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OAV101/onasemnogene abeparvovec

Clinical Trial Protocol/ NCT05089656

A randomized, sham-controlled, double-blind study to evaluate the efficacy and safety of intrathecal (IT) OAV101 in patients with later onset Type 2 spinal muscular atrophy (SMA) who are ≥ 2 to < 18 years of age, treatment naive, sitting, and never ambulatory

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List of abbreviations

AAV	adeno-associated virus
AAV2	adeno-associated virus serotype 2
AAV9	adeno-associated virus serotype 9
aPTT	Activated partial thromboplastin clotting time
CCI	CCI
AE	Adverse Event
AESI	Adverse event of special interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ASMA	Anti-smooth muscle antibody
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
Beta-hCG	Blood beta-human chorionic gonadotropin
BiPAP	Bi-Level Positive Airway Pressure
BMI	Body Mass Index
CB	Chicken-β-Actin-Hybrid
CDC	Centers for Disease Control and Prevention
cDNA	Complementary Deoxyribonucleic Acid
CFR	Code of Federal Regulations
CCI	CCI
CCI	CCI
CCI	CCI
CI	Confidence interval
CK	Creatine Kinase
CCI	CCI
ClinRO	Clinician Reported Outcomes
CMV	Cytomegalovirus
CNS	Central Nervous System
CNT	Cannot Test
COA	Clinical Outcome Assessment
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSF	Cerebrospinal fluid
CSR	Clinical study report
CCI	CCI
CTCAE	Common Terminology Criteria for Adverse Events
CTR	Clinical trial registration
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DRG	Dorsal Root Ganglia
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
eCOA	Electronic Clinical Outcome Assessment

EDC	Electronic Data Capture
EOS	End of Study
eSource	Electronic Source
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GLDH	Glutamate Dehydrogenase
GMFM	Gross Motor Function Measure
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HEENT	Head, Eyes, Ears, Nose and Throat
HEV	Hepatitis E
HFMSE	Hammersmith Functional Motor Scale Expanded
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IN	Investigator Notification
IRB	Institutional Review Board
IRT	Interactive Response Technology
IT	Intrathecal
ITR	Inverted terminal repeats
ITT	Intent-to-treat
IV	intravenous
kg	Kilogram(s)
LFT	Liver function test
LPLV	Last participant last visit
LSMs	Least square means
LVEF	Left ventricular ejection fraction
LVFS	Left ventricular fractional shortening
MAP	Meta-analytic-predictive
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MMRM	Mixed model with repeated measurements
CCI	CCI
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PNCR	Pediatric Neuromuscular Clinical Research
CCI	CCI

PT	prothrombin time
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
CCI	CCI
RNA	Ribonucleic acid
RSV	Respiratory Syncytial Virus
RULM	Revised Upper Limb Module
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SMA	Spinal muscular atrophy
SMN1	Survival of Motor Neuron 1
SMN2	Survival of Motor Neuron 2
SNAP	Sensory nerve action potential
TBL	Total bilirubin
TMA	Thrombotic Microangiopathy
ULN	upper limit of normal
US	United States
vg	vector genome
WHO	World Health Organization

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g., any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g., 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate

Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Investigational Product/ Investigational Medicinal product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference (such as an active comparator) in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study or the participant allocated to an invalid stratification factor
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e., concomitant or rescue therapy)
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
CCI [redacted]	CCI [redacted]
Period	The subdivisions of the trial design (e.g., Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant
Rescreening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited twice for a new Screening visit after medical judgment and as specified by the protocol
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource

Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy.
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the investigator will conduct the trial.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g., as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

Amendment 4 (17-May-2024)

The main purpose of this amendment is to enhance the consultation between the Principal Investigator and Sponsor for patients retesting of abnormal laboratory that could be transient or measurement error for Period 2 eligibility.

The inclusion of Hy's Law reporting text was added to Section 10.2.2: SAE reporting to ensure compliance with FDA request for expedited reporting of potential Hy's Law cases.

Key changes to the protocol and the rationale for changes are summarized in the following table. Changes to specific sections of the protocol are shown using strike through red font for deletions and red text for insertions. Editorial changes for clarity are not included in the summary of changes table.

CCI

Amendment 3 (02-Jun-2023)

The main purpose of this protocol amendment is to revise several exclusion criteria so that they are now anchored to the Day 1 visit (day of OAV101 administration or the sham procedure).

Secondly, the number of participants listed in the five strata has been removed. CCI [redacted]

Finally, a theoretical risk of tumorigenicity due to vector DNA integration has been added to the OAV101 risks Section 4.5.3. The risk language has been revised to include the theoretical risk of tumorigenicity due to the very low potential incorporation of AAV vector DNA into chromosomal DNA that has been noted based on published literature for AAV-based therapies.

Summary of changes

Key changes to the protocol and the rationale for changes are summarized in the following table. Changes to specific sections of the protocol are shown using strike through red font for deletions and red text for insertions. Editorial changes for clarity as well as changes to align with an updated Novartis Clinical Trial Protocol Template are not included in the summary of changes table.

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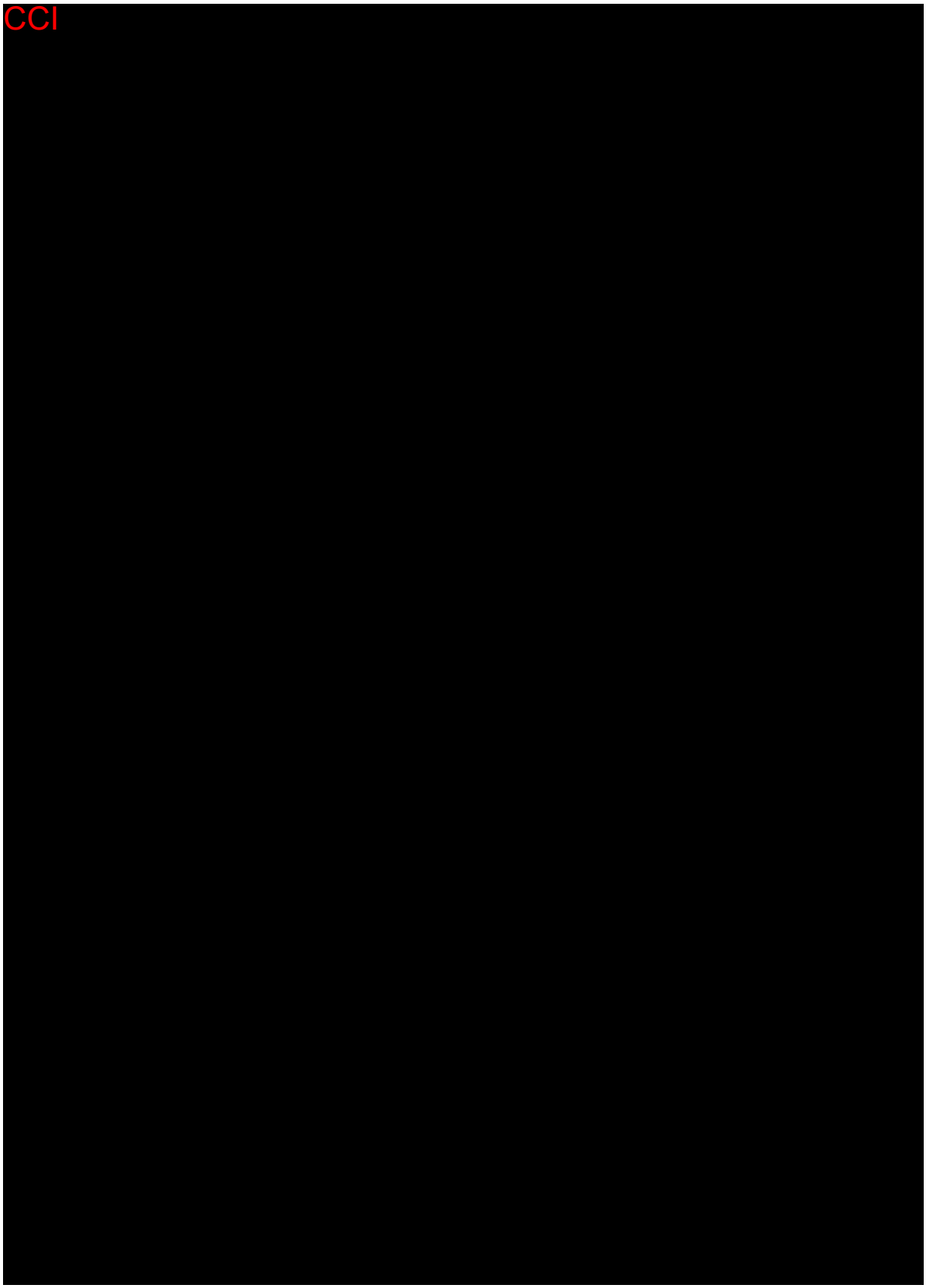
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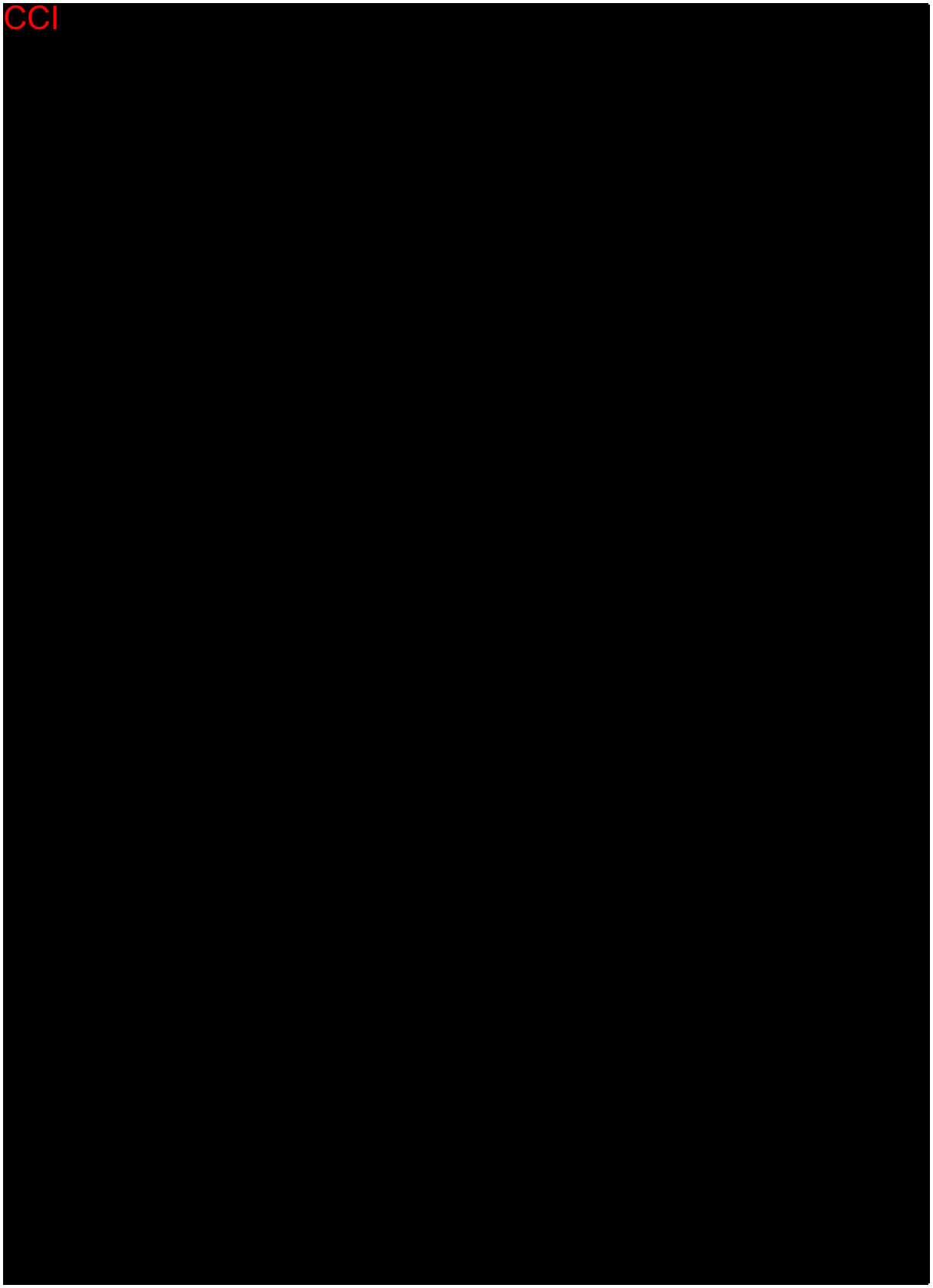
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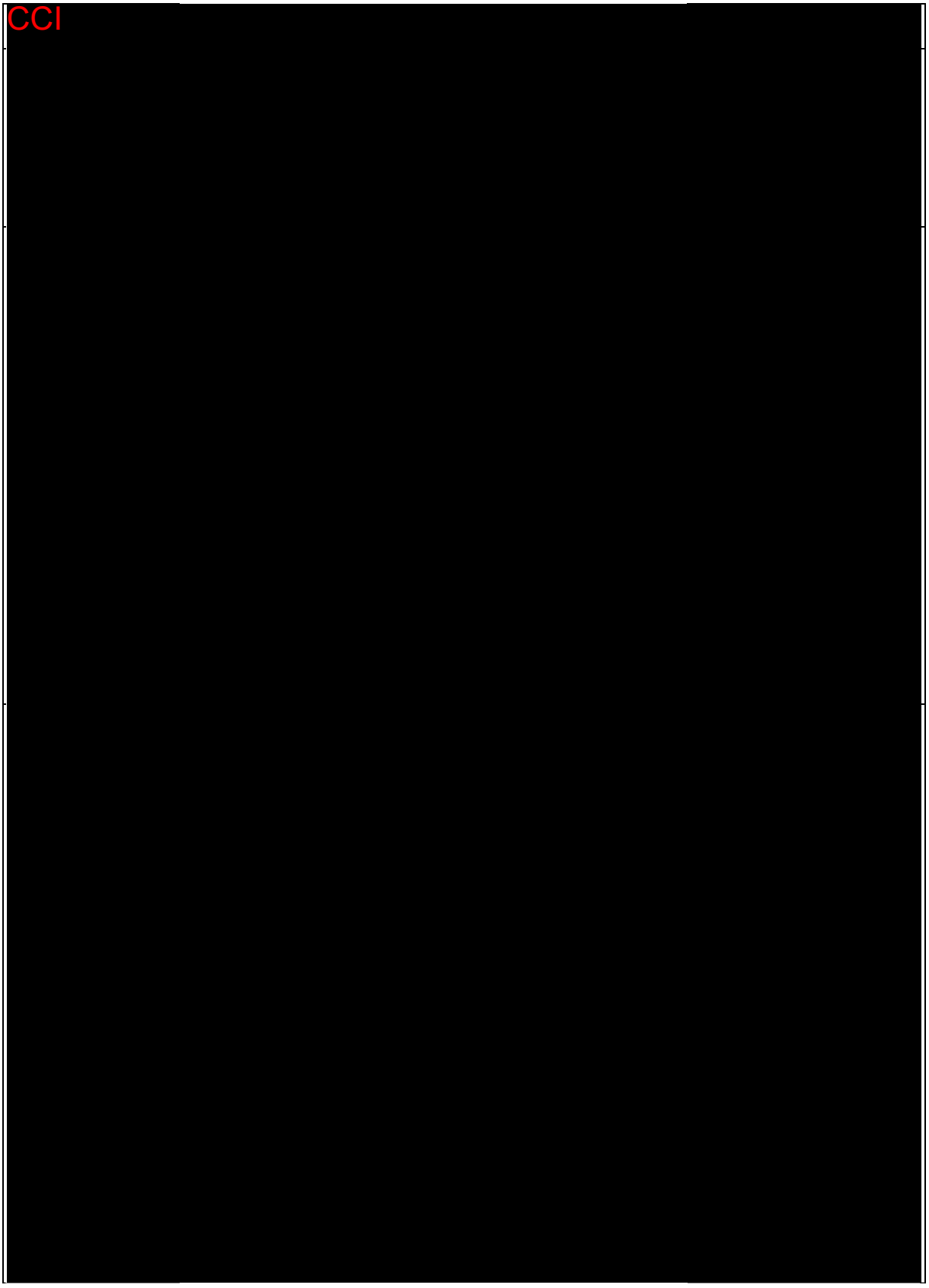
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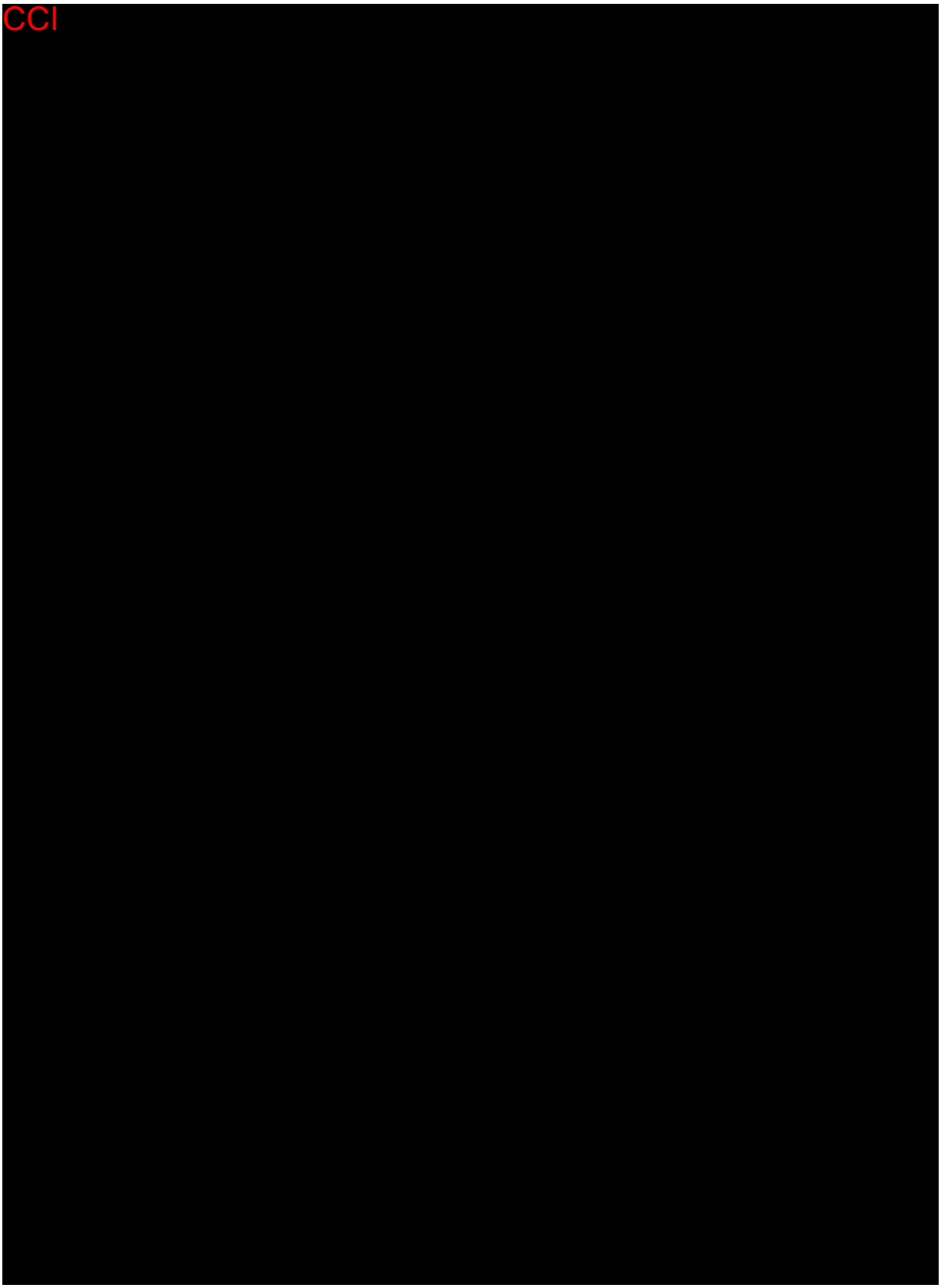
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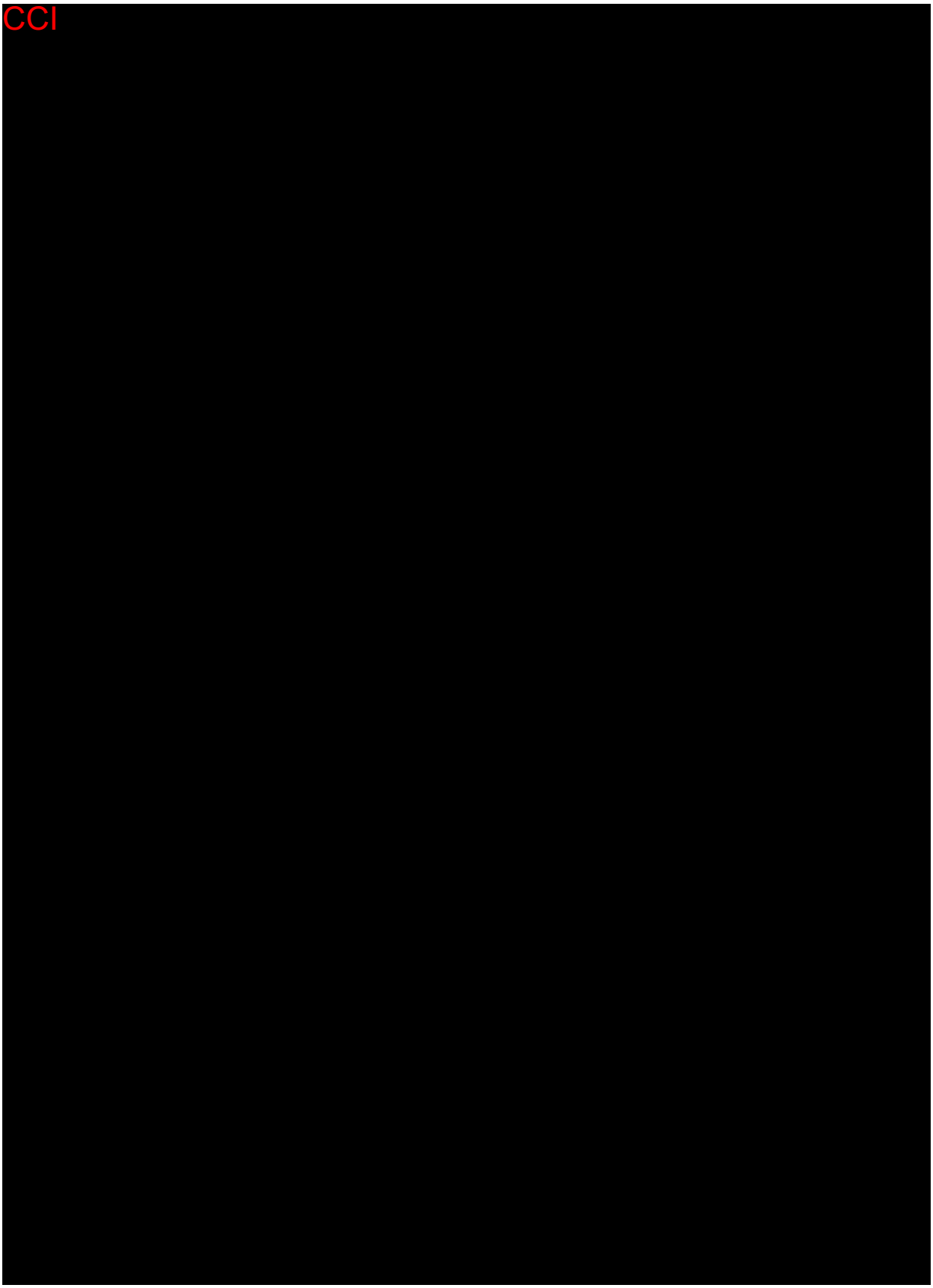
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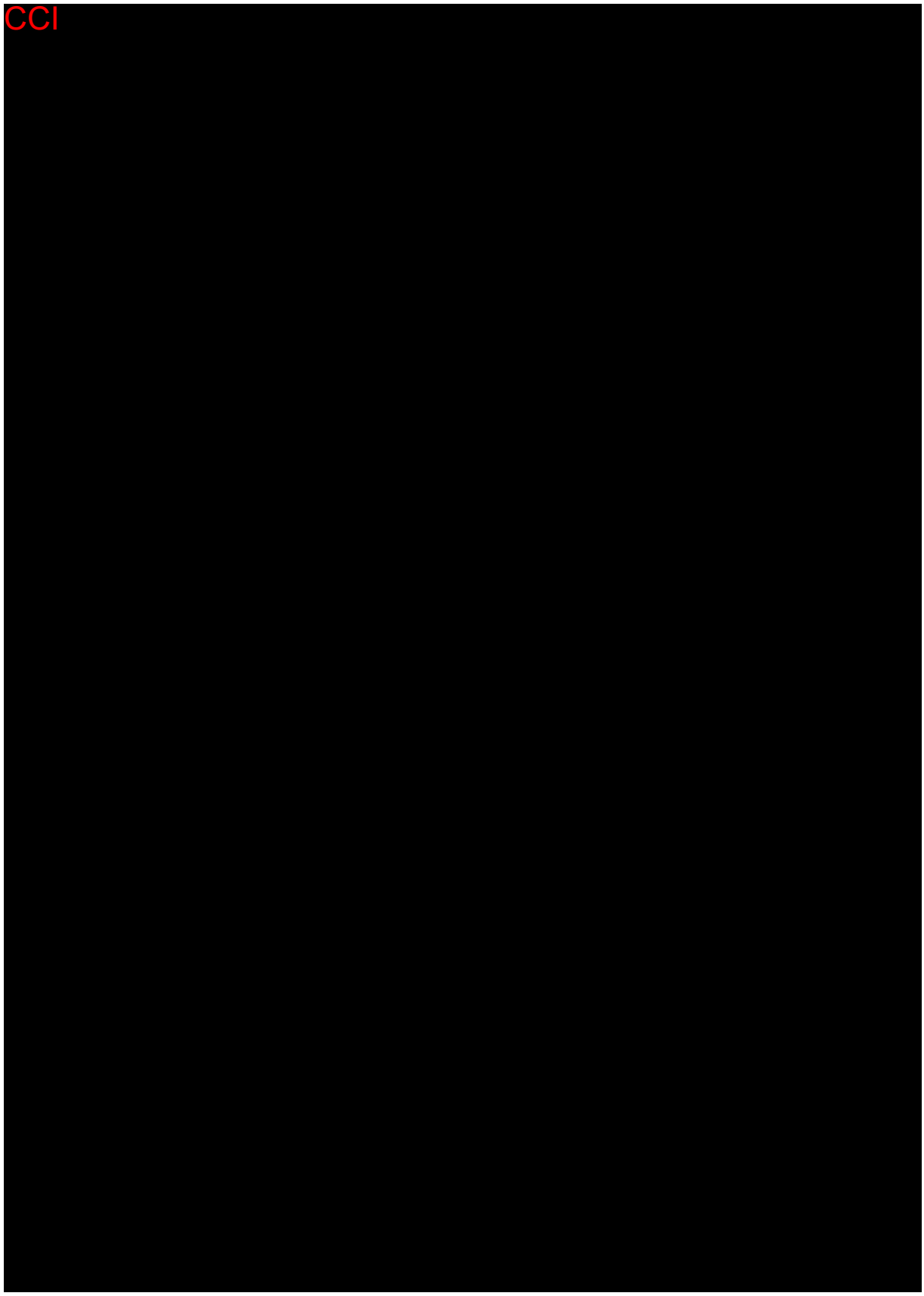
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IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 2 (08-Aug-2022)

The main purpose of this protocol amendment is to remove the use of the Central Treatment Site (hybrid model), which has not been utilized and is therefore not applicable for study execution.

