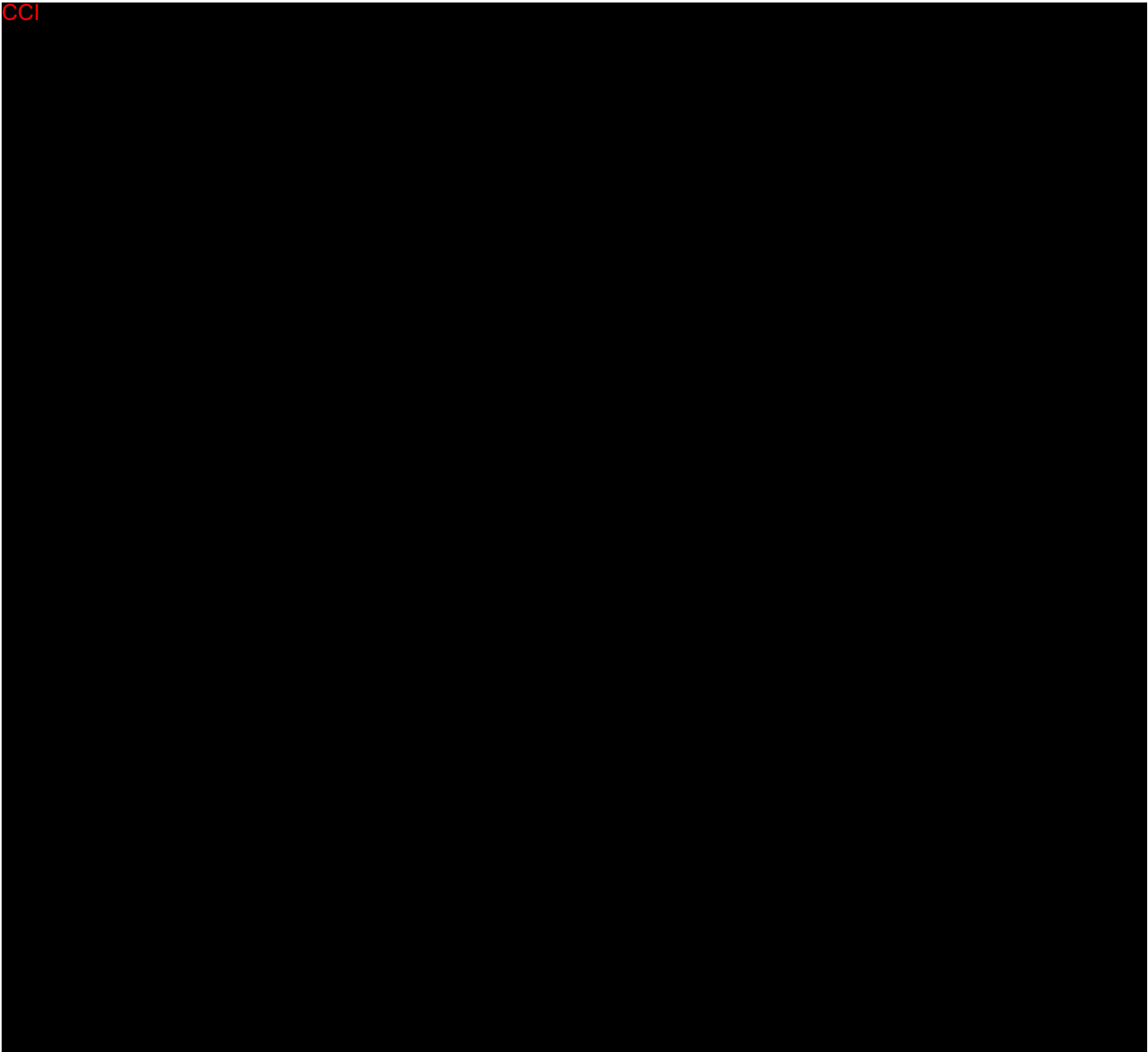
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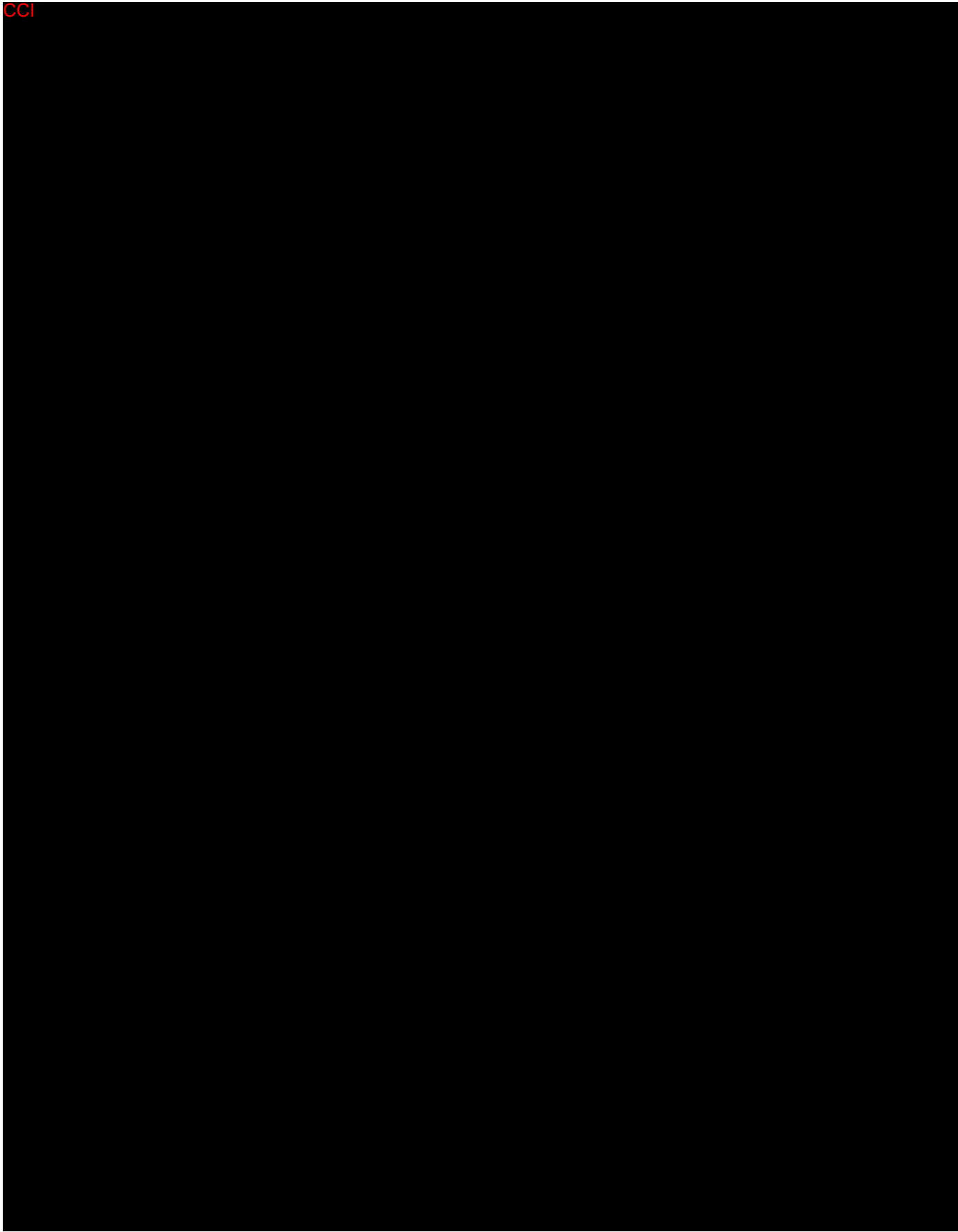


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SIGNED AGREEMENT OF THE CLINICAL STUDY PROTOCOL

Clinical Trial Number (CTN):

43USTH2201

Title of the Clinical Study Protocol (CSP):

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

I, the undersigned, have read and understand the CSP specified above, and agree on the contents. The CSP, the Clinical Trial Agreement (CTA) and the additional information given in the Instructions for Use (IFU) and Report of Prior Investigations (ROPI) will serve as a basis for co-operation in this study.

Principal Investigator

Printed name

Signature

Date

Study site

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SPONSOR SIGNATURES

The Clinical Study Protocol is electronically signed in the document management system within the Q-Med AB quality management system.

Senior Medical Expert:	PPD 
Head of Clinical Project Management:	PPD 
Global Head of Clinical Scientists:	PPD 
Senior Clinical Scientist:	PPD 
Statistician:	PPD 

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