Secondly, adaptations have been made to clarify that the threshold used for anti-AAV9 antibody titer is one that is reported to be elevated. The anti-AAV9 antibody titer testing lab may be changed to a new lab that is able to meet the documentation and procedures necessary for an investigational device exemption (IDE) by the FDA. Due to the nature of the immunoassay used to evaluate anti-AAV9 antibody titer, the reported titer value as elevated may be different.

In addition, further adaptations have been made for clarity including, mirroring exclusion criteria in treatment period 2 from treatment period 1 for safety considerations, and updating Section 4.5.3 on OAV101 risks. The risks of inaccurate anti-AAV9 antibody testing results was added because the test that's currently being used to assess eligibility has not been approved by regulatory authorities for this purpose. As of June 2022, in the post-marketing setting, acute liver failure cases have been reported, including 2 cases with fatal outcomes. Therefore, this update was included to the OAV101 risks section.

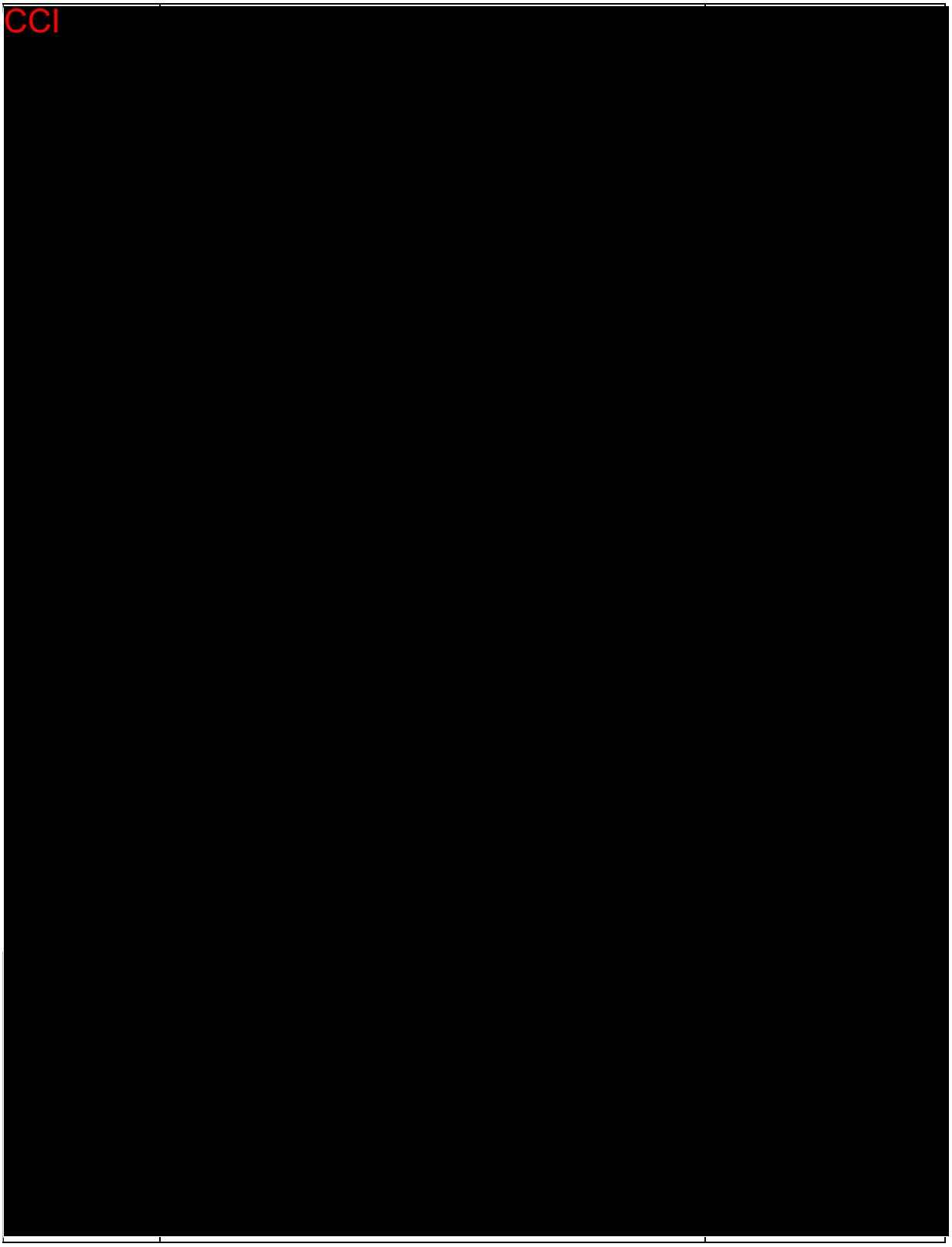
The visit schedule for troponin I collection was modified to better align with timepoints for electrocardiogram and echocardiogram assessments. Troponin I is a non-specific biomarker, which will likely provide limited value based on data from prior OAV101 studies. To date, all observed troponin I elevations have been isolated lab value elevations without associated signs or symptoms. ECG and ECHO, which are already incorporated into the study, will be used for cardiac safety monitoring. The revised visit schedule for troponin I now aligns with ECG and ECHO, as well as with other ongoing OAV101 studies.

Finally, sensory nerve action potential (SNAP) evaluation on asymptomatic participants is no longer applicable and therefore was removed for clarity. All patients will undergo a neurological exam and SNAP at screening, and those with clinically significant sensory abnormalities in the neurological examination or those who are unable to obtain SNAP, will not be eligible. Post-treatment, SNAP will ONLY be performed if there are sensory abnormalities in the neurological examination. Therefore, there will be no cases of asymptomatic participants for SNAP evaluation.

Editorial changes have been made throughout for clarity and are not included in the Summary of key changes table. Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

Summary of changes

Key changes to the protocol and the rationale for changes are summarized in the following table. Changes to specific sections of the protocol are shown using strike through red font for deletions and red text for insertions.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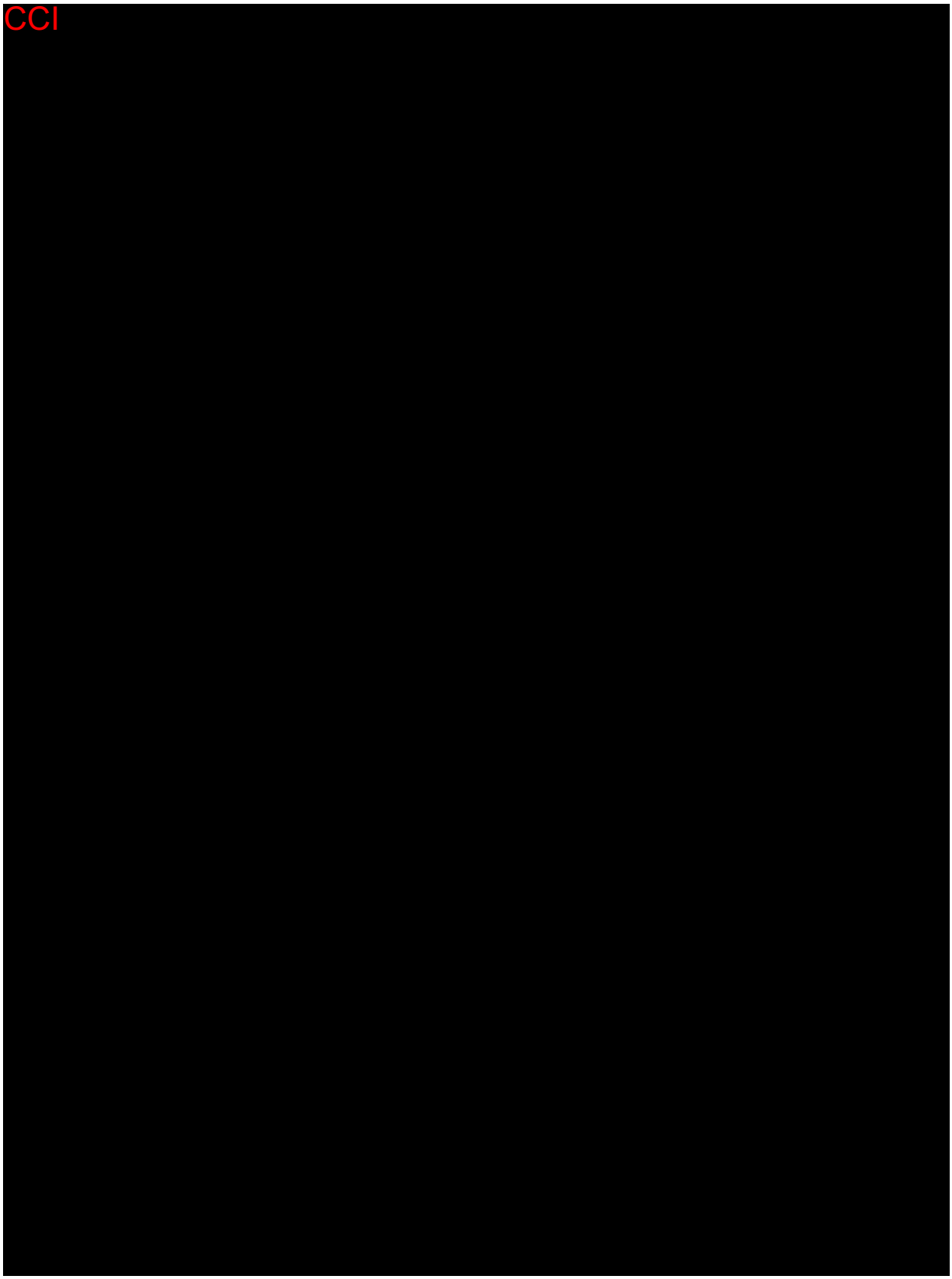

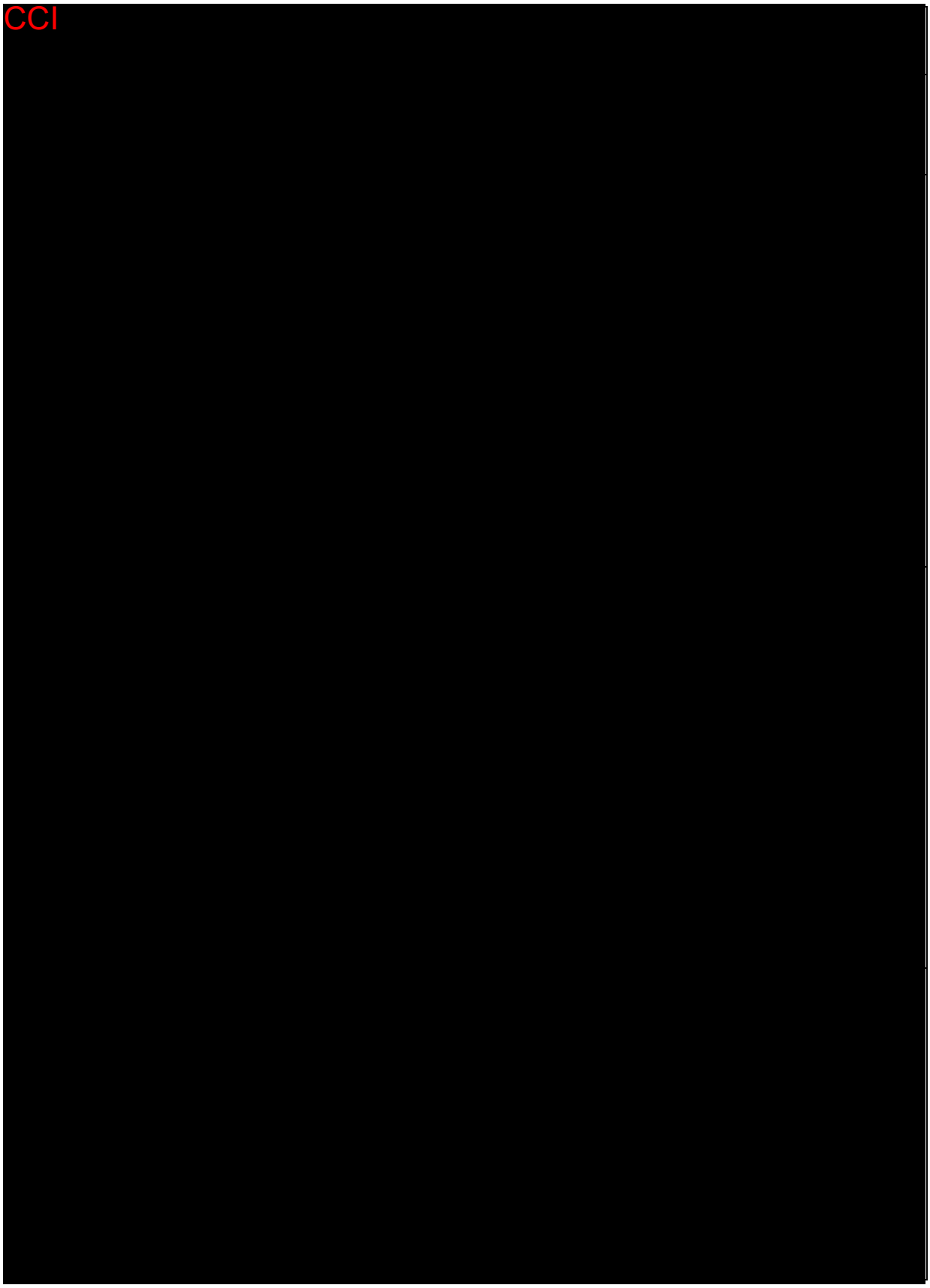
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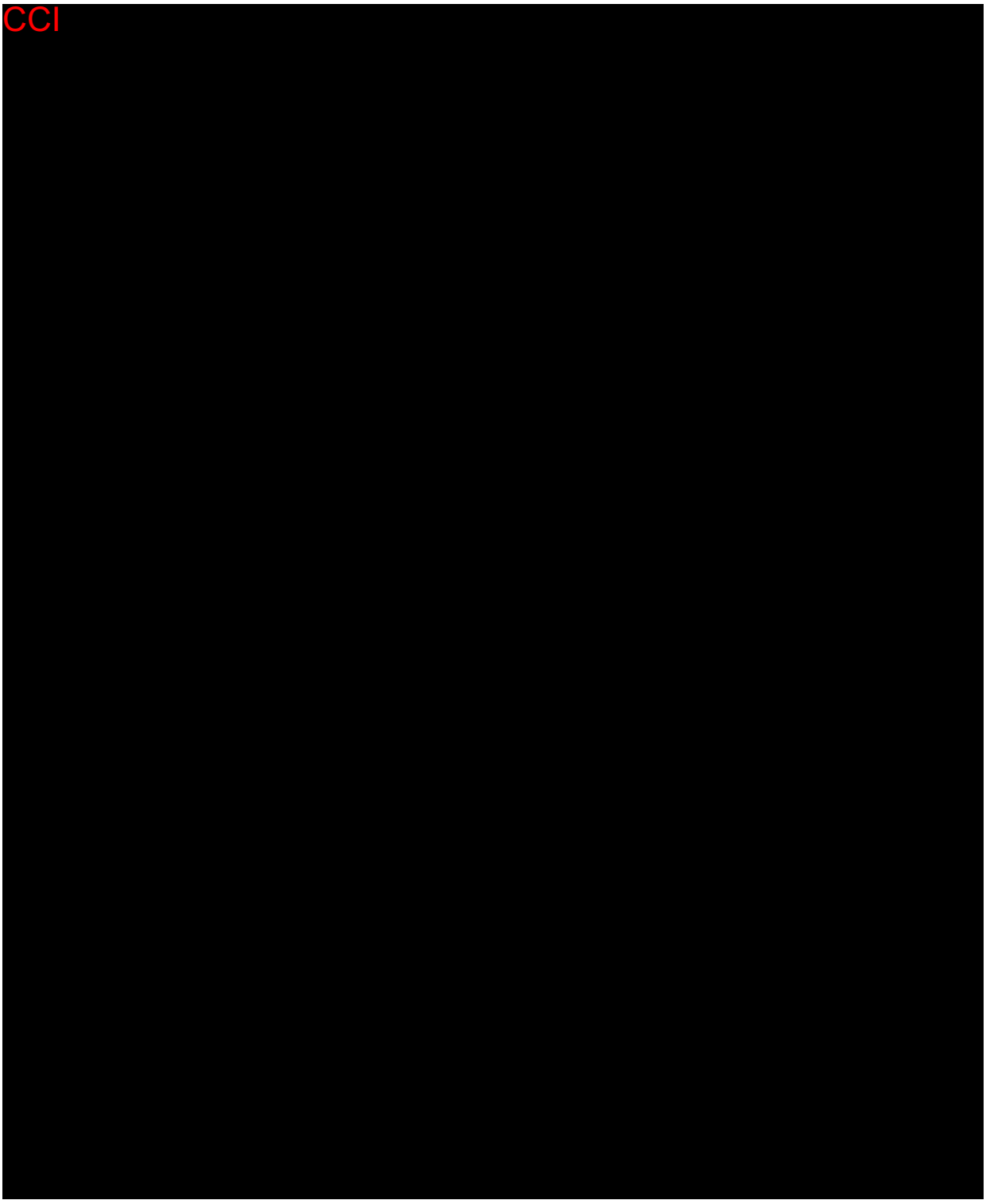
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Amendment 1 (11-Mar-2022)

CCI [redacted] The data analysis and statistical methods section were revised to include the following two secondary endpoints:

- Achievement of at least a 3-point improvement from baseline in HFMSE total score at the end of Follow-up Period 1 in the overall study population
- Achievement of at least a 3-point improvement from baseline in HFMSE total score at the end of Follow-up Period 1 in the ≥ 2 to < 5 years age group

In addition, the schedule of sensory nerve action potential (SNAP) assessments has been modified in view of ethical consideration and clinical best practice to ensure evaluation and monitoring of potential neurotoxicity SNAPs will be evaluated in all patients at screening as described in the previous protocol version. However SNAP evaluation at five post-treatment visits has been adjusted. The neurological examination, which is already incorporated in the protocol at every post-treatment visit, will be used to primarily evaluate potential sensory abnormalities in patients. Upon detection of a potential sensory abnormality, a SNAP assessment will then be performed as a secondary evaluation. The core rationale for the change is as follows:

- Standard clinical practice is to begin with a neurological exam, which is expected to be more sensitive than SNAP in detecting sensory abnormalities
- Given the range of expertise in electrophysiology across clinical sites for this global study, the SNAP data are expected to be variable (as confirmed by our clinical expert on SNAP)
- The SNAP procedure is not benign and can be quite painful to a child and may pose discomfort to patients across multiple study visits

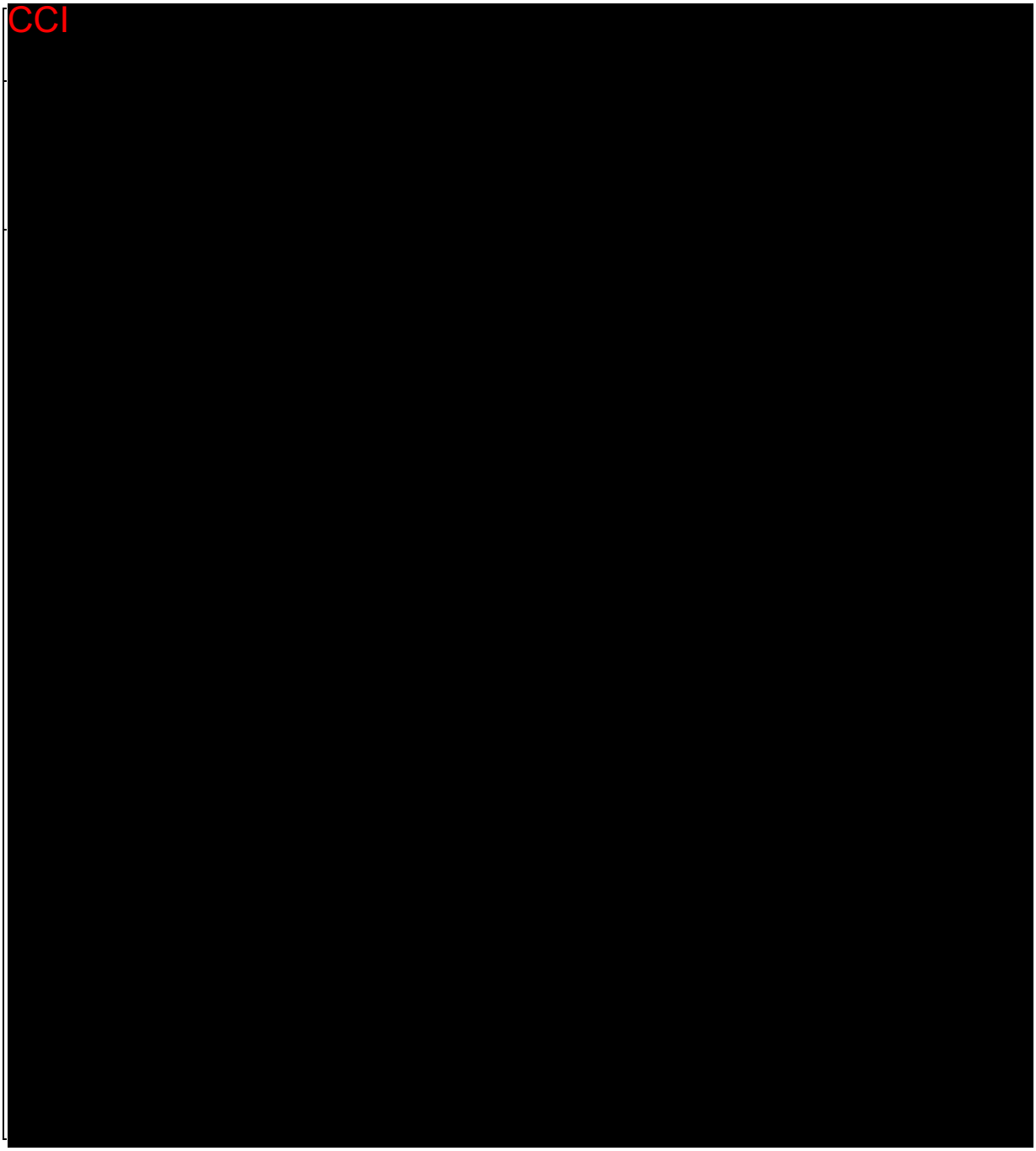
Finally, edits were made to the inclusion and exclusion criteria to provide additional clarity. Inclusion criterion #2 related to CCI [redacted] is not critical to defining the study population of Type 2 SMA. The study population can be defined by genetic confirmation of 5q SMA along with clinical symptoms of being able to sit independently but never having walked independently (inclusion criterion #7). Due to feedback from investigators at sites, several of the exclusion criteria were revised to provide more clarity, such as adding specific timeframes. In addition, several exclusion criteria were added with rationale provided in the Summary of key changes table.

Editorial changes as well as changes to align with Novartis' Clinical Trial Protocol Template Version 5.0 (14-Jan-2022) have been made throughout for clarity and are not included in the Summary of key changes table. Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation.

Summary of changes

Key changes to the protocol and the rationale for changes are summarized in the following table. Changes to specific sections of the protocol are shown using strike through red font for deletions and red text for insertions.



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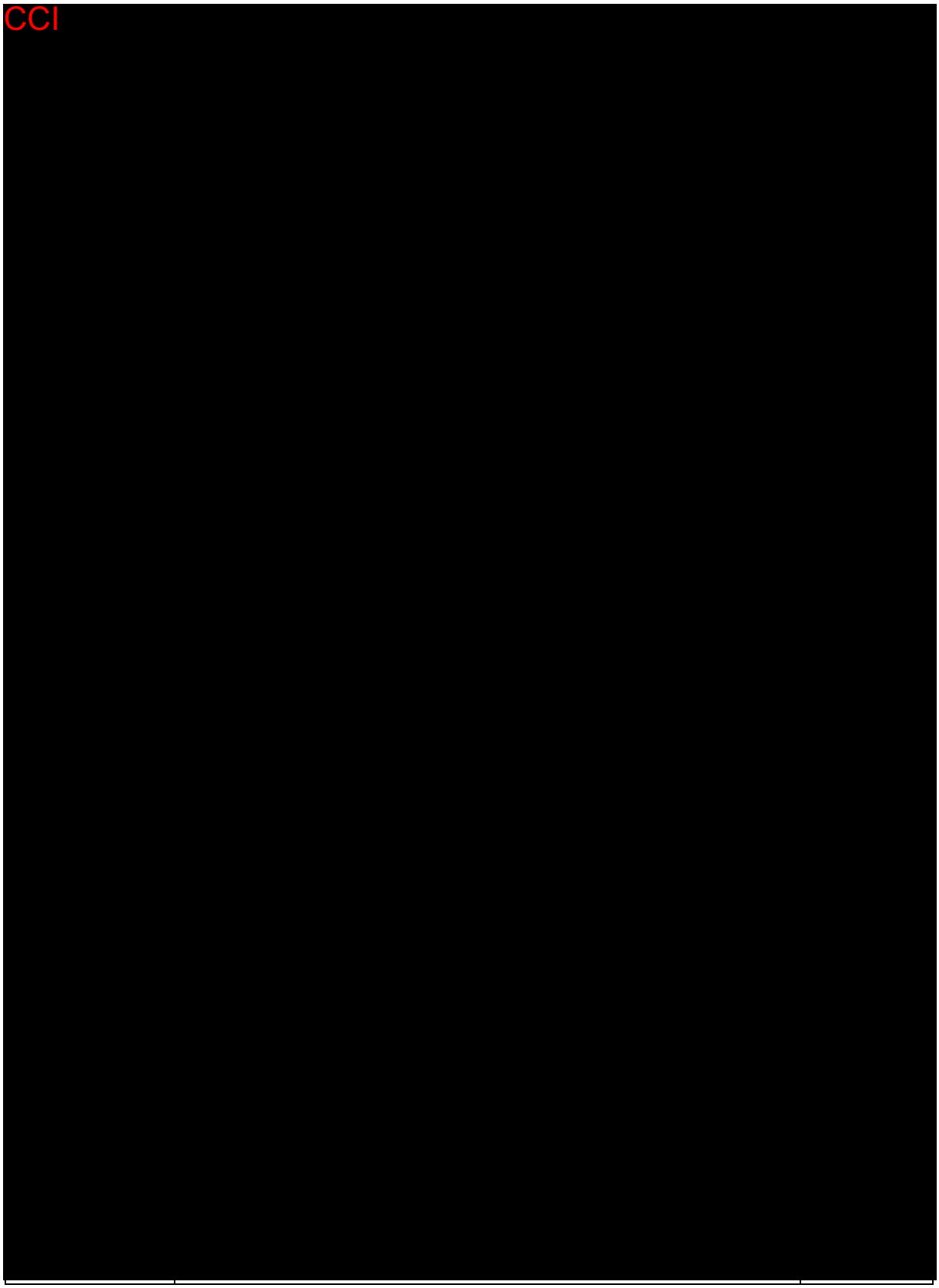
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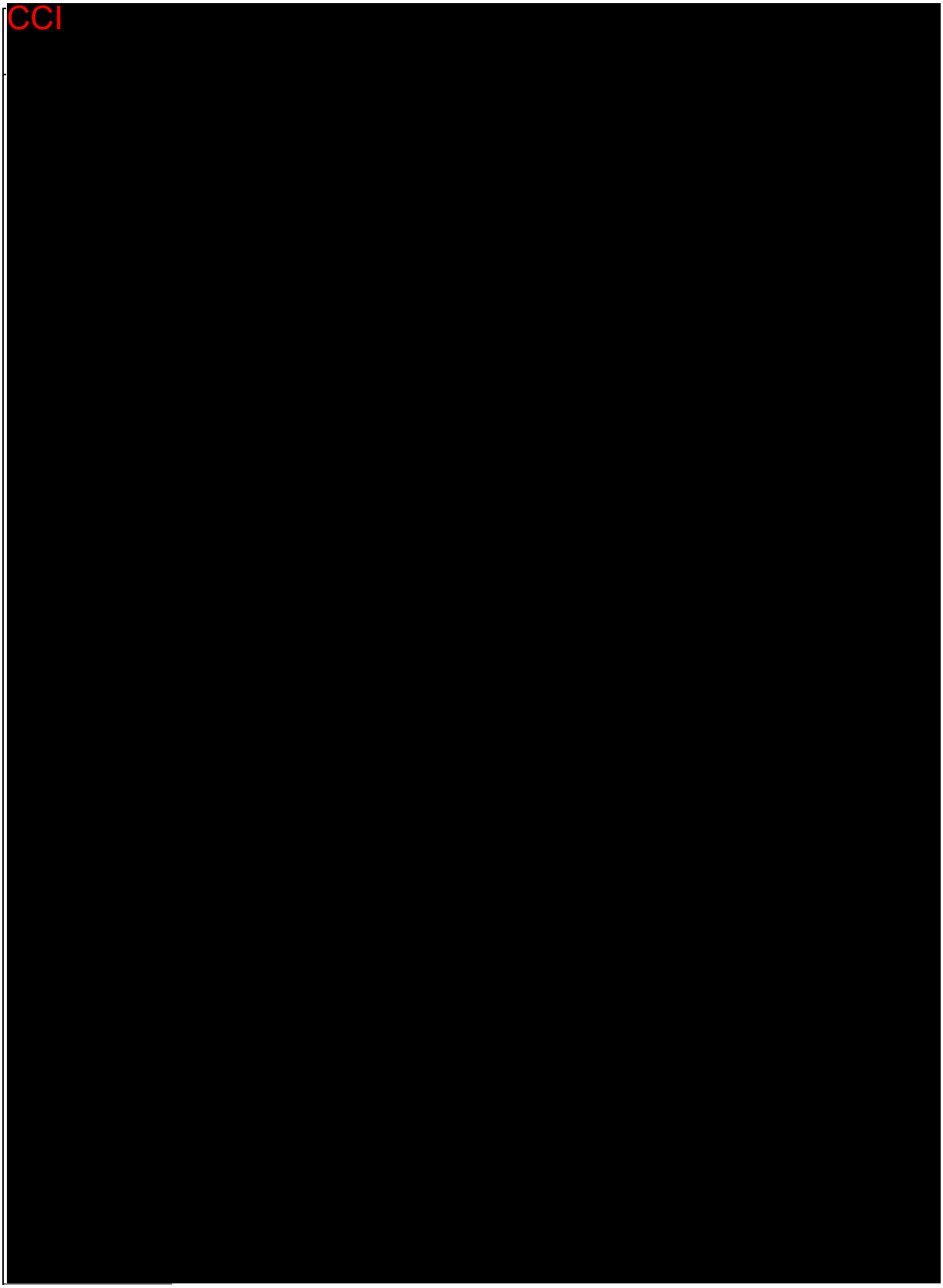
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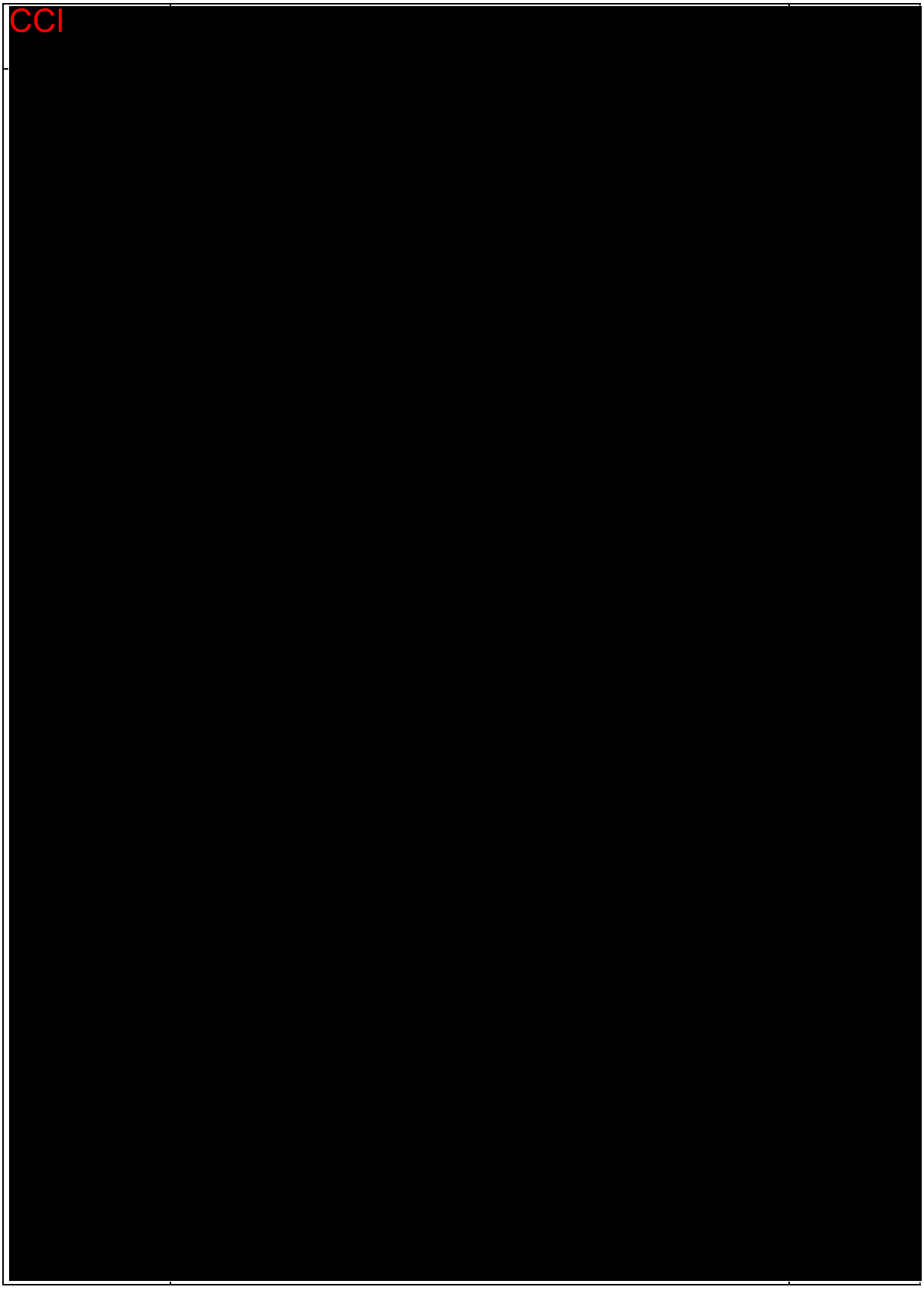
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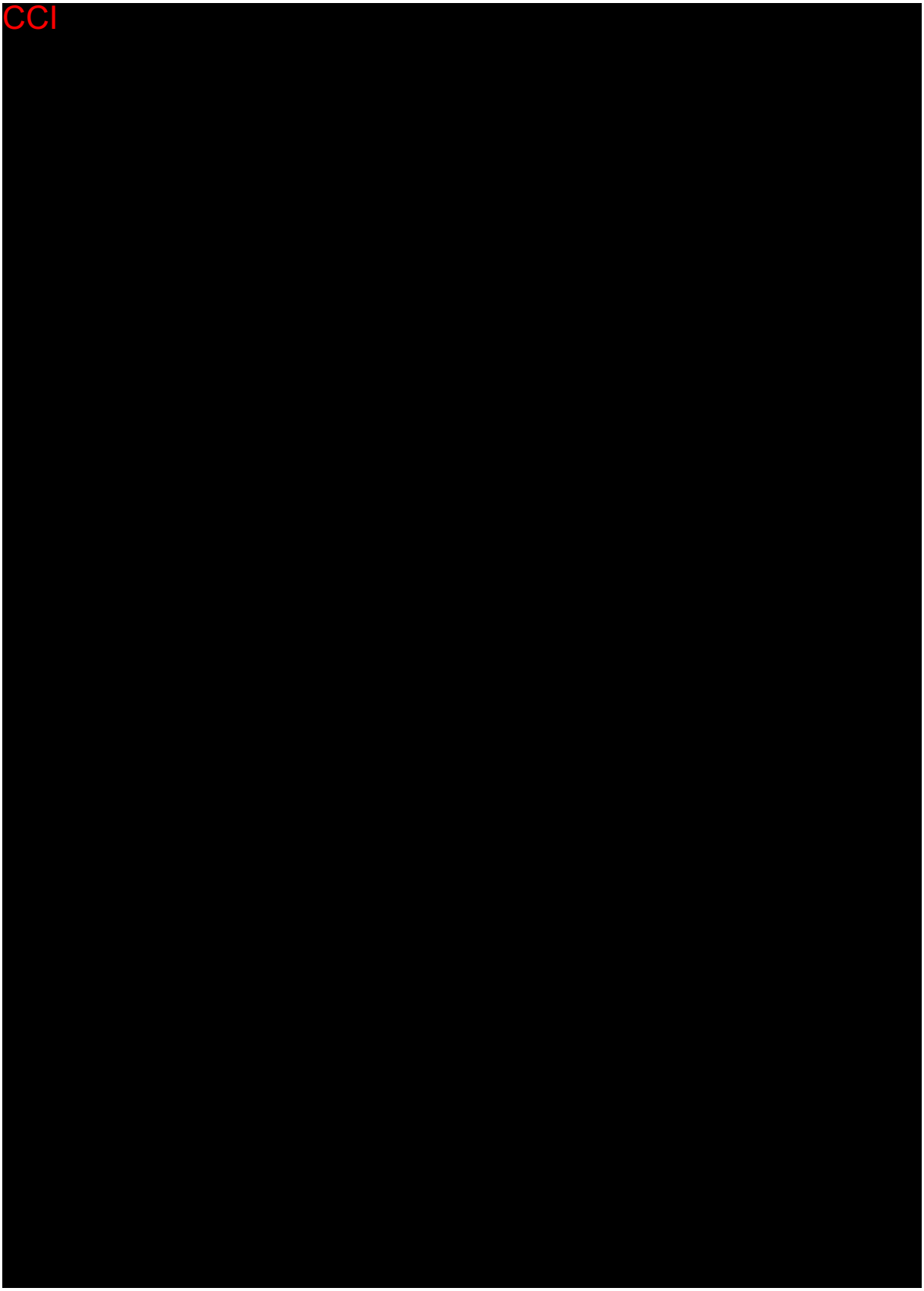
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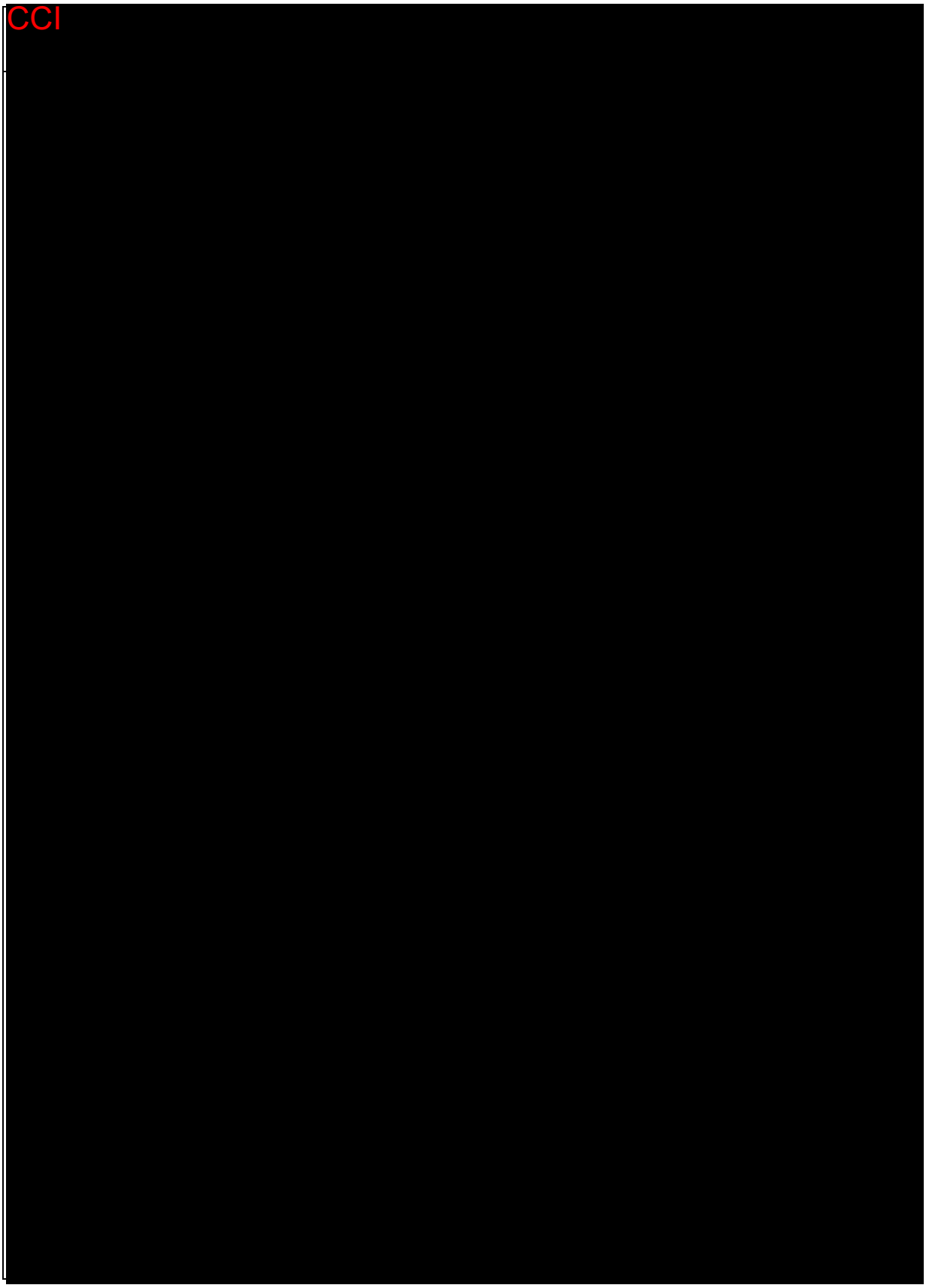
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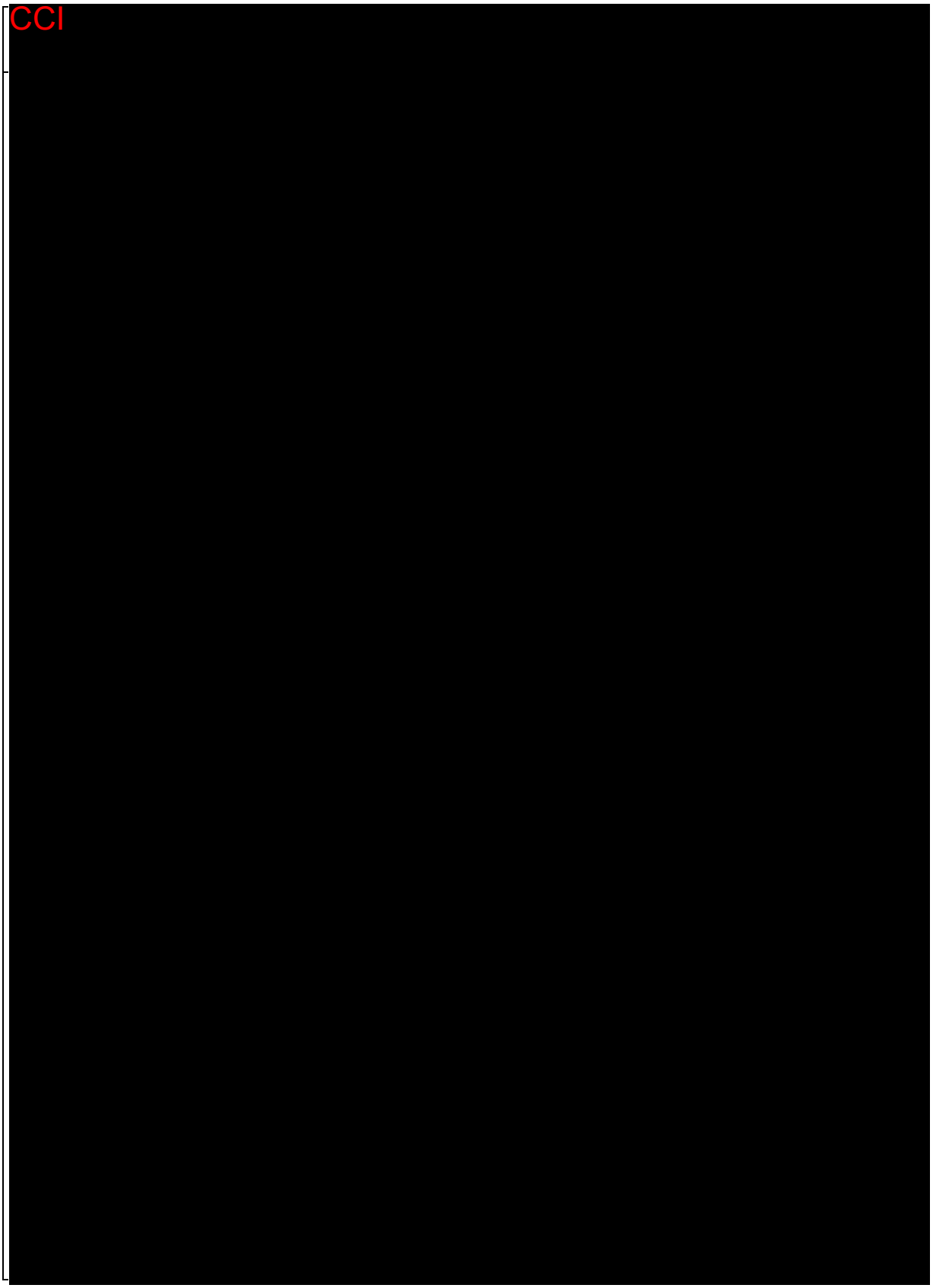
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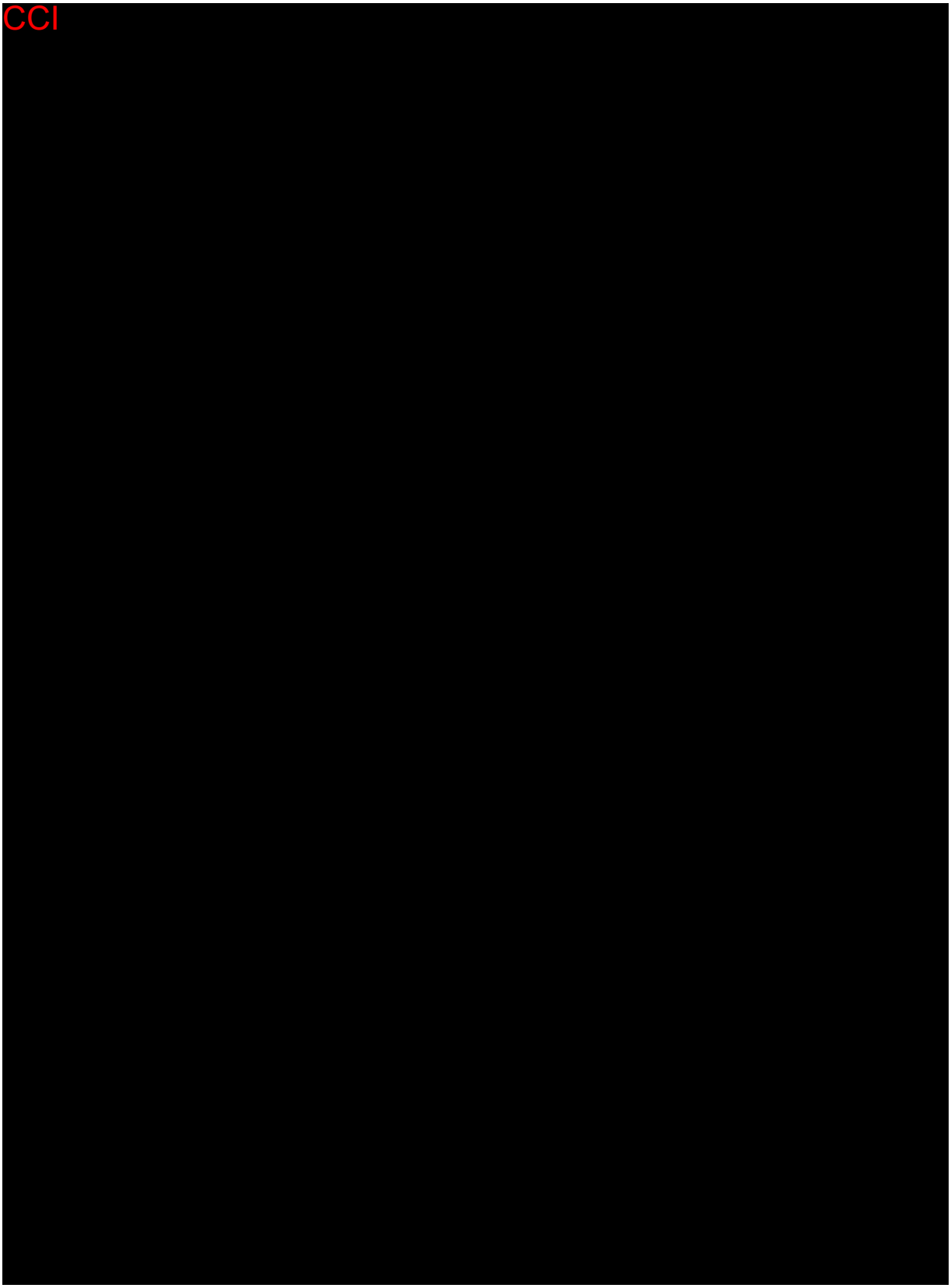
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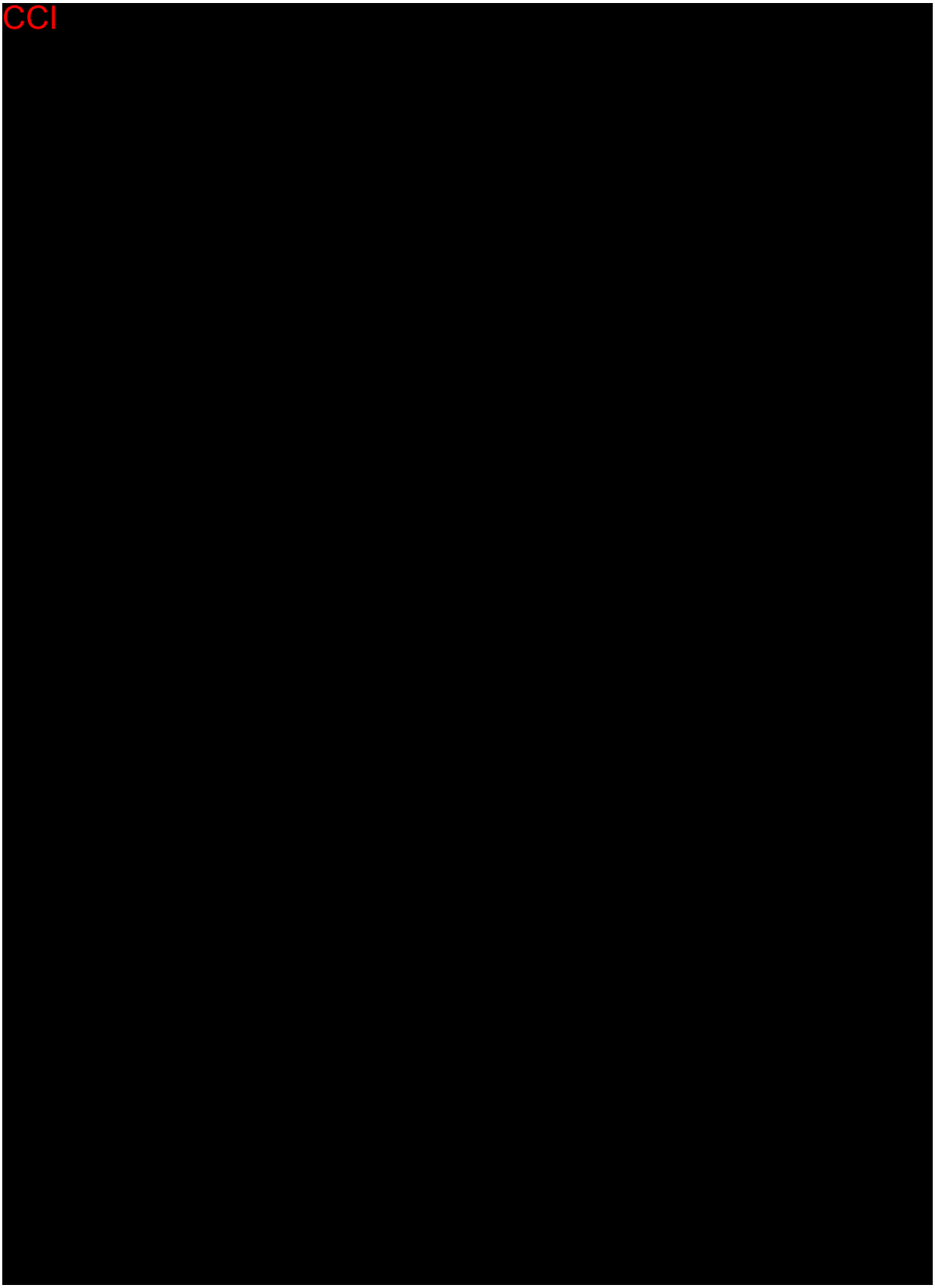

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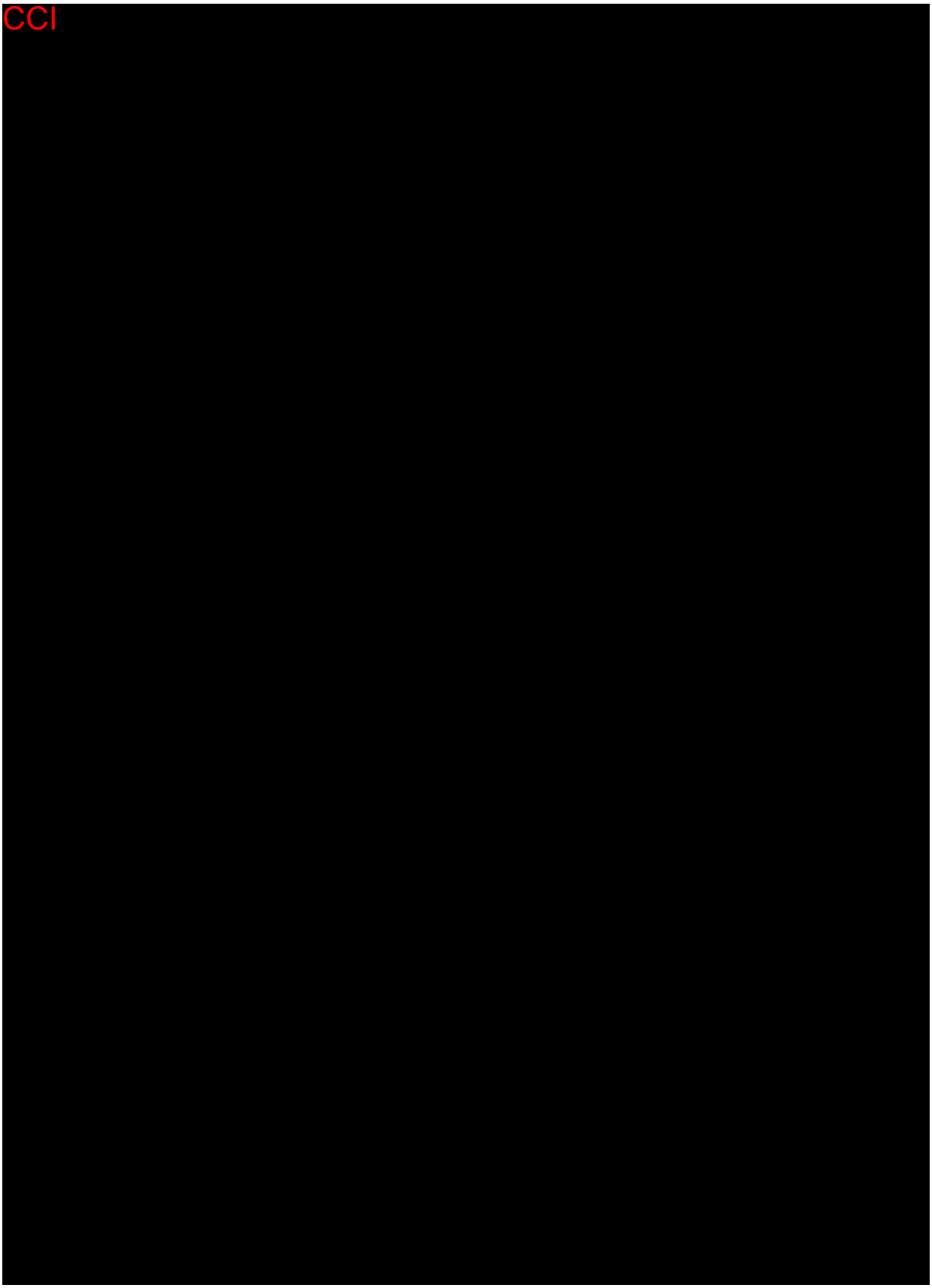

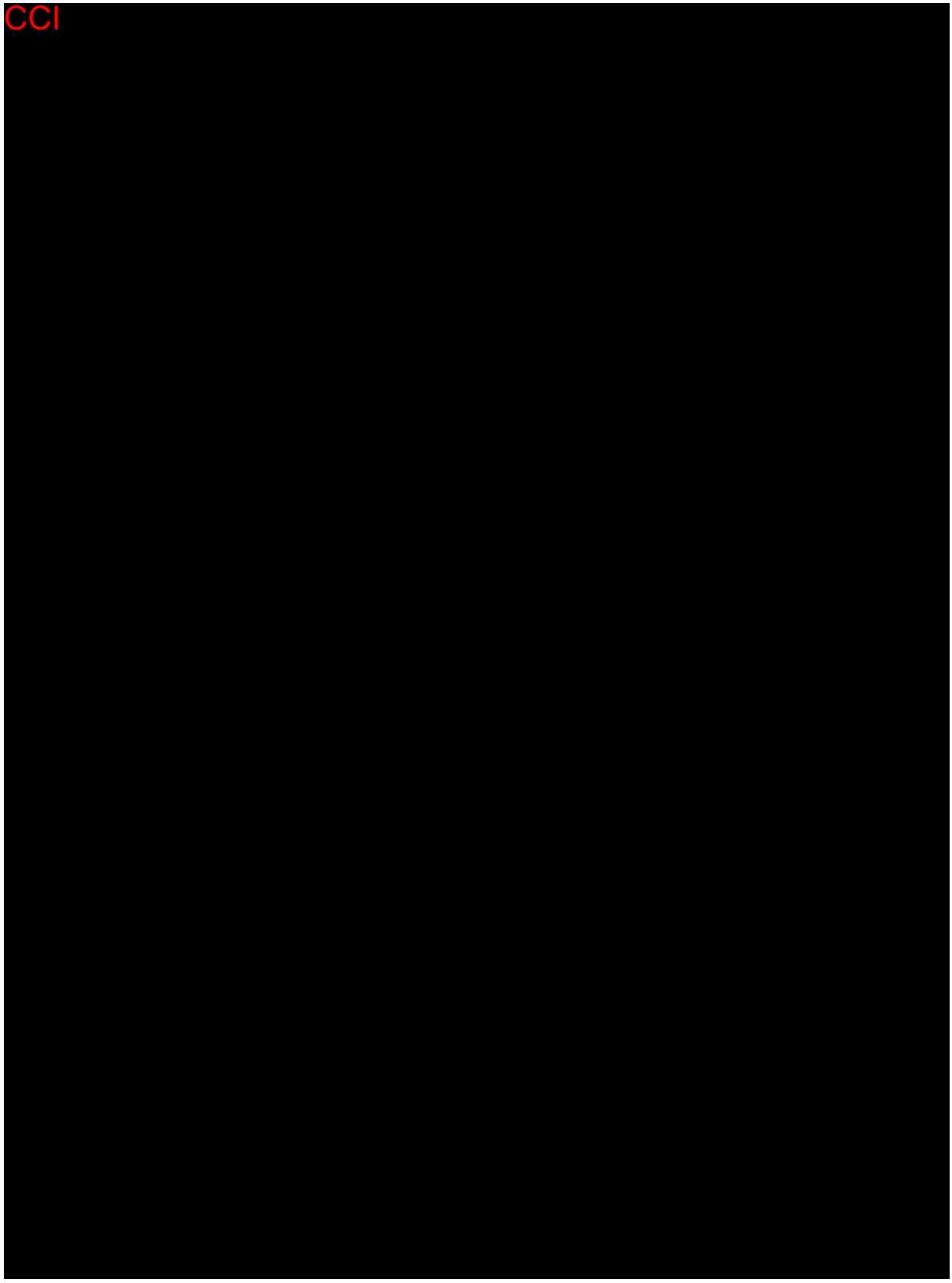
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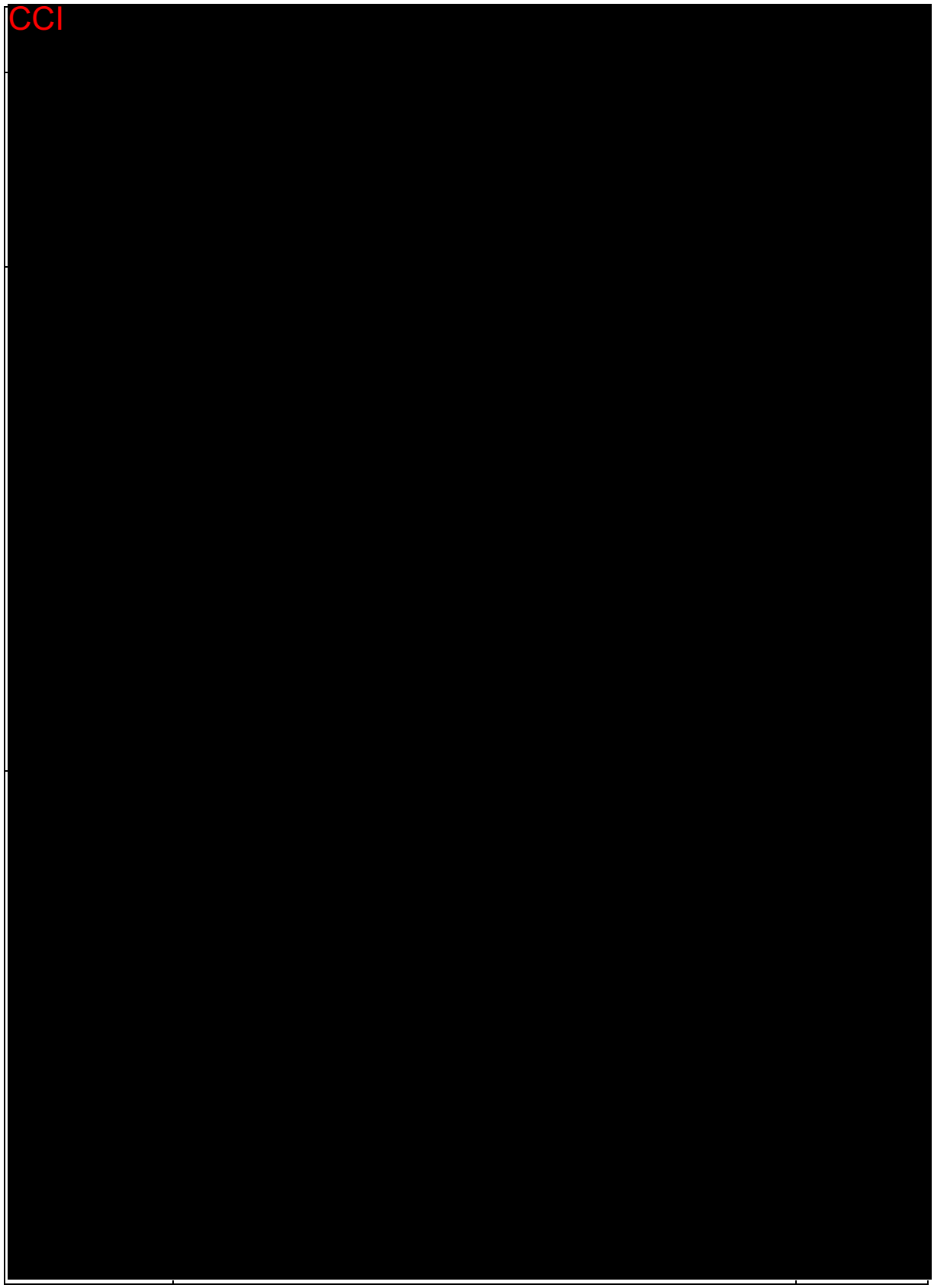
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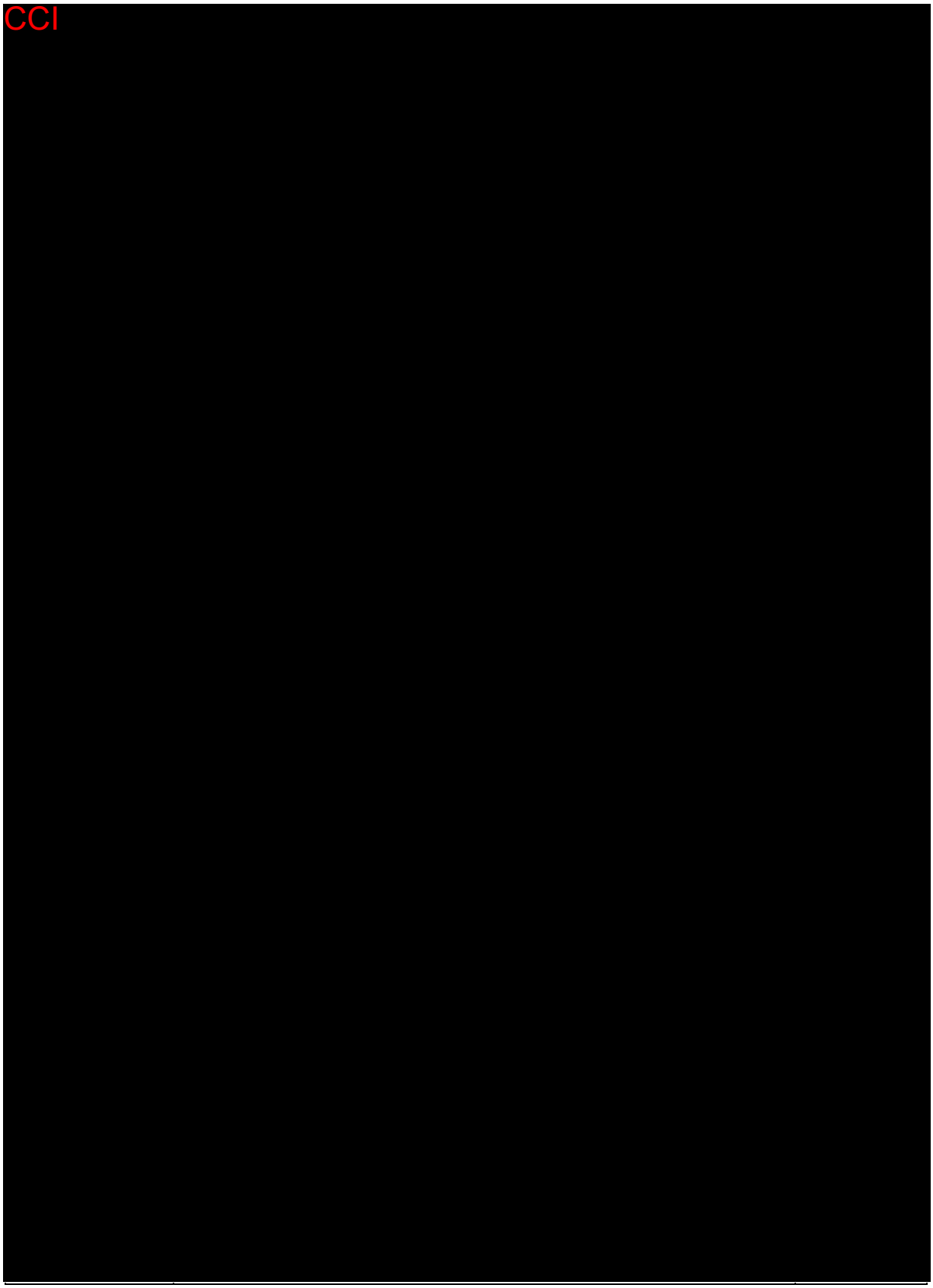
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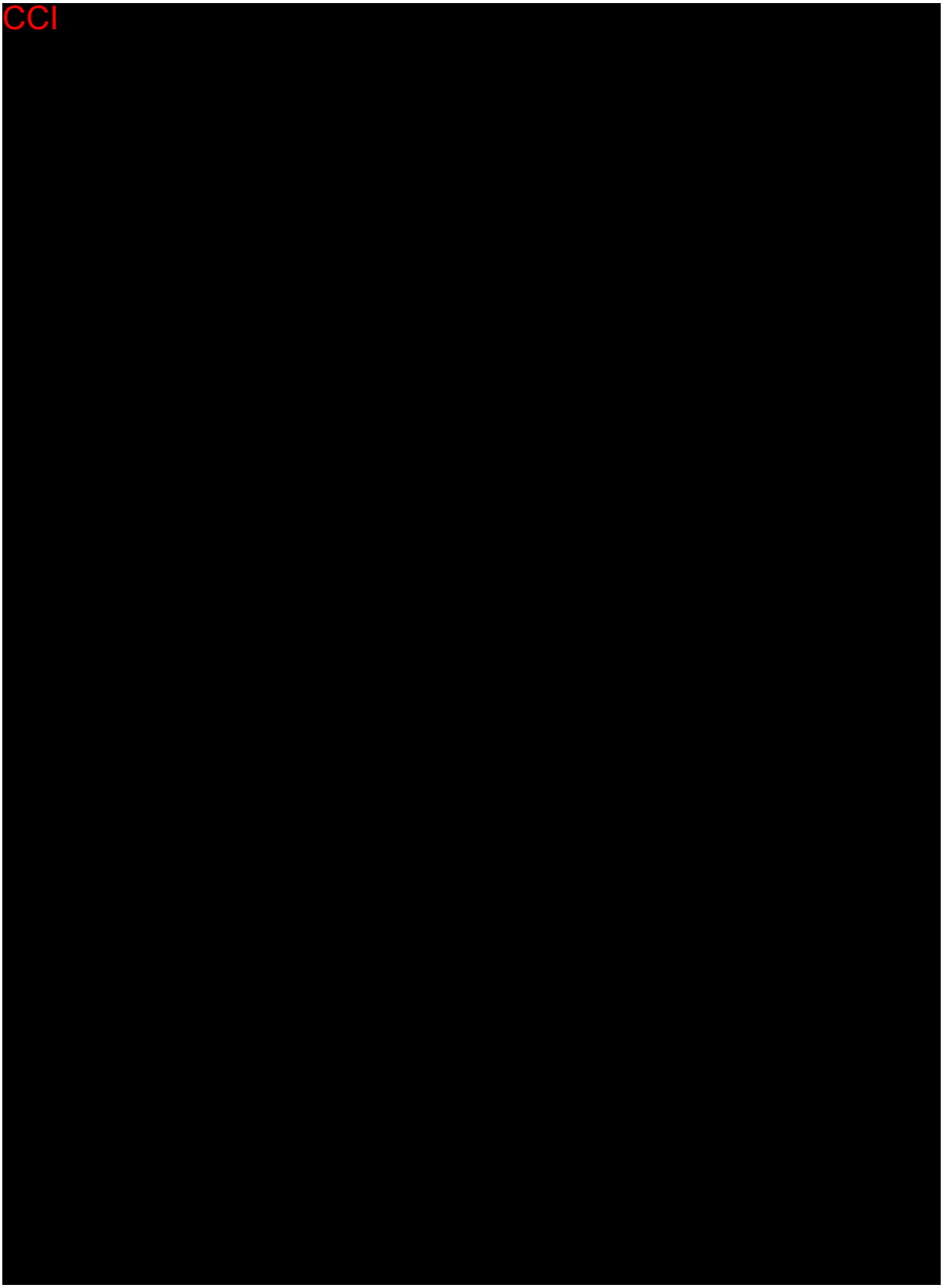
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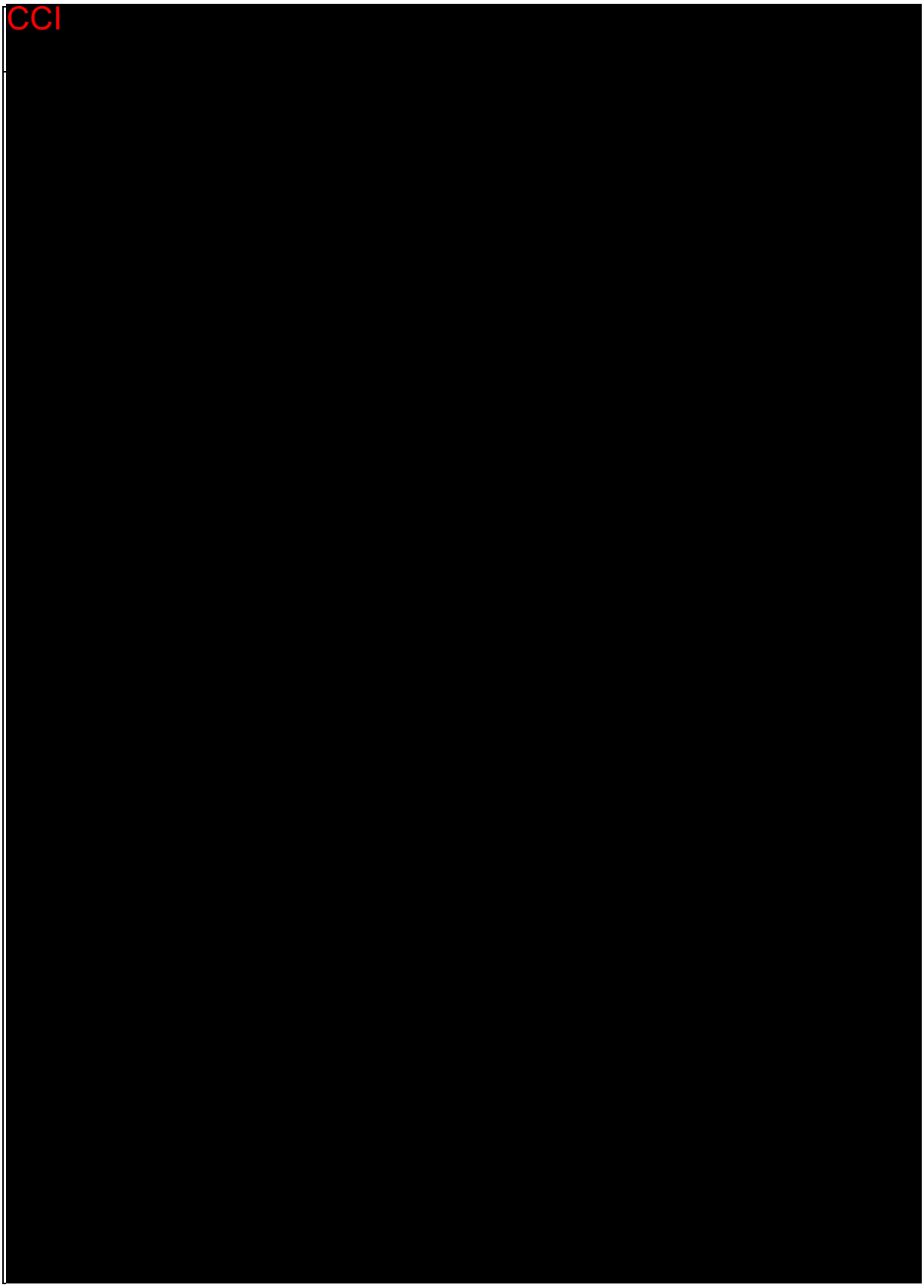
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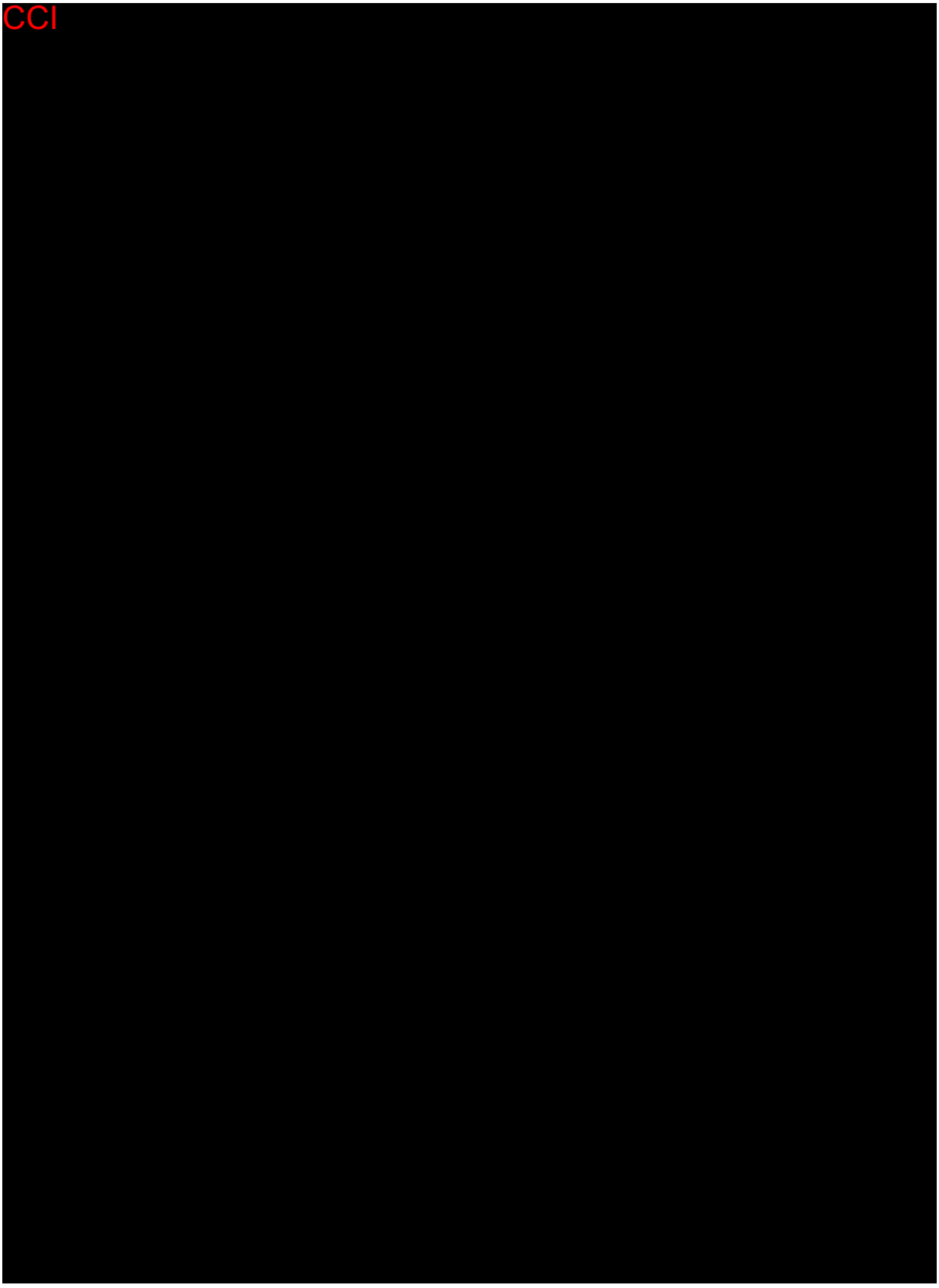
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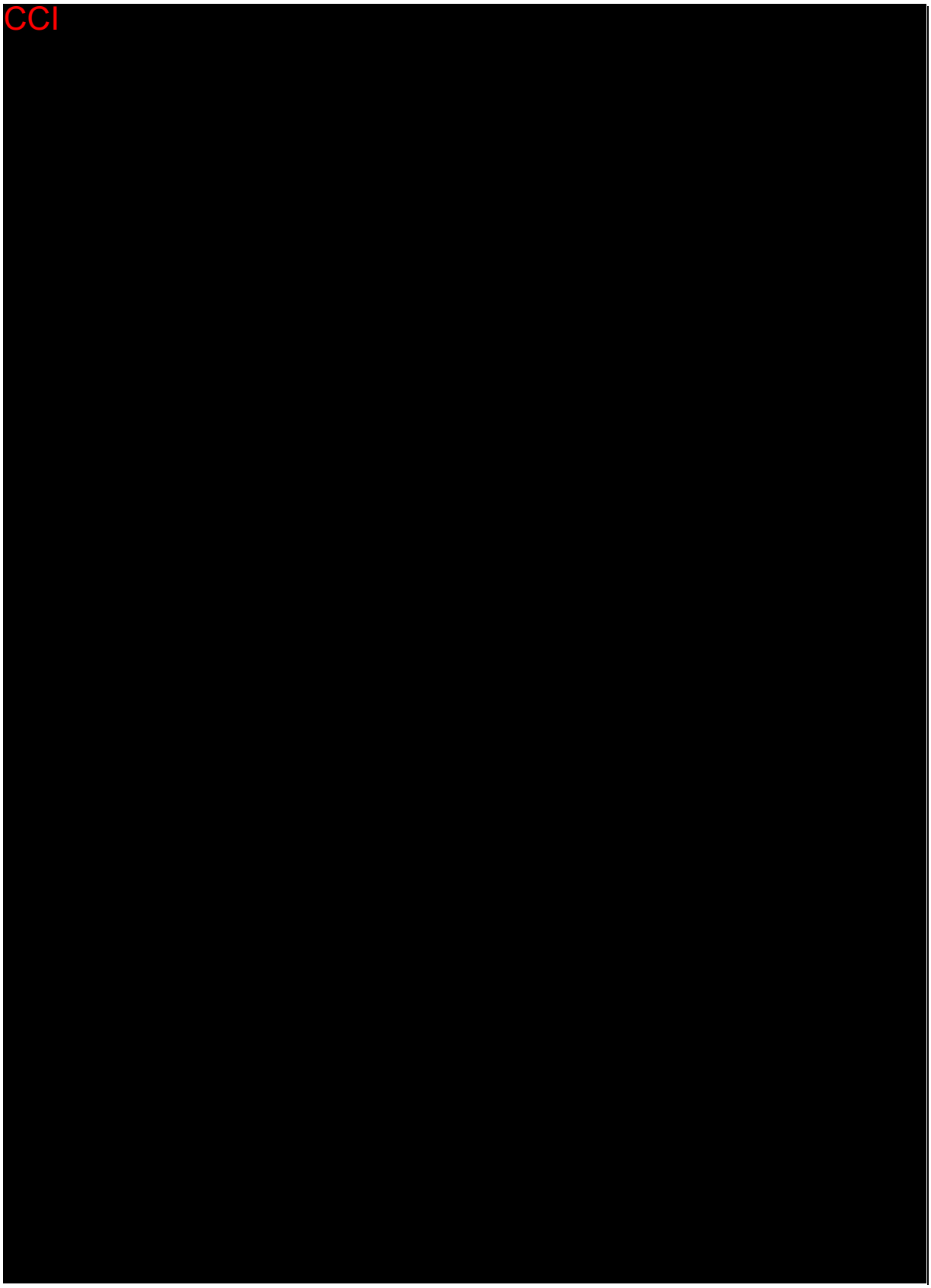
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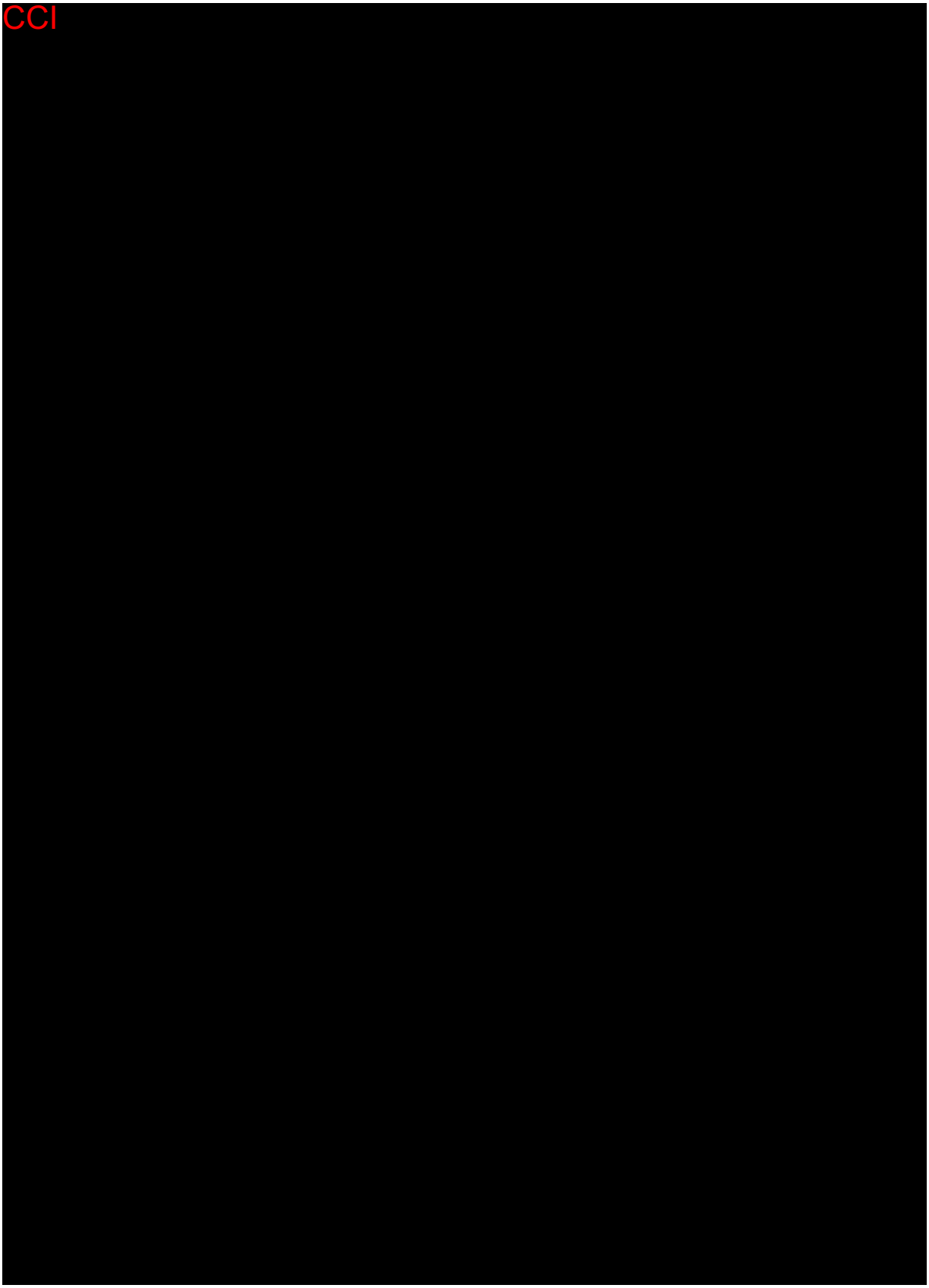
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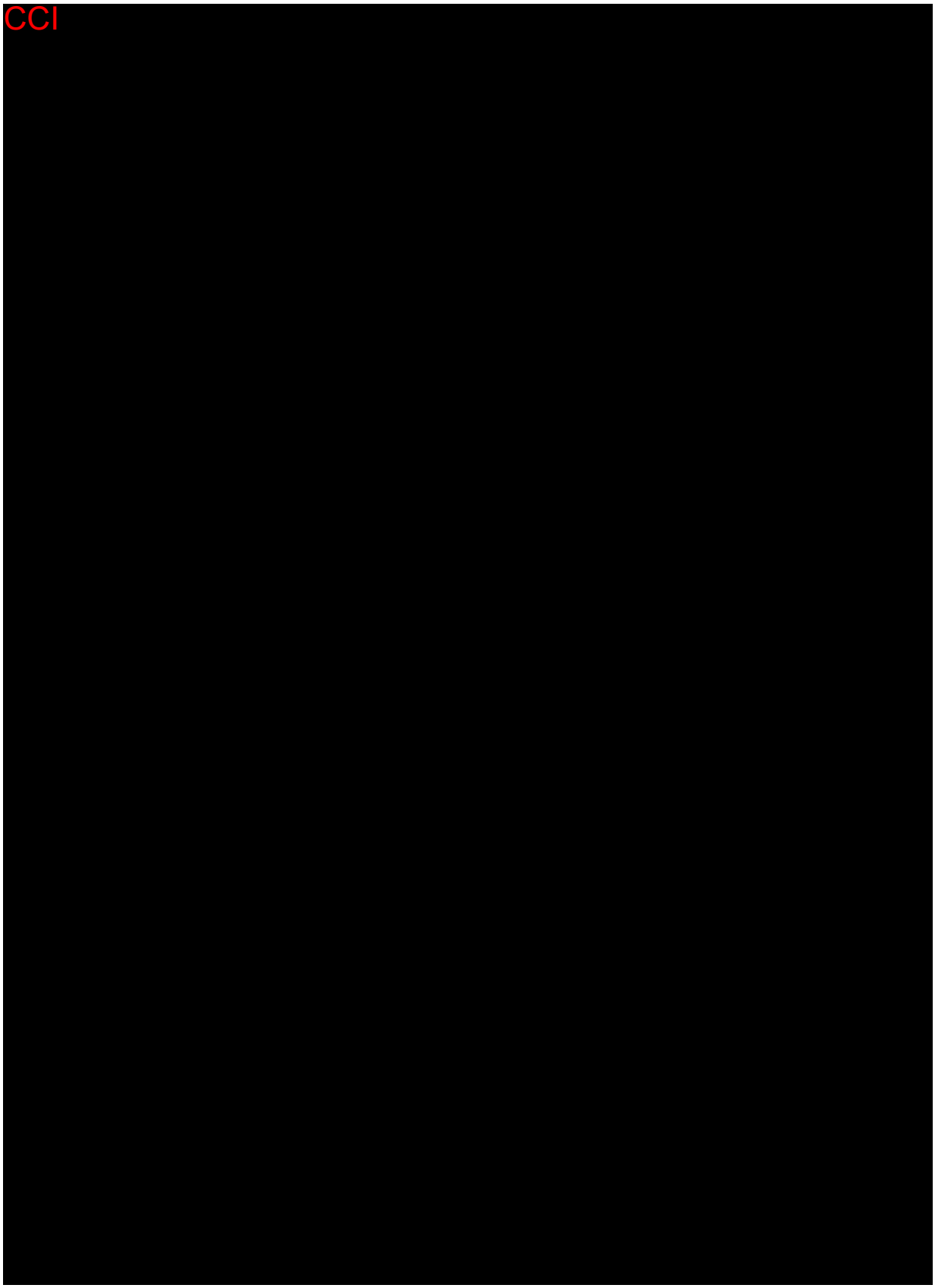
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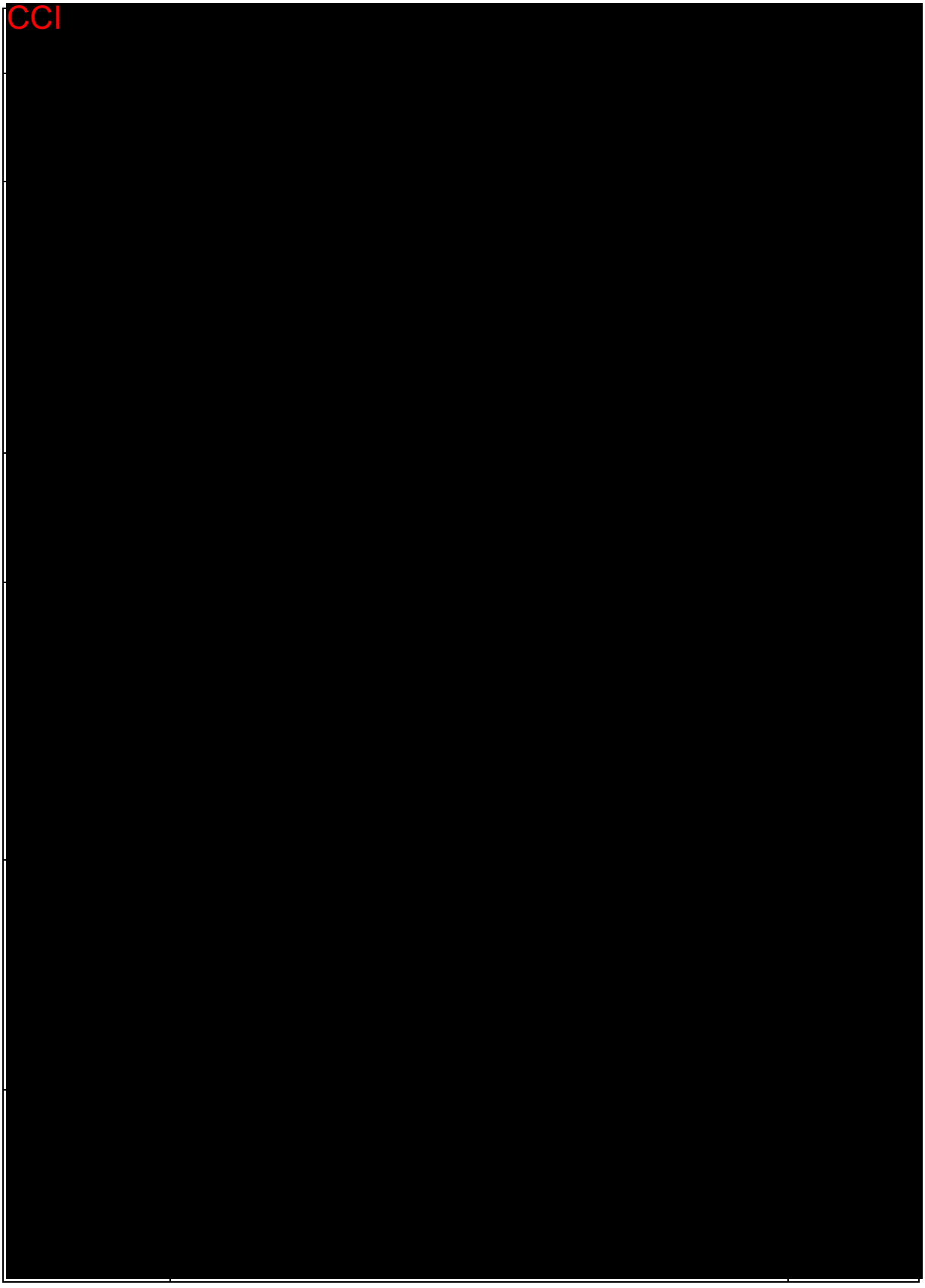
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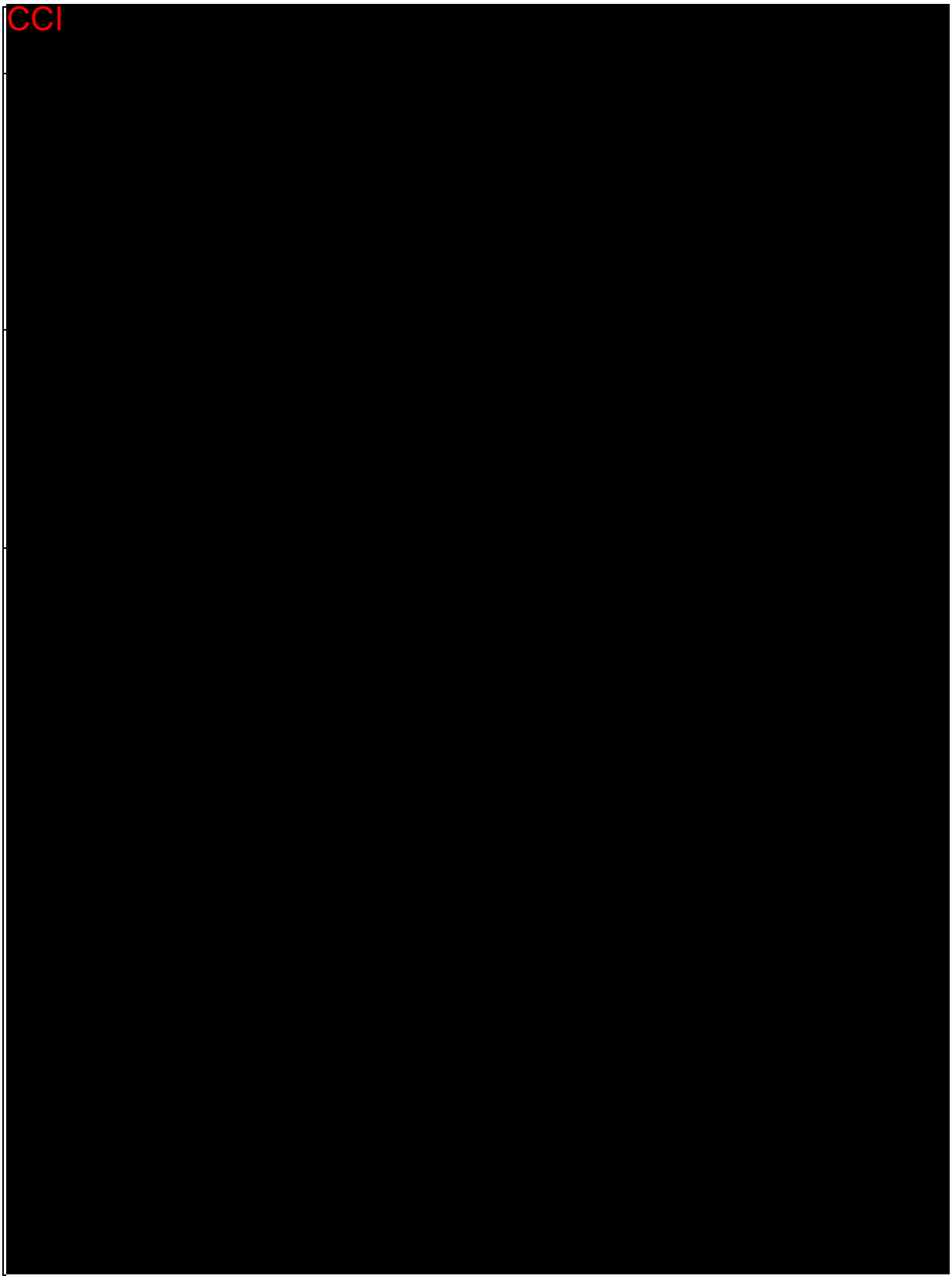
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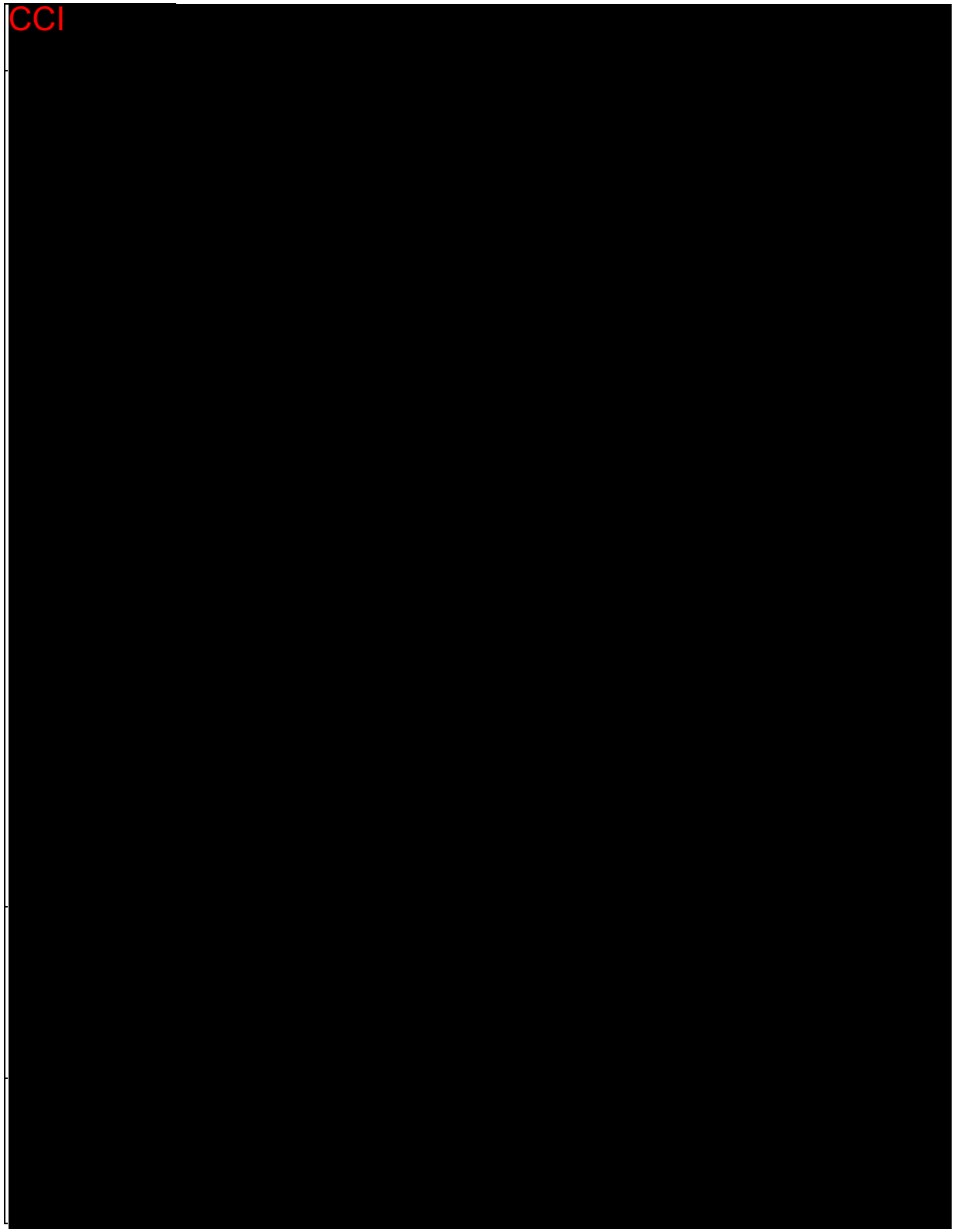
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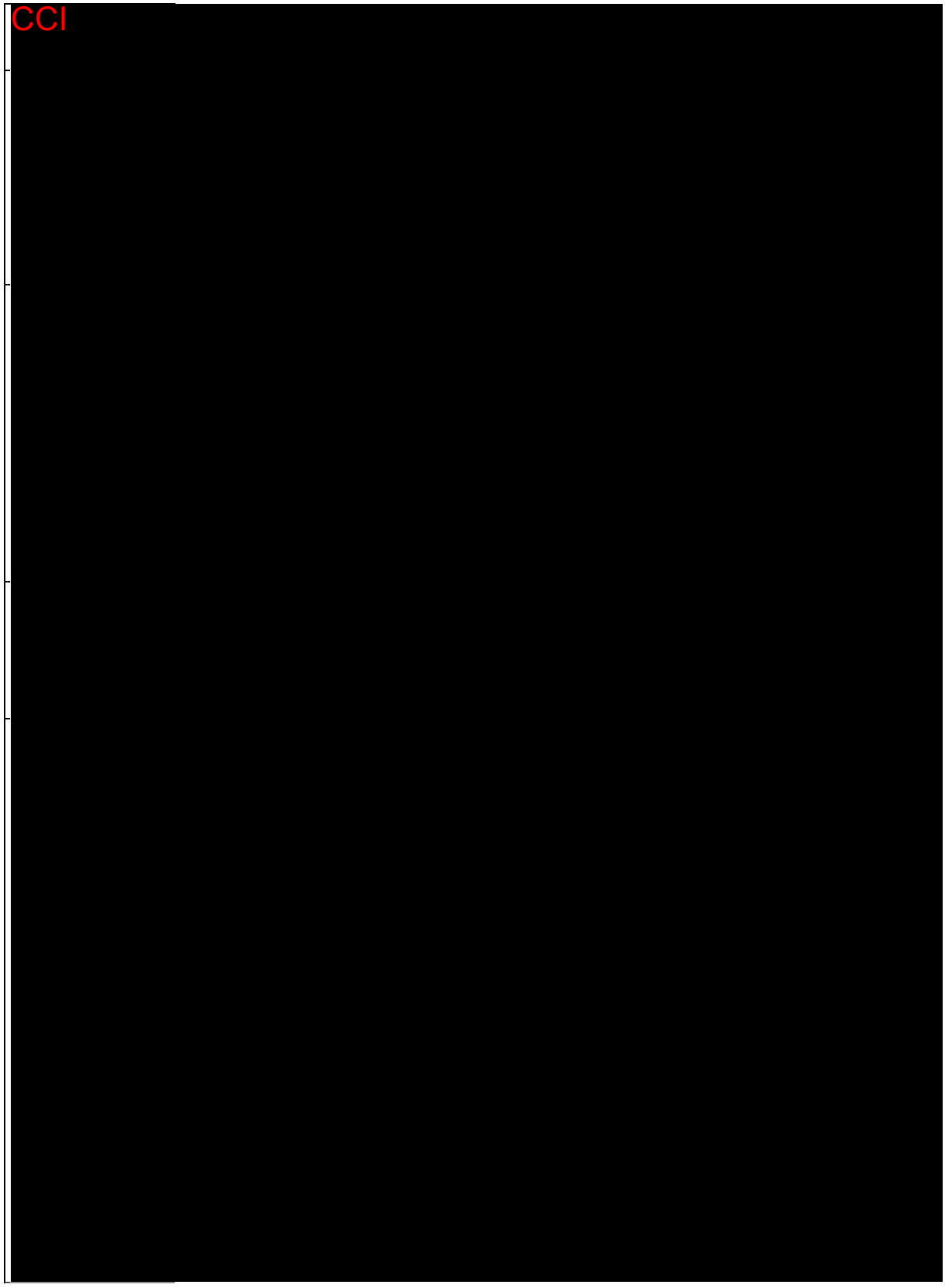
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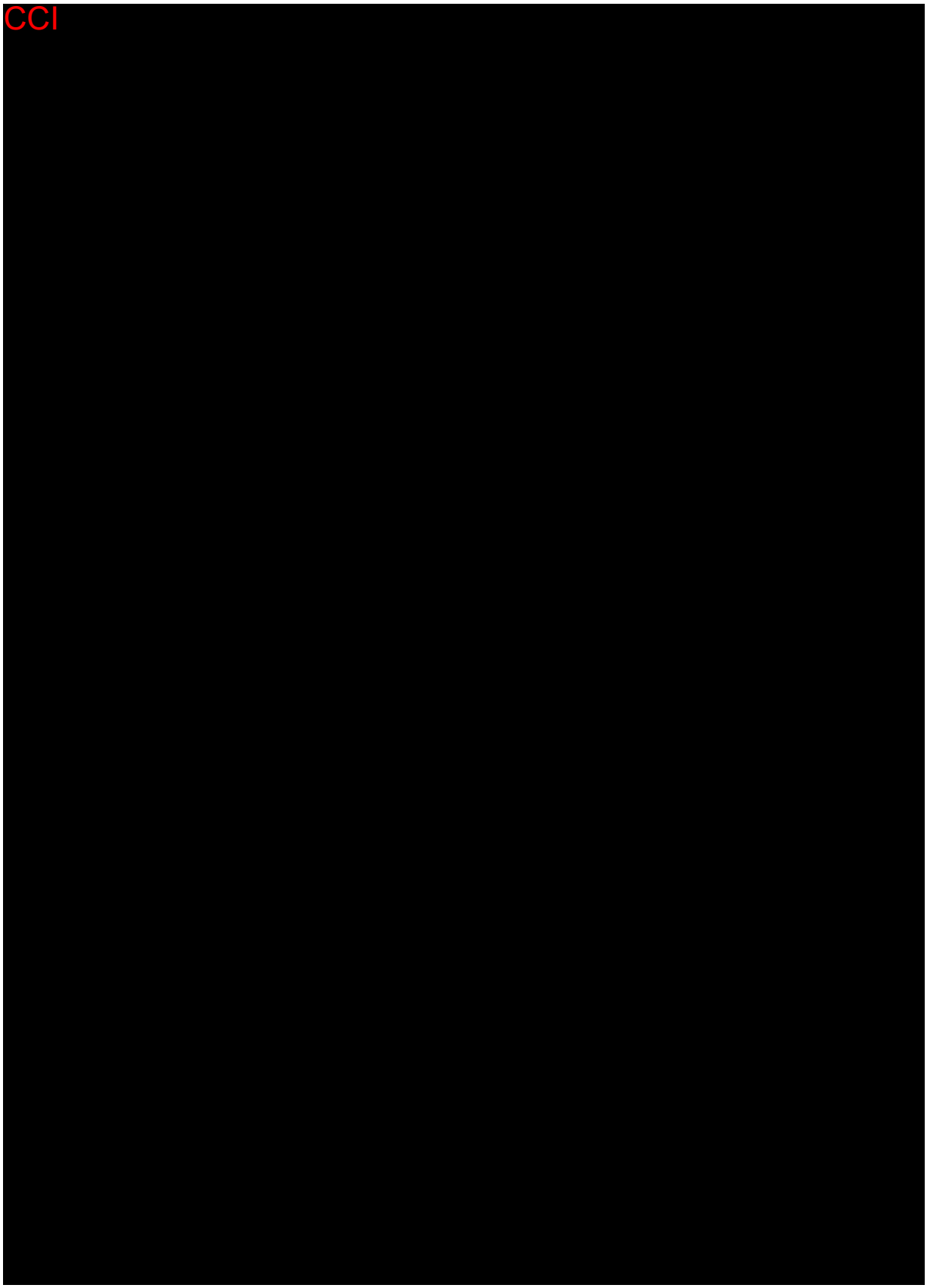

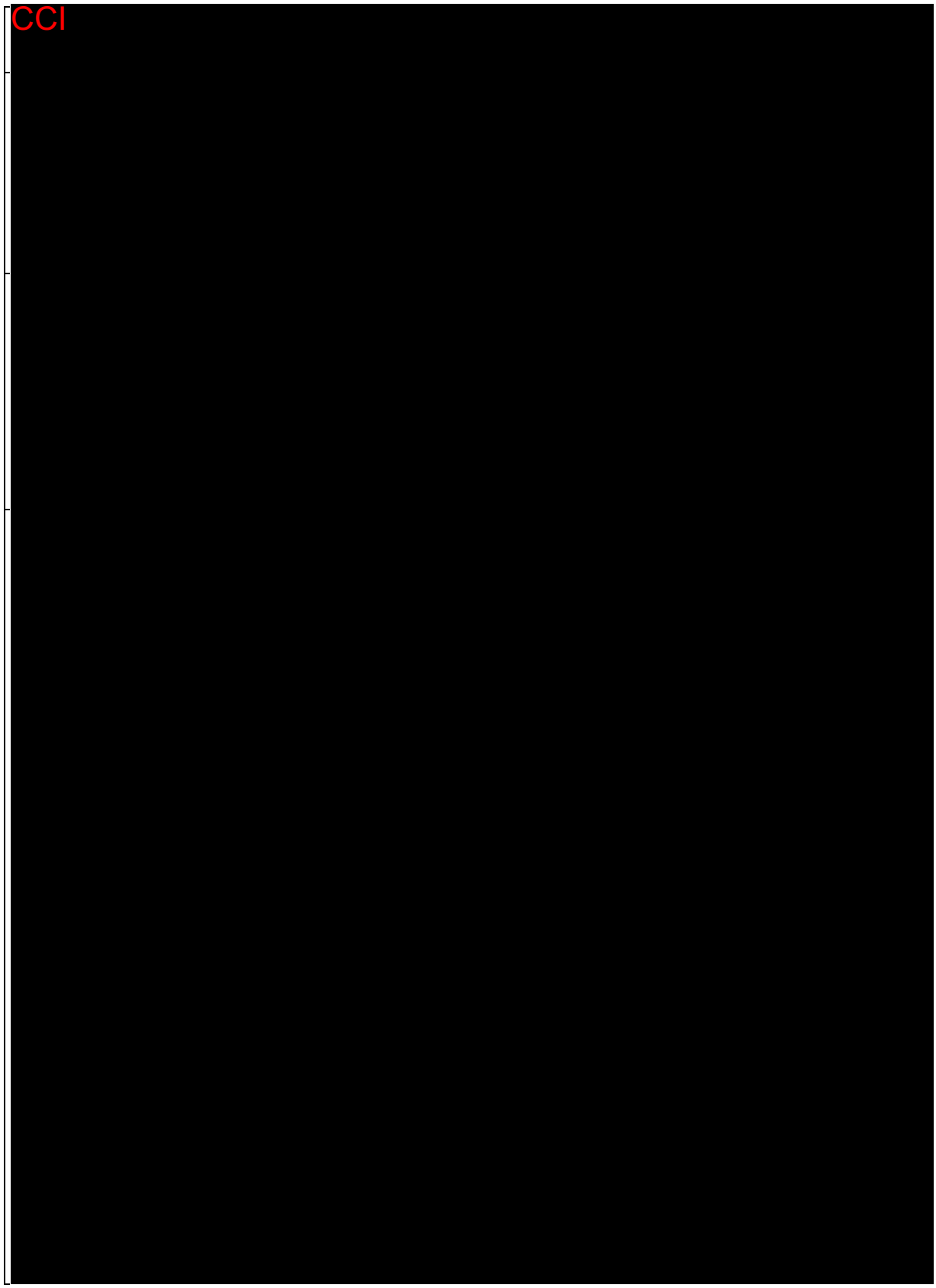
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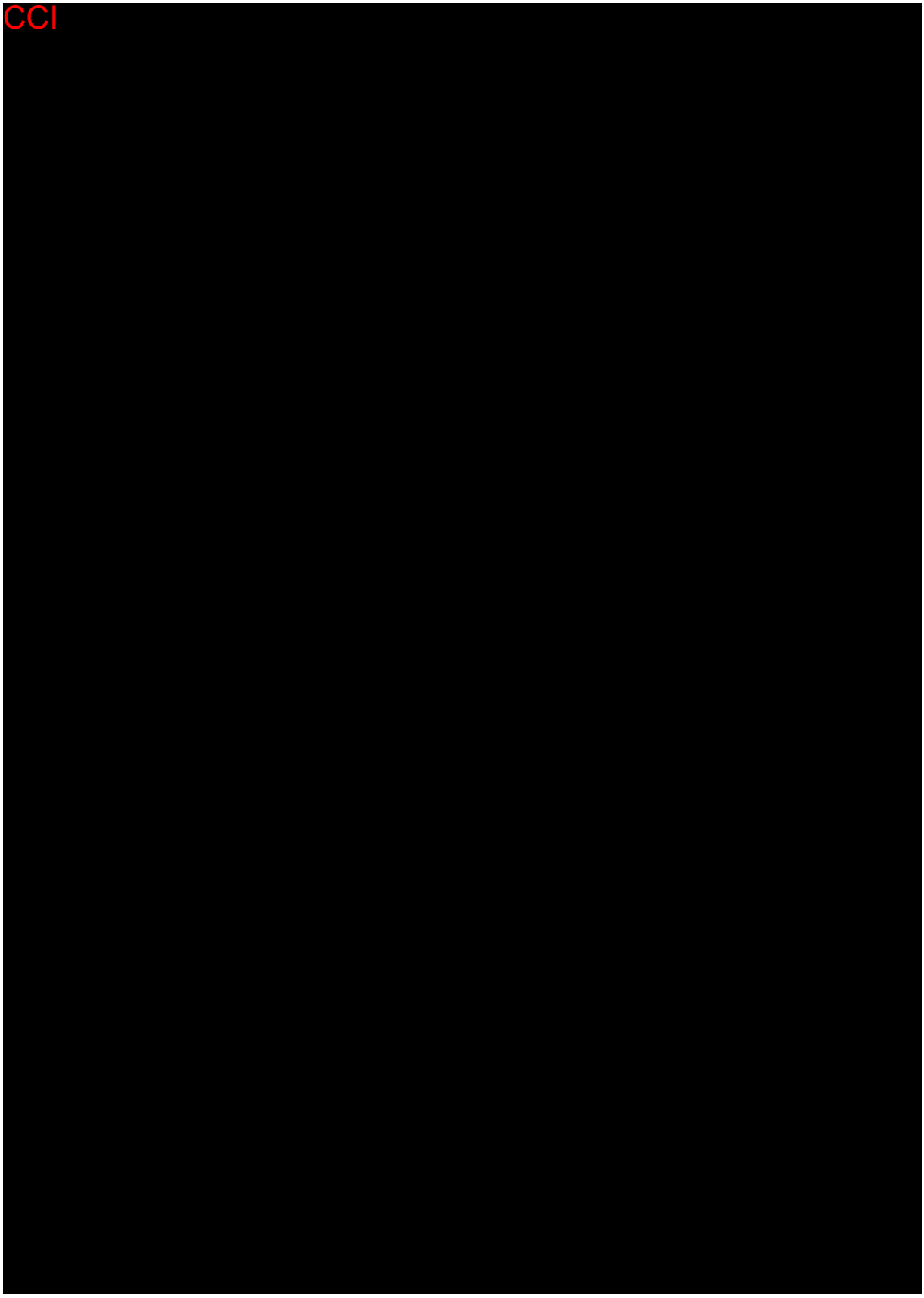

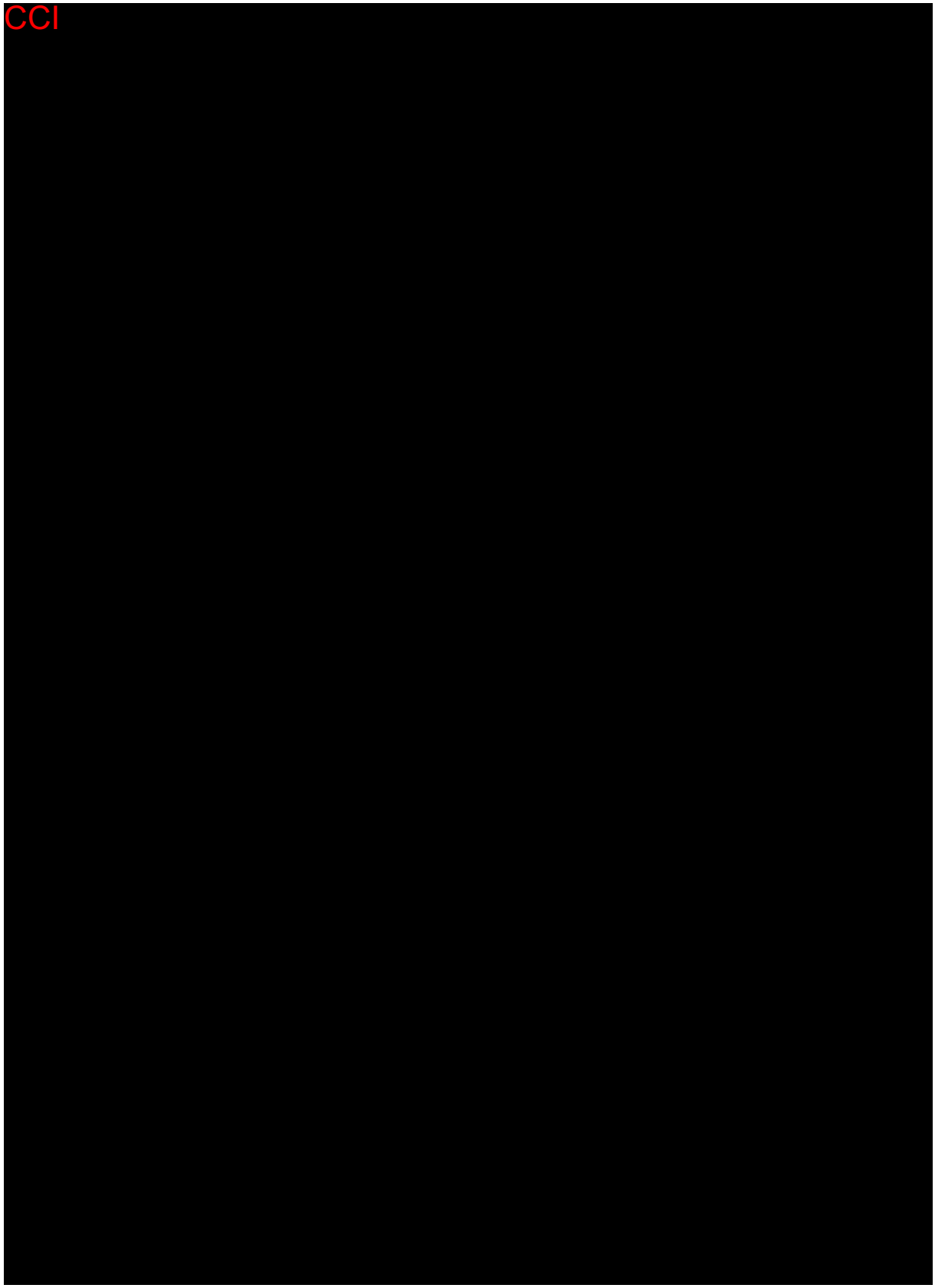
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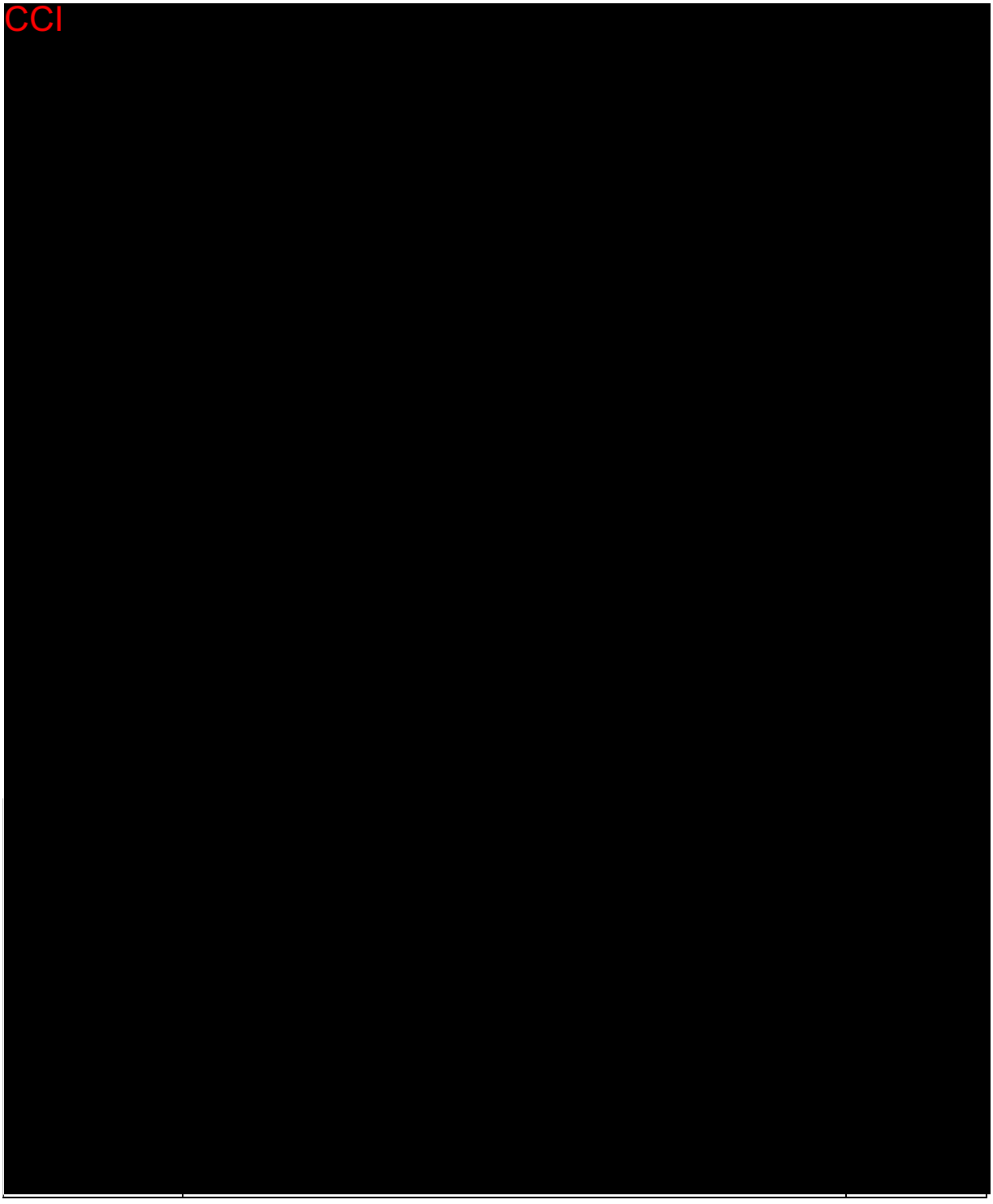
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Protocol summary

Protocol number	COAV101B12301
Full Title	A randomized, sham-controlled, double-blind study to evaluate the efficacy and safety of intrathecal (IT) OAV101 in patients with later onset Type 2 spinal muscular atrophy (SMA) who are ≥ 2 to < 18 years of age, treatment naive, sitting, and never ambulatory
Brief title	Randomized, sham-controlled, double-blind trial to evaluate the efficacy and safety of intrathecal (IT) OAV101 in patients with later onset Type 2 spinal muscular atrophy (SMA).
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Biological
Study type	Interventional
Purpose	The purpose of this phase III multi-center, single dose (1.2×10^{14} vector genomes), randomized, sham-controlled, double-blind trial is to investigate the safety, tolerability, and efficacy of intrathecal (IT) OAV101 in treatment naive, sitting and never ambulatory Type 2 SMA patients ≥ 2 to < 18 years.
Primary Objective	The primary objective of this study is to compare the efficacy of OAV101 IT vs. sham control as measured by the change from baseline in Hammersmith Functional Motor Scale-Expanded (HFMSE) total score. The primary question of interest is: What is the effect of OAV101 treatment versus the sham procedure on change from baseline in HFMSE total score after treatment in sitting but never ambulatory patients aged ≥ 2 to < 18 years with Type 2 SMA, regardless of study discontinuation or receipt of prohibited concomitant medications not for the intent to treat SMA?
Secondary Objectives	To compare the efficacy of OAV101 IT vs. sham control in two patient age groups: ≥ 2 to < 5 years (HFMSE, Revised Upper Limb Module (RULM)); ≥ 2 to < 18 years (RULM) To evaluate the safety and tolerability of OAV101 IT vs. sham control in patients ≥ 2 to < 18 years
Study design	This is a randomized, double-blind, sham-controlled study to evaluate the clinical efficacy, safety, and tolerability over 52 weeks of a single, nominal dose (1.2×10^{14} vector genomes) of intrathecal OAV101 in patients with Type 2 SMA who are ≥ 2 to < 18 years of age, able to sit, but have never walked. Approximately 125 patients aged ≥2 to <18 years will be recruited consisting of ~65 patients between the ages of ≥ 2 to < 5 years and ~60 patients between the ages of ≥ 5 to < 18 years. Participants will be randomized in a 3:2 ratio to receive OAV101 (1.2×10^{14} vector genomes) by lumbar intrathecal injection (n=~75) or to receive a sham procedure (n=~50).
Rationale	Safety and clinically meaningful efficacy with IT delivery of OAV101 was observed in the open label CL-102 study [Investigator's Brochure]. Hence, OAV101 IT may provide a safe, one time treatment option leading to clinically meaningful benefit in patients with SMA Type 2 age 2 to < 18 years.

Study population	Study population attributes are described below. The population attribute will be represented by the entire study population. **Genotype** · 5q SMA as defined by biallelic *SMN1* pathogenic variants **Age range, randomization, and number of participants** · Approximately 125 participants who are ≥ 2 to < 18 years will be recruited for the COAV101B12301 trial · This study population will consist of ~65 patients between the ages of ≥ 2 to < 5 years and ~60 patients between the ages of ≥ 5 to < 18 years (Screening Visit 1 must occur before the patient's 18th birthday) · Randomization is 3:2 ratio (treated:control) to receive OAV101 (1.2×10^{14} vector genomes) by lumbar intrathecal injection (n=~75) or to receive a sham procedure (n=~50) CCI [redacted]
Key Inclusion criteria	· Diagnostic confirmation during screening period of 5q SMA · The patient must be treatment naive (historical or current use) for all SMN-targeting therapies (e.g., risdiplam (Evrysdi) and nusinersen (Spinraza)) · ≥ 2 years and < 18 years of age at screening visit 1 · Onset of clinical signs and symptoms at ≥ 6 months of age · Patient must have a complete HFMSE assessment, with an available total score, as administered by qualified clinical evaluator during the screening period for trial eligibility · Able to sit independently at screening, but has never had the ability to walk independently - Definition of sitting independently: Child sits up straight with the head erect for at least 10 seconds without using arms or hands to balance body or support position (Wijnhoven et al 2004) - Definition of walking independently: The child is able to balance the body and control forward stepping movements without assistance (Wijnhoven et al 2004)

Key Exclusion criteria	· Anti-adeno-associated virus serotype 9 (AAV9) antibody titer reported as elevated (reference to > 1:50 or a validated result consistent with being elevated) at screening as determined CCI [redacted] · Presence of any of the following: · An active infectious process requiring systemic therapy intended to eliminate the infection within 30 days prior to dosing of OAV101 or the sham procedure · An active but untreated viral or bacterial infectious process within 30 days prior to dosing of OAV101 or the sham procedure · Febrile illness within 30 days prior to OAV101 treatment or sham procedure · Hepatic dysfunction (i.e., alanine aminotransferase (ALT), total bilirubin (TBL), gamma-glutamyl transferase (GGT) or glutamate dehydrogenase (GLDH), > upper limit of normal (ULN) (i.e., Common Terminology Criteria for Adverse Events (CTCAE) grade1 or greater) at Screening Visit 1. NOTE: In the absence of other liver laboratory abnormalities, isolated AST elevation is not considered exclusionary · Requiring invasive ventilation, awake noninvasive ventilation for > 6 hours during a 24-hour period, noninvasive ventilation for > 12 hours during a 24-hour period, or requiring tracheostomy at screening and up to Day 1 · Complications at screening that would interfere with motor efficacy assessments including but not limited to: · Presence of severe contractures (e.g., hip flexion contracture) which limits the participant's ability to be positioned in prone for HFMSE item administration ·Scoliosis with a Cobb angle > 40 degrees evident on x-ray examination at Screening · Surgery for scoliosis or hip fixation in the 12 months prior to Screening or planned within the next 64 weeks
Study treatment	OAV101 or sham procedure
Treatment of interest	OAV101 is a single administration of a nominal dose of 1.2 x 10^{14} vector genomes as part of a randomized, double blind, sham procedure controlled clinical trial (COAV101B12301).
Key efficacy assessments	· HFMSE · RULM
Key safety assessments	· Adverse event monitoring · Vital Signs · Age-appropriate neurological examinations CCI [redacted] · Chemistries including Troponin I and hepatic enzymes · Hematology · Urinalysis · Anthropometry · Electrocardiogram (ECG) · Echocardiogram (ECHO) · Neurological examination · Neurophysiology for sensory neuronopathy (Dorsal root ganglia (DRG) toxicity) monitoring: Sensory Nerve Action Potential

	(SNAP), if applicable based on abnormalities in neurological examination
Other assessments	CCI [redacted]
Data analysis	**Mixed Effect Model with Repeated Measures (MMRM) for continuous primary and secondary endpoints; Generalized Linear Mixed Effects Model for dichotomous secondary endpoints (**Section 12.4 **and** Section 12.5**)** Between-group differences in the change from Baseline in HFMSE or RULM total score at the end of Follow-up Period 1 will be evaluated using a Mixed Model with Repeated Measurements (MMRM). The model will include the observed change from Baseline in HFMSE or RULM total score at all post-Baseline visits (through the end of Follow-up Period 1) as the dependent variable. The fixed effects will include treatment, scheduled visit, the treatment by visit interaction, strata, and pre-treatment HFMSE or RULM total score as covariates. An unstructured covariance matrix will be used. Least square means (LSMs) for each treatment group, standard errors, associated 95% CIs, difference of LSMs compared to the sham procedure group, the associated 95% CIs for the difference, as well as the two-sided p-values will be tabulated by visit and treatment. Between-group differences for the dichotomous endpoint of proportion of participants who achieve at least a 3-point improvement from baseline in HFMSE total score at the end of Follow-up Period 1 will be analyzed using a Generalized Linear Mixed Effects Model with fixed effects including treatment, CCI [redacted] NOTE: In order to account for variability in the completion of motor assessments (HFMSE or RULM) occurring at the Week 52 visit that could impact the MMRM assessment, the motor assessment score at Week 48 and Week 52 will be averaged for the purposes of creating the end of Follow-up Period 1 time point.
Key words	Type 2 SMA, Late onset SMA, Phase III, double blind, randomized trial, HFMSE, RULM, gene therapy, recombinant AAV9, SMN, survival motor neuron, OAV101

1 Introduction

1.1 Background

Clinical description: SMA is a neurogenetic disorder caused by a loss or mutation in the survival motor neuron 1 gene (*SMN1*) on chromosome 5q13, which leads to reduced SMN protein levels and a selective dysfunction of motor neurons. SMA is an autosomal recessive, early childhood disease with an incidence of approximately 1:10,000 live births (Sugarman et al 2012). SMA is the leading cause of infant mortality due to genetic diseases. Disease severity and clinical prognosis depends on the number of copies of *SMN2*. In its most common and severe form (Type 1), hypotonia and progressive weakness are recognized in the first few months of life, leading to diagnosis by 6 months of age and then death due to respiratory failure by age 2 years. Motor neuron loss in SMA Type 1 is profound in the early postnatal period (or may even start in the pre-natal period), whereas motor neurons in Type 2 and 3 SMA patients adapt and compensate during development and persist into adult life. The findings from various neurophysiological and animal studies have shown an early loss of motor neurons in the embryonic and early postnatal periods (Swoboda et al 2005, Le et al 2011, Farrar et al 2013).

SMN protein depletion is the root cause across all SMA patient phenotypes and the disease pathogenesis, regardless of age. SMA is caused by abnormally low levels of the ubiquitously expressed SMN protein, resulting from a combination of homozygous deletions or mutations of the telomeric copy of the SMN gene (*SMN1*) on chromosome 5q and the presence of 1 or more copies of *SMN2* (Lefebvre et al 1995), an almost identical but only partially functional centromeric copy which is unique to humans (Rochette et al 2001). The relevant difference between these two genes, a single nucleotide transition at exon 7, affects a splice site enhancer such that the majority of transcripts of *SMN2* lack exon 7 (SMNΔ7), resulting in greatly reduced levels of functional, full-length SMN protein (Monani et al 1999). When the *SMN1* gene is unable to supply SMN protein to the motor neurons, the only source of SMN protein is the *SMN2* gene. The amount of neuronal SMN protein determines patient phenotype primarily by the number of *SMN2* genes.

In support of the hypothesis that gene copy numbers of *SMN2* primarily drive phenotypic presentation of SMA, a large review examined the association between *SMN2* copy number and SMA phenotype (Calucho et al 2018). The authors showed that 79% of patients with two copies of *SMN*2 developed SMA Type I, 16% developed SMA Type 2 and 5% developed SMA Type 3; 54% of patients with three copies of *SMN*2 developed SMA Type 2, 31% developed SMA Type 3 and 16% developed SMA Type 1; and among patients with four copies of *SMN*2, most had mild SMA variants with only 1% developed SMA Type 1 and 11% developed SMA Type 2. In keeping with the importance of SMN production by *SMN*2, few individuals with *SMN*1 mutations and ≥6 copies of *SMN*2 develop symptoms and those who are affected develop only mild forms of SMA (Bernal et al 2010, Riessland et al 2017). SMN is part of the machinery which assembles spliceosomal components (Pellizzoni et al 1998). Ventral spinal cord motor neurons are specifically sensitive to SMN deficiency and are affected in all types of SMA (Burghes and Beattie 2009).

Irrespective of phenotypic classification, expert consensus is that all patients with biallelic pathogenic *SMN1* variants and up to 4 *SMN2* copies should receive SMN dependent therapy (Glascock et al 2018, Glascock et al 2020). Therapeutically increasing SMN levels leads to the most striking results in patients with SMA Type 1 (Pechmann et al 2018, Mercuri et al 2018a, Pane et al 2019, Aragon-Gawinska et al 2020). These results are thought to be mainly due to early intervention, preventing neurodegeneration and the associated progressive deterioration that is seen in all Type 1 SMA infants. These patients now experience improvement in their functional abilities and attain developmental milestones that had never previously been achieved in this population (Pechmann et al 2018, Mercuri et al 2018a, Pane et al 2019, Aragon-Gawinska et al 2020. A proportion of these infants acquire the ability to sit independently, and treatment can enable them to stand (usually with support), depending on how soon treatment is initiated after onset of symptoms. In children with SMA Type 2, treatment also clearly reduces progression of the disease compared with the natural history. For patients with mild SMA Type 2, developing the ability to walk is a possibility.

SMA is conventionally classified into 4 phenotypes on the basis of age of onset and highest motor function achieved, with an additional phenotype (Type 0) to describe the severe forms of antenatal-onset spinal muscular atrophy (Kolb and Kissel 2011, Mercuri et al 2012). The classification of SMA is shown below (Table 1-1). SMA Type 1 patients present with symptoms within the first 6 months of life and by definition never attain independent sitting. SMA Type 1 is the leading genetic cause of infant death. In contrast, SMA Type 2 manifests within the first 18 months of life and follows a slower disease progression as compared to SMA Type 1. Children with SMA Type 2 are able to maintain sitting unassisted but never walk independently and have a life expectancy of 20-40 years of age. SMA Type 3 patients attain the ability to walk unaided (Type 3a have onset < 3 years of age; Type 3b have onset > 3 years of age). SMA Type 4 is an adult onset form of the disease. Table 1-1 summarizes SMA subtypes and associated clinical features as well as the relationship of the SMA subtypes to *SMN2* copy numbers (Schorling et al 2020).

Table 1-1 Spinal Muscular Atrophy Classification

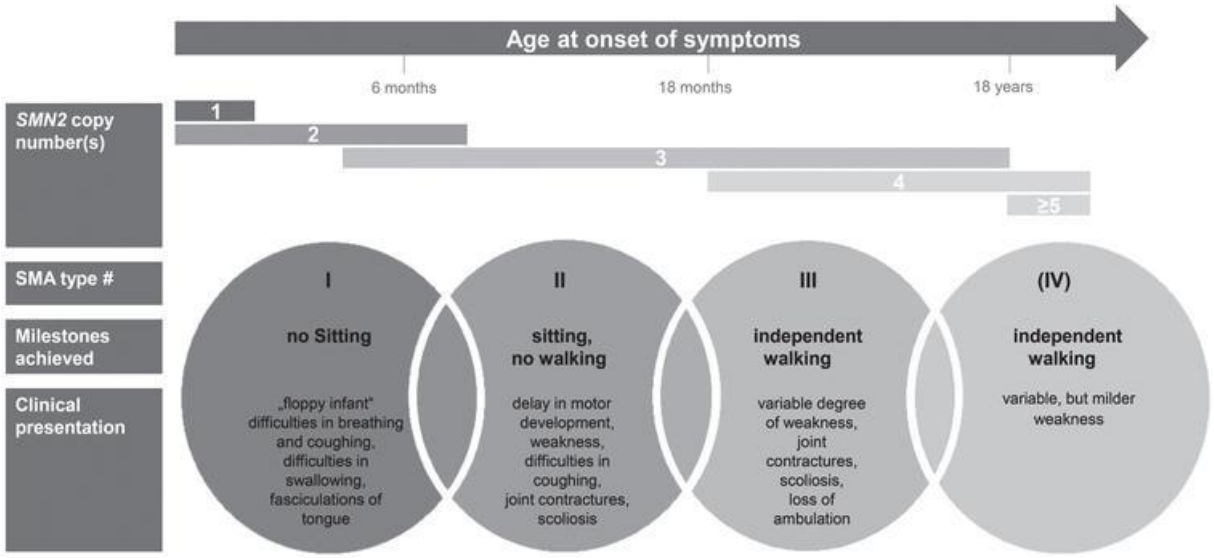
Type	**Age at Symptom Onset**		**Maximum Motor Function**	**Life Expectancy**	***SMN2* Copy No.**
0	Fetal		Nil	Days – Weeks	1
1	< 6 Months	1A: < 2 Weeks 1B: < 3 months 1C: > 3 months	Never sits	< 2 years	1, **2**, 3
2	6 – 18 Months		Never walks	20 – 40 years	2, **3**, 4
3	1.5 – 10 Years	3A: < 3 Years 3B: > 3 Years	Walks, regression	Normal	3, **4**, 5
4	> 35 Years		Slow decline	Normal	4, 5

SMN2 = survival motor neuron 2 gene

bold = predominant *SMN2* copy number that defines the SMA Type, the other copy numbers represent a small percentage of the designated SMA Type

Source: Adapted from Kolb and Kissel 2011

Figure 1-1 Clinical Classification of SMA subtypes according to onset, milestones achieved, and clinical presentation. Typically associated *SMN2* copy numbers are displayed.



Source: Schorling et al 2020

OAV101 gene therapy mechanism of action: OAV101 is an in vivo gene therapy intended for a single treatment with 5q SMA. OAV101 is a non-replicating recombinant adeno-associated virus serotype 9 (AAV9) containing the human SMN complementary deoxyribonucleic acid (cDNA) under the control of the cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid (CB) promoter (Figure 1-2). One of the two adeno-associated virus (AAV) inverted terminal repeats has been modified to promote intramolecular annealing of the transgene, thus forming a double-stranded transgene ready for transcription.

Figure 1-2 OAV101 Vector Construct

The mechanism of action of OAV101 is the delivery of a functional copy of the gene encoding for the SMN protein into target cells, the loss of which is the root cause of all forms of (5q) SMA. The goal is to increase SMN protein levels in motor neurons prior to the development of irreversible injury and motor neuron loss, thereby modifying the patient's SMA phenotype to a milder course with improved quality of life and prolonged survival.

Recombinant AAVs are not known to actively integrate into the host genome, but rather persist episomally within the target cells. Thus, its expression is eventually lost in a dividing cell population (Hudry and Vandenberghe 2019). OAV101 is specifically designed to form a circular concatemeric transgene that harbors even lower potential for deoxyribonucleic acid (DNA) integration or alteration. Moreover, AAVs cannot replicate within the host cell in

absence of a helper virus, such as adenovirus, herpes simplex virus, human papillomavirus or vaccinia virus for productive infection.

1.2 Purpose

The purpose of this phase III multi-center, single dose (1.2×10^{14} vector genomes), randomized, sham-controlled, double-blind trial is to investigate the safety, tolerability, and efficacy of intrathecal (IT) OAV101 in treatment naive, sitting and never ambulatory Type 2 SMA patients ≥ 2 years to < 18 years (Screening Visit 1 must occur before the patient's 18th birthday).

2 Objectives, endpoints and estimands

Objectives and related endpoints are described in Table 2-1.

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• **EFFICACY:** To compare the efficacy of OAV101 IT vs. sham control as measured by the change from baseline in HFMSE total score	• Change from baseline in HFMSE total score at the end of Follow-up Period 1 (defined in Section 12.4.1) in the overall study population (≥ 2 to < 18 years age group)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To compare the efficacy of OAV101 IT vs. sham control in two patient age groups: ≥ 2 to < 5 years (HFMSE, RULM); ≥ 2 to < 18 years (RULM)	• Change from baseline in HFMSE total score at the end of Follow-up Period 1 in the ≥ 2 to < 5 years age group • Achievement of at least a 3-point improvement from baseline in HFMSE total score at the end of Follow-up Period 1 in the overall study population • Achievement of at least a 3-point improvement from baseline in HFMSE total score at the end of Follow-up Period 1 in the ≥ 2 to < 5 years age group • Change from baseline in RULM at the end of Follow-up Period 1 in the ≥ 2 to < 18 years age group • Change from baseline in the RULM at the end of Follow-up Period 1 in the ≥ 2 to < 5 years age group
• **SAFETY:** To evaluate the safety and tolerability of OAV101 IT vs. sham control in patients ≥ 2 to < 18 years	• Incidence of treatment emergent adverse events (TEAEs) and serious (SAEs) • Number of participants with adverse events of special interest (AESIs) • Evaluation of changes from baseline in vital signs, physical/neurological examinations, laboratories (chemistry, hematology, liver functions tests), echocardiogram, ECG, anthropometry, and CCI • Number (and percentage) of patients with intracardiac thrombi • Number (and percentage) of patients with low cardiac function

Objective(s)	Endpoint(s)
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
• To assess the changes in motor function from baseline over 52 weeks in treated patients compared to sham controls and natural history data in the overall study population (≥ 2 to < 18 years)	[redacted]
• To assess the changes in motor function from baseline over 52 weeks in treated patients compared to sham controls	[redacted]
• To assess changes in [redacted] from baseline over 52 weeks in treated patients compared to sham controls in ≥ 2 to < 5 years and in the ≥ 5 to < 18 years age groups	• Change in [redacted]
• To assess changes in [redacted] from baseline over 52 weeks in treated patients compared to sham controls in each of three age groups: ≥ 2 to < 18 years, ≥ 2 to < 5 years, ≥ 5 to < 18 years	• Change in [redacted] over 52 weeks in each of three age groups: ≥ 2 to < 18 years, ≥ 2 to < 5 years, ≥ 5 to < 18 years
• To assess the [redacted] of SMA over 52 weeks in treated patients compared to the sham controls in each of three age groups: ≥ 2 to < 18 years, ≥ 2 to < 5 years, ≥ 5 to < 18 years	[redacted]
• To assess the [redacted] over 52 weeks in treated patients compared to the study sham controls in each of three age groups: ≥ 2 to 18 years, ≥ 2 to < 5 years, ≥ 5 to < 18 years	• Change in [redacted] over 52 weeks in each of three age groups: ≥ 2 to < 18 years, ≥ 2 to < 5 years, ≥ 5 to < 18 years
• To assess for [redacted] in treated patients compared to sham controls in each of three age groups: ≥ 2 to < 18 years, ≥ 2 to < 5 years, ≥ 5 to < 18 years	• To assess [redacted] in each of three age groups: ≥ 2 to < 18 years, ≥ 2 to < 5 years, ≥ 5 to < 18 years.
• To assess for changes [redacted] in treated patients compared to sham controls	• Change from baseline over 52 weeks for [redacted]
• To assess [redacted] post OAV101	• Evaluation of [redacted] in treated patients

2.1 Primary estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g., premature discontinuation of treatment).

The primary clinical question of interest is: *What is the effect of OAV101 treatment versus the sham procedure on change from baseline in HFMSE total score after treatment in sitting but never ambulatory patients aged ≥ 2 to < 18 years with Type 2 SMA, regardless of study discontinuation or receipt of prohibited concomitant medications not for the intent to treat SMA?*

The justification for the primary estimand is that it will capture both the effect of OAV101 and the effect of additional medications not for the intent to treat SMA, mirroring the conditions in clinical practice. Further details can be found in Section 12.

The primary estimand is described by the following attributes:

1. Population: Sitting but never ambulatory patients aged ≥ 2 to < 18 years with Type 2 SMA. Further details about the population are provided in Section 5.
2. Endpoint: Change from baseline to the end of Follow-up Period 1 in HFMSE total score.
   - CCI [redacted]
3. Summary measure: difference between treatment groups in least squares mean change from baseline in HFMSE total score up to the end of Follow-up Period 1
4. Treatment of interest: The randomized treatment (OAV101 or sham procedure) with or without the use of prohibited concomitant medications not for the intent to treat SMA. Further details about the investigational treatment and control are provided in Section 6.

Handling of intercurrent events:

1. Study discontinuation due to reasons other than death: It is assumed that participants discontinuing the study prior to Week 52 would follow the same trend as participants who continued and remained in the study for the full 52 weeks. Data collected up to the point of discontinuation will be included in the Mixed Model for Repeated Measurements (MMRM) (Hypothetical strategy).
2. Use of prohibited concomitant medications not for the intent to treat SMA: Assessments collected while/after receiving prohibited concomitant medications will be included in the analyses (Treatment policy strategy).
3. Use of prohibited concomitant medications for the intent to treat SMA (i.e., nusinersen, risdiplam): Assessments collected while/after receiving prohibited concomitant medications will not be included in the analyses. Only data collected up to the point of initiating a prohibited medication for the intent to treat SMA will be included in the MMRM and the data collected after the initiation of prohibited medication for the intent to treat SMA will be considered as missing (Hypothetical strategy).

4. Study discontinuation due to death: The worst score for HFMSE will be imputed for participants who discontinue the study due to death, and this imputed score will be utilized in the analysis. The "worst score" refers to the worst (lowest) HFMSE score collected for the participant who had the death event throughout the trial (considering both the baseline and post-baseline period). It is anticipated that this intercurrent event is unlikely to occur during this study.

2.2 Secondary estimands

The secondary estimand for the continuous secondary efficacy endpoints is defined similarly to the primary estimand.

The secondary estimand for the dichotomous secondary efficacy endpoint (i.e., achievement of at least a 3-point improvement from baseline in HFMSE total score at the end of Follow-up Period 1) is described by the attributes listed below.

1. Population of interest: Sitting but never ambulatory patients aged ≥ 2 to < 18 years with Type 2 SMA
2. Endpoint: Proportion of participants achieving at least a 3-point improvement from baseline in HFMSE total score at the end of Follow-up Period 1.
    - CCI [redacted]
3. Summary measure: odds ratio between treatment groups for the proportion of participants achieving at least a 3-point improvement from baseline in HFMSE total score at the end of Follow-up Period 1.
4. Treatment of interest: The randomized treatment (OAV101 or sham procedure) with or without the use of prohibited concomitant medications not for the intent to treat SMA.

Handling of intercurrent events:

1. Study discontinuation due to reasons other than death: It is assumed that participants discontinuing the study prior to Week 52 would follow the same trend as participants who continued and remained in the study for the full 52 weeks. Data collected up to the point of discontinuation will be included in the Generalized Linear Mixed Effects Model (Hypothetical strategy).
2. Use of prohibited concomitant medications not for the intent to treat SMA: Assessments collected while/after receiving prohibited concomitant medications will be included in the analyses (Treatment policy strategy).
3. Use of prohibited concomitant medications for the intent to treat SMA (i.e., nusinersen, risdiplam): Assessments collected while/after receiving prohibited concomitant medications will not be included in the analyses. Only data collected up to the point of initiating a prohibited medication for the intent to treat SMA will be included in the Generalized Linear Mixed Effects Model and the data collected after the initiation of prohibited medication for the intent to treat SMA will be considered as missing (Hypothetical strategy).

4. Study discontinuation due to death: The worst score for HFMSE will be imputed for participants who discontinue the study due to death, and this imputed score will be utilized in the analysis. The "worst score" refers to the worst (lowest) HFMSE score collected for the participant who had the death event throughout the trial (considering both the baseline and post-baseline period). It is anticipated that this intercurrent event is unlikely to occur during this study.

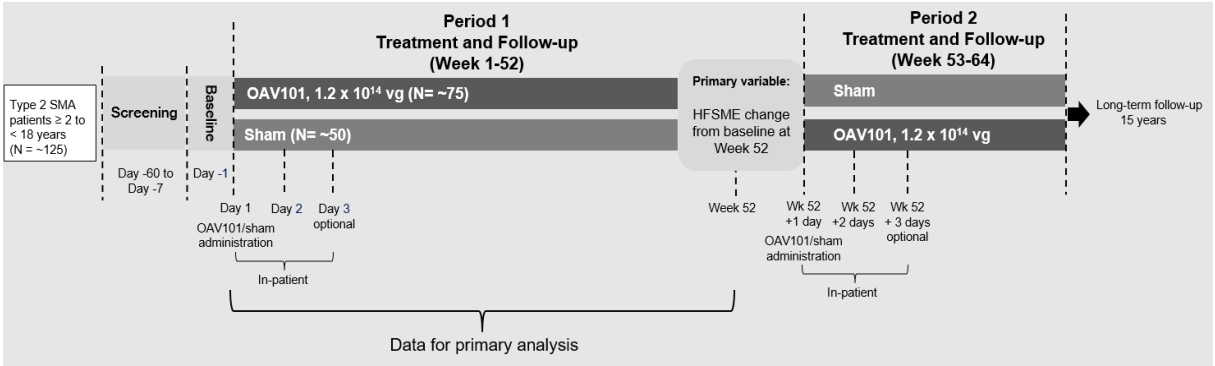
3 Study design

The study consists of a Screening and Baseline Period followed by two Treatment and follow-up Periods.

Treatment Period 1 consists of OAV101/sham administration with in-patient hospitalization on Study Day 1, Day 2 and Day 3 (optional). Treatment Period 1 is followed by a 52-week out-patient follow-up period (Follow-up Period 1; Week 1-52) for safety and efficacy assessments (Figure 3-1; Figure 3-2).

At the point each participant completes Follow-up Period 1, those who are eligible (see Treatment Period 2 eligibility criteria below) will subsequently enter into Treatment Period 2. Entry into Treatment Period 2 will occur in a rolling, seamless fashion as participants complete Follow-up Period 1. In Treatment Period 2, eligible participants who received a sham procedure on Study Day 1 of Treatment Period 1 will be hospitalized to receive OAV101 and participants who received OAV101 on Study Day 1 of Treatment Period 1 will be hospitalized to receive a sham procedure on the Week 52 +1 Day visit. In-patient observation will continue on Week 52 +2 Days and Week 52 +3 Days (optional). Treatment Period 2 is followed by a 12-week follow-up period (Follow-up Period 2; Week 53-64) for safety and efficacy assessments (Figure 3-1; Figure 3-3). The total duration of the study is 64 weeks. At the end of study all participants who received OAV101 will be eligible to enroll in a long-term follow-up study (15 years) to monitor long-term safety and efficacy.

Figure 3-1 Study design



This is a phase III multi-center, single dose (1.2×10^{14} vector genomes), randomized, sham-controlled, double-blind trial that investigates the safety, tolerability, and efficacy of OAV101 IT in treatment naive, sitting and never ambulatory Type 2 SMA patients ≥ 2 to < 18 years. Approximately 125 patients aged ≥ 2 to < 18 years will be recruited. Approximately 65 recruited patients will be between ≥ 2 and < 5 years and approximately 60 patients will be

between ≥ 5 and < 18 years. Participants will be randomized in a 3:2 ratio to receive OAV101 (1.2×10^{14} vector genomes) by lumbar intrathecal injection (n=~75) or to receive a sham procedure (n=~50).

CCI

CCI

Figure 3-2 Summary of Screening Period to end of Follow-up Period 1

Screening, Baseline, Treatment and Follow-up Period 1			
Screening period Days -60 to -7	Baseline period Day -1	OAV101 or Sham administration Day 1	Week 1 to 52 data collection
Randomization and stratification*	Double-Blind Efficacy and Safety Assessment		

Description of study periods

Screening and Baseline periods, Treatment and Follow-up Period 1

- ***Screening period*** *(Day -60 to Day -14)*: After obtaining Informed Consent, participants will undergo a screening evaluation (Table 8-1).
  - *Screening Visit 1 (Day -60)*: Clinical and laboratory data, including coagulation testing, is obtained for eligibility assessment.
  - *Screening Visit 2 (Day -21):* At this time, inclusion and exclusion criteria are reviewed and motor assessments are performed as well.
  - *Screening Visit 3 (Day -14):* If the participant is determined to be eligible for the trial, randomization will occur, and the double-blind period of the trial will begin
  - *Screening period motor assessments:* For each participant, an assessment of the HFMSE and RULM is performed (Section 8.3.1.1 and Section 8.3.1.2). In order to meet eligibility requirements for the trial, the participant must have a complete HFMSE administration with total score during the screening period (Section 5.1), thus assuring that at least one complete pre-treatment HFMSE assessment is available to assess OAV101 efficacy. If the HFMSE is unable to be completed to allow for a total score, a repeat of the assessment is required during the Screening period (Section 8.1). See Section 8.3.1.1and Section 8.3.1.2 for completion of HFMSE and RULM motor assessments.

- ***Baseline Period*** *(Day -1):* The Baseline Period occurs 1 day prior to intrathecal OAV101 or the sham procedure. All eligible participants will undergo pre-dosing evaluations (Table 8-1).
  - *Baseline Day -1 visit motor assessments:* A HFMSE and RULM assessment is performed at the Baseline Day -1 visit. If either the HFMSE or RULM is unable to be completed providing a total score, no repeat of the assessment is required (Section 8.3.1.1 and Section 8.3.1.2).
  - *Baseline Day -1 Prophylactic Prednisolone and placebo administration:* In an attempt to dampen the host immune response to the adeno-associated virus (AAV) derived therapy, participants randomized to the treatment arm will receive oral prophylactic prednisolone CCI [redacted] Participants randomized to the sham procedure arm will receive a matching placebo. Treatment or placebo will continue for CCI [redacted]
- ***Treatment Period 1***
  - *OAV101 treatment or sham procedure (Day 1, Day 2, optional Day 3*): Participants will be admitted to the study center on Day 1 (or on Day -1 as per local standard of care). Participants randomized to the treatment cohort will receive intrathecal OAV101. Participants randomized to the control group will receive a sham procedure that consists of only a needle prick. CCI [redacted] in accordance with the Assessment Schedule (Table 8-1). Lumbar puncture and OAV101 administration should be performed using an atraumatic spinal needle (e.g. Whitacre, 22 or 25 gauge) which significantly lowers the incidence of blood patch treatment (Hatfield et al 2008). Following the OAV101 administration/sham procedure on Study Day 1, participants will remain at the study center for 24 to 48 hours for post-procedure for safety monitoring.
- ***Follow-up Period 1***
  - *Visit Week 1 to Visit Week 12:* Assessments proceed as outlined in Table 8-1.
  - *Visit Week 16 to Visit Week 48*: Assessments proceed as outlined in Table 8-1.
  - *End of Follow-up Period 1 (Week 52):* Participants complete End of Follow-up Period 1 (Week 52) when each participant returns to the treatment center for final follow-up evaluations as per the Assessment Schedule (Table 8-1).
  - Blinding will be maintained through the end of study (Week 64). When all participants complete the Week 52 visit, all data collected through Week 52 will be analyzed (Primary analysis). Data will be reported in a Registration Clinical Study Report (CSR) for health authority data submission. *See Treatment Period 2 description for further discussion of implications of elevated anti-AAV9 antibodies for trial blinding.*
  - To minimize the time that the control group is untreated (Section 4.2), participants will be assessed for eligibility to enter Treatment Period 2 at the Follow-up Period 1 Week 48 visit. Eligible participants will begin Treatment Period 2 (Week 52 +1 day visit) immediately after completion of Follow-up Period 1.

- Data collected at Week 48 (e.g., laboratory analyses and medical status) is used to assess patient eligibility for Treatment Period 2.
- CCI [redacted]
- CCI [redacted] for eligibility for treatment with OAV101 in Period 2. CCI [redacted]
- A small number of control patients (estimated as ≤ 5 participants) may not receive OAV101 treatment at Week 52+1 day Visit due to elevated anti-AAV9 antibodies and would be unblinded. No further follow-up in the trial will be needed for these participants.
- Prednisolone or placebo prednisolone will be administered CCI [redacted] CCI [redacted] Week 52 + 1 day Visit and will continue as per Section 6.2.

Participants who complete the double-blind Follow-up Period 1 of the trial are assessed for eligibility for Treatment Period 2. Treatment Period 2 will consist of eligibility assessment (described below), administration of a single dose OAV101 or sham treatment, and a 12-week follow-up period (Figure 3-3). Blinding is maintained for all patients during Treatment Period 2. Anti-AAV9 antibody results CCI [redacted] will be supplied to designated unblinded Novartis personnel (Table 6-3). Designated unblinded Novartis personnel will communicate to the site physician when a participant (who received sham procedure in Period 1) has an anti-AAV9 antibody titer reported as elevated. These patients will be unblinded and no further follow-up will be required after the Week 52 Visit. Global Clinical Supply will ship OAV101 for participants in the sham group in Period 1 only if anti-AAV9 antibody titer is not reported as elevated (reference to > 1:50 or a validated results consistent with being elevated).

Treatment and Follow-up Period 2

Eligibility

Participants meeting any of the following exclusion criteria at conclusion of Follow-up Period 1 (Week 52) are not eligible for inclusion in the Treatment Period 2. Retesting of abnormal laboratory and other clinical parameters that could be transient or measurement error may be allowed based on judgement of the Principal Investigator and approval by the Sponsor Medical Monitor.

1. Any medical condition considered clinically significant, that in the opinion of the Principal Investigator, would interfere with the overall interpretation of safety
2. Anti-AAV9 antibody titer reported as elevated (reference to > 1:50 or a validated result consistent with being elevated) CCI [redacted] This criterion does not apply to the OAV101 group from Period 1 as their anti-AAV9 antibody titers will be elevated after OAV101 treatment.

3. Clinically significant abnormalities in laboratory test results as determined by the Principal Investigator at week 48.
4. Presence of any of the following:
   - An active infectious process requiring systemic therapy intended to eliminate the infection within 30 days prior to the OAV101 administration or sham procedure
   - An active but untreated viral or bacterial infectious process within 30 days prior to the OAV101 administration or sham procedure
   - Febrile illness within 30 days prior to the OAV101 administration or sham procedure
5. Clinical or radiological signs of aspiration within 30 days prior to the OAV101 treatment/sham procedure
6. Hepatic dysfunction (i.e., ALT, TBL, GGT or GLDH, > ULN (i.e., CTCAE grade 1 or greater)) at week 48

   NOTE: In the absence of other liver laboratory abnormalities, isolated AST elevation is not considered exclusionary
7. Contraindications for lumbar puncture procedure (including but not limited to cutaneous infection at the treatment site and signs or symptoms of increased intracranial pressure), active administration of any intrathecal therapy, presence of an implanted shunt for the drainage of CSF, presence of an implanted central nervous system (CNS) catheter, or any impediment to CSF access
8. Requiring ventilation for > 16 hours during a 24-hour period or requiring tracheostomy within 30 days prior to OAV101 treatment/sham procedure
9. Awake hypoxemia (defined as O^2 saturation < 95% in room air) within 30 days prior to the OAV101 treatment/sham procedure, that is clinically significant, as per investigator judgement

   NOTE: For altitudes > 1000 m, awake hypoxemia is defined as O_2 saturation < 92% in room air

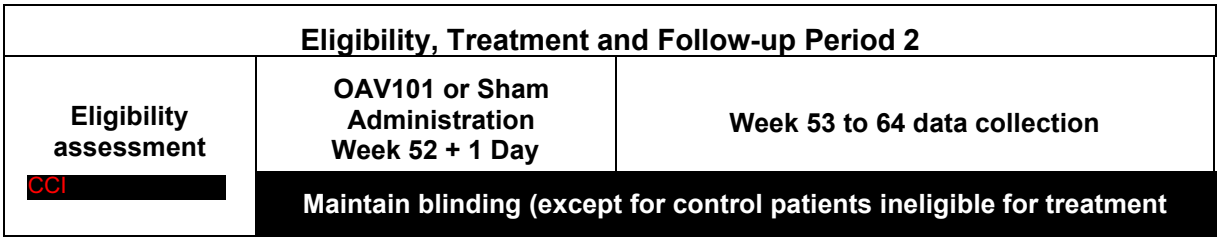
   NOTE: For altitudes > 2500m, awake hypoxemia is defined as O_2 saturation < 90% in room air
10. BMI < 3rd percentile, if considered clinically significant by the Investigator

    NOTE: BMI is based on the WHO Child Growth Standards (WHO 2022a) and WHO Growth reference data for 5-19 years (WHO 2022b).
11. Positive for human immunodeficiency virus (HIV), hepatitis B, or hepatitis C, including latent infections that may be susceptible to reactivation due to corticosteroids.

    Note: Other pathogens that may be endemic to specific regions/countries (e.g., human T-lymphotropic virus or mycobacterium tuberculosis) may be tested, as per investigator discretion and discussion with Sponsor.
12. Platelet count < lower limit of normal (LLN) at Week 48
13. Platelet transfusion within 60 days prior to the OAV101 treatment/sham procedure
14. Clinically significant sensory abnormalities in the neurological examination at Week 48
15. Use of prohibited SMN-targeting therapy during Period 1
16. Does not meet age-appropriate institutional criteria for use of anesthesia/sedation as assessed by the physician responsible for administering anesthesia/sedation

17. Female participants who are sexually active or have reached menarche have a positive pregnancy test at Week 48
18. Administration of vaccines within 2 weeks prior to injection of OAV101 or sham procedure
19. Concomitant use of any of the following medication categories within 90 days prior to study treatment (Week 52 + 1 Day):
    - Ongoing systemic immunosuppressive therapy (e.g., corticosteroids (except for prophylactic use for OAV101 dosing), cyclosporine, tacrolimus, methotrexate, cyclophosphamide, intravenous immunoglobulin, rituximab), plasmapheresis, immunomodulators (e.g., adalimumab)
20. Inability to tolerate corticosteroids administered by mouth or gastrostomy tube
21. Any medication deemed by Principal Investigator to pose an unacceptable safety risk for gene therapy administration

Figure 3-3 Summary of Period 2 eligibility assessment, Treatment and Follow-up Period 2



Description

Treatment Period 2

- *OAV101 treatment or sham procedure (Week 52 + 1 Day visit, Week 52 + 2 Day visit; Week 52 + optional 3rd Day visit*): Participants will be admitted to the study center at the Week 52 + Day 1 visit (or on Week 52 as per local standard of care). Participants previously treated with OAV101 will receive only a needle prick and previously untreated participants who meet eligibility requirements will receive intrathecal OAV101. If study treatment visit at the Week 52 + 1 visit is not possible due to a national emergency or other unforeseen reason, extensions to the visit window may be discussed with the Sponsor.
- *Prophylactic Prednisolone and placebo:* Prednisolone or placebo will be administered daily CCI

Follow-up Period 2

- *Visit Week 53 to Visit Week 64:* All participants will be monitored for safety and efficacy until Week 64. Participants who prematurely discontinue the trial during the Treatment Period 2 will be offered enrollment in a separate Long Term Follow-Up study. Data collected during Treatment Period 2 will not be used for any endpoint analyses. Safety and efficacy data collected during Follow-up Period 2 will be presented using descriptive statistics in tables and listings and will be reported as a final CSR report.

- *Visit Week 64 End of Study*: The end of study is last participant; last visit. Novartis, parents/caregivers, and key study site personnel will be blinded to the participant's treatment assignment excluding any patients unblinded during the trial (e.g., controls ineligible for OAV101 treatment discussed above).

Following end of study, participants will be invited to enroll in a Novartis-sponsored long-term follow-up study to monitor long-term safety and efficacy.

4 Rationale

Safety and clinically meaningful efficacy with IT delivery of OAV101 was observed in the open label AVXS-101 CL-102 study (see Investigator's Brochure). Hence, OAV101 IT may provide a safe, one-time treatment option leading to prolonged, clinically meaningful benefit in older and heavier SMA patients.

4.1 Rationale for study design

Table 4-1 Rationale for study design

Overall	This is a randomized, sham-controlled, double-blind study to evaluate the efficacy, safety, and tolerability of OAV101 in sitting but never ambulatory participants aged ≥ 2 to < 18 years with Type 2 SMA. The primary efficacy endpoint is the change from baseline in HFMSE total score at the end of Follow-up Period 1 in the ≥ 2 to < 18 years age group. Secondary efficacy endpoints will evaluate the change from baseline HFMSE total score at the end of Follow-up Period 1 in the ≥ 2 to < 5 year age group, the achievement of at least a 3-point improvement in HFMSE total score at the end of Follow-up Period 1 in both the ≥ 2 to < 18 year age group and the ≥ 2 to < 5 year age group, and the change from baseline in RULM total score at the end of Follow-up Period 1 in both the ≥ 2 to < 18 year age group and the ≥ 2 to < 5 year age group. ***Rationale using HFMSE and RULM motor scales for primary and secondary endpoints:*** ***HFMSE:*** The HFMSE is an SMA-specific 33-item questionnaire that is easily administered by clinical evaluators in a short period of time, requires minimal equipment, and is not fatiguing to individuals (Krosschell et al 2006, Krosschell et al 2011). The scale was originally developed with 20 scored activities devised for use in children with SMA Types II and III with limited ambulation to give objective information on motor ability and clinical progression (Main et al 2003). The expanded scale includes an additional module of 13 selected items from the Gross Motor Function Measure (GMFM) to allow for motor function evaluation in ambulatory children with SMA (O'Hagen et al 2007) Each motor skill item is scored on a 3-point Likert scale from 0 (no response) to 2 (full response), with a total score range of 0 to 66 (Main et al 2003). Evaluation of inter-rater reliability and test-retest reliability demonstrated that these functional assessments could be performed reliably in a multicenter clinical trial with rigorous initial, annual, and periodic retraining and support to ensure standardization (Mercuri et al 2006). A Phase 1 study of nusinersen reaffirmed that the HFMSE is sensitive to change, with a 3-point change in score considered clinically meaningful and indicates that a child improved on at least 2 HFMSE motor skills (Mercuri et al 2018b). The HFMSE has well-established psychometric properties in high-functioning children with SMA and has high

	reliability and correlation with the GMFM and GMFM-75 (Ramsey et al 2017). The HFMSE was used in the AveXis open label CL-102 trial of intrathecal OAV101 administration which allowed determination of efficacy response parameters in the 2 to 5 years age group important for COAV101B12301 trial. In addition to use with SMN-targeting therapies for SMA, the HFMSE is correlated with various aspects of SMA disease severity with positive associations found with *SMN2* copy number, compound muscle action potential (CMAP), forced vital capacity (FVC) and muscle strength, making it clearly a disease-specific outcome measure of choice for clinical trials (Glanzman et al 2011, Kaufmann et al 2012, Farrar et al 2013). ***RULM:*** The RULM is a validated SMA-specific outcome measure that assesses upper limb functional abilities in individuals with SMA, including young children and non-ambulatory young children and weaker individuals who have a floor effect or very low score on the HFMS (Pera et al 2019). The original test consists of 9 items, but the revised version of the test consists of 19 scorable items: 18 items scored on a 0 (unable) to 2 (full achievement) scale, as with the HFMSE, and one item that is scored from 0 (unable) to 1 (able). These item scores are summed to give a total score ranging from 0 to 37 points with lower scores reflecting poorer ability (Pera et al 2019). The RULM consists of upper limb performance items that are reflective of reachable space and activities of daily living (i.e., raise a can to mouth as if drinking, take a coin and place it in a box, and remove the lid of a container) (Pera et al 2019). The RULM is quickly administered, well tolerated by children of 30 months of age to adults, suitable for use in multicenter settings, and has been evaluated in clinical trials assessing the efficacy of SMN--targeting therapy (Mercuri et al 2018b). Since the RULM is being administered in a blinded fashion to treated participants and controls across the 2 to 18 years age range, all patients will be scored.
Randomization (strata, allocation ratio)	Approximately 125 participants will be randomized 3:2 to receive OAV101 (N= ~75) or a sham procedure (N= ~50). The unequal randomization ratio limits the number of participants allocated to the sham-procedure arm. It is anticipated that approximately 65 randomized participants will be aged ≥ 2 to < 5 years and approximately 60 randomized participants will be aged ≥ 5 to < 18 years. CCI [redacted] to assess if OAV101 is efficacious, safe, and well-tolerated in this population. CCI [redacted] thereby maximizing statistical power for detecting differences in each age group. . CCI [redacted] **rationale:** The primary endpoint for the trial is the change in HFMSE over 52 weeks in the ≥ 2 to < 18 years age group.

	Natural history assessment of late onset SMA patients demonstrates CCI [redacted] CCI [redacted] **rationale:** CCI [redacted]
Participant and investigator blinding	Blinding of participants, physical/occupational therapist (or national equivalent) who performs HFMSE and RULM, and the investigator controls for bias during study endpoint assessment.
Duration of study	A clinical study duration of 52 weeks optimizes the probability of clearly demonstrating the potential clinical efficacy of OAV101 for IT administration while limiting the time SMA participants randomized to the sham procedure arm are required to remain on a non-active-treatment regimen. The data for assessment of endpoints is based on a 52-week follow-up period.
Sham procedure comparator	The use of a sham procedure as a comparator will provide a comparison group for an unbiased collection and assessment of efficacy, safety and tolerability. The sham procedure will consist of a small needle prick on the lower back at the location where the lumbar puncture injection is normally made. The needle will break the skin but no needle insertion for lumbar puncture will occur. Lumbar puncture and OAV101 administration should be performed using an atraumatic spinal needle (e.g., Whitacre, 22 or 25 gauge) which significantly lowers the incidence of blood patch treatment (Hatfield et al 2008).
Observation period	Review of data from the previous AVXS-101-CL-102 study confirmed the importance of following participants for 52 weeks to evaluate the statistical significance and clinical meaningfulness of the observed changes. Data analysis at time points before 52 weeks may not have sufficient power to adequately evaluate therapeutic efficacy. Although blinding is maintained at 52 weeks when a second blinded OAV101 treatment of control patients and sham procedure with needle prick is performed on treated participants, the data for assessment of endpoints is based on a 52-week follow-up period.

4.1.1 Rationale for choice of background therapy

The study allows for standard of care, non-disease modifying SMA therapy, including respiratory and nutritional support, physical therapy, and prevention of infection therapies in accordance to treatment guidelines and local practice.

Participants are expected to have access to respiratory equipment (e.g., cough assist machine) in the event they are required during the course of the study (e.g., develop a respiratory illness). Sites should have a plan in place to provide respiratory equipment (including for inside and outside hospital settings), if required, to those who do not have access. This will further mitigate safety and efficacy confounders.

Physiotherapy, occupational therapy and other forms of supportive therapies are allowed but the frequency should remain the same throughout the duration of the clinical study, if possible.

The use of concomitant therapies or procedures must be documented on the appropriate Case Report Form (CRF) (Section 6.2.1).

4.2 Rationale for dose/regimen and duration of treatment

OAV101 will be administered in this trial as a single intrathecal injection as a nominal dose of 1.2×10^{14} vector genomes (vg).

The primary, secondary and exploratory evaluation will be conducted over a 52-week follow-up period. A clinical study duration of 52 weeks optimizes the probability of clearly determining the potential clinical efficacy of OAV101 for IT administration while limiting the time SMA participants randomized to the sham OAV101 administration-control arm are required to remain on a non-active-treatment regimen. This conclusion is based on the clinically meaningful and statistically significant motor improvements over 52 weeks observed in the ≥ 2 to < 5 year age group from AVXS-101-CL-102 and from the late onset SMA natural history data which carefully investigates the ≥ 2 to < 18 year old age group over 52 weeks (Coratti et al 2020b, Coratti et al 2020a).

a. AVXS-101-CL-102 in the ≥ 2 to < 5 year age group supports a trial duration of 52 weeks.

Efficacy assessment in participants from the AVXS-101-CL-102 study who received IT OAV101, indicate that a 52-week follow-up period for the primary endpoint is appropriate for the COAV101B12301 clinical trial (see Investigator's Brochure). Based on a mixed model with repeated measurement analysis of change from baseline in HFMSE scores, participants aged 2-5 years treated with OAV101 experienced a progressive improvement in motor skills over the 12 month observation period (LS mean change from baseline at Month 12 6.0; 95% confidence interval 3.7 to 8.3) whereas the natural history controls (Pediatric Neuromuscular Clinical Research (PNCR) dataset) showed smaller change of motor skills (LS mean change from baseline at Month 12 0.5; 95% confidence interval -2.2 to 3.2 (see Investigator's Brochure). The estimated difference in LS means (95% confidence interval) relative to the PNCR dataset for the change in HFMSE from baseline to Month 12 was 5.5 (1.9, 9.0) points with a p-value of 0.0027 (see Investigator's Brochure).

The limited gross motor changes over 52 weeks observed in the CL-102 PNCR natural history cohort were recently confirmed in a large multi-national natural history study consisting of 267 Type 2 SMA patients 30 months to 33.4 years of age (Coratti et al 2020b). Children from the 2

to 5 year old age group from this natural history study were able to sit but not walk at baseline which was similar to the clinical features of the CL-102 participants. The 12-month HFMSE change from baseline in this 2 to 5 year old natural history group demonstrated a mean ± standard deviation of 0.40 ± 4.09 (Coratti et al 2020b).

Review of the LS mean at various points in the study confirmed the importance of following the participants for 52 weeks to evaluate the statistical significance and clinical meaningfulness of the observed changes. Data analysis at time points before 52 weeks may not have sufficient power to adequately evaluate therapeutic efficacy.

b. Late onset SMA patient natural history supports a trial duration of 12 months for appropriate assessment of change from baseline in motor function (Coratti et al 2020a, Coratti et al 2020b).

In the largest and most comprehensive natural history study to date in 267 Type 2 SMA patients (age range 30 months to 33.4 years), the detailed data based on 652 assessments allows delineation of age groups based on disease progression as well as patient motor abilities (Coratti et al 2020b, Coratti et al 2020a). Of the 652 assessments, 541 were from patients who could sit but were never ambulatory and all but one patient had 2 to 4 *SMN2* copies. These key clinical features are aligned with the study population inclusion criteria for COAV101B12301. Although patient motor function declined with age in this natural history study, 12 months of assessment allowed clear characterization of changes across the age range, further supporting the 12-month trial duration chosen for the COAV101B12301 study population.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

The generally slow rate of decline observed in patients with late onset SMA combined with provision of treatment within 12 months for those in the sham control group, provides a strong rationale for the study design. Patients randomized to the sham control group will receive OAV101 after they complete Week 52. Additionally, to improve treatment access for participants during the study, randomization is set at 3:2 which limits the number of patients in whom treatment is delayed.

Prednisolone prophylaxis and placebo: participants randomized to the treatment arm will receive prophylactic prednisolone CCI [redacted], to dampen the host immune response. Prednisolone is continued CCI [redacted], as indicated in Table 6-2. Participants randomized to the sham procedure arm will receive a placebo instead of prednisolone and follow the same administration protocol. The same administration protocol of prednisolone or placebo will be followed in Period 2.

4.4 Purpose and timing of interim analyses/design adaptations

No formal interim analysis is planned for this trial.

The data collected during this study will be reported two times. Once the last participant completes the Week 52 visit, formal cleaning procedures will be initiated and the database will be soft-locked in preparation for the primary analysis. Treatment assignments will be unblinded to designated sponsor personnel and a full analysis of all efficacy and safety data will be

conducted and reported to health authorities. This will constitute the first analysis of data. Once the last participant completes the Week 64 visit, formal cleaning procedures will be initiated and the database will be hard-locked in preparation for the final analysis. Efficacy data collected during Treatment Period 2 will be summarized descriptively in tables and listings. Safety data collected during Treatment Period 2 will be combined with safety data collected during Treatment Period 1 to provide a comprehensive safety analysis of data collected over the full 64-week study duration.

4.5 Risks and benefits

The ability of OAV101 to achieve sustained expression of SMN in motor neurons with one-time dosing is a clear unmet need in later onset SMA Type 2. Uninterruptable and constant SMN protein production within motor neurons positively impacts the clinical phenotype by allowing motor development which leads to stability in motor function. Clinical data strongly suggest OAV101 is safe and well tolerated with an acceptable benefit/risk profile when administered to patients with 5qSMA with 2 or 3 survival motor neuron 2 *(SMN2*) copies or a clinical diagnosis of SMA. Safety and clinically meaningful efficacy with IT delivery of OAV101 was observed in CL-102 (see Section 4.2). The risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring. Refer to the Investigator's Brochure for a summary of OAV101 efficacy data. Categories of risks and benefits are discussed below.

4.5.1 Potential benefits to participants

The ability of OAV101 to achieve sustained expression of SMN in motor neurons with one time dosing is a clear unmet need in later onset SMA patients. Uninterruptable and constant SMN protein production within motor neurons positively impacts the clinical phenotype by allowing motor development which leads to stability in motor function. Safety and clinically meaningful efficacy with IT delivery of OAV101 was observed in the open label CL-102 clinical trial (See Investigator's Brochure). Hence, OAV101 IT may provide a safe, one time treatment option leading to clinically meaningful benefit in patients with Type 2 SMA age 2 to < 18 years.

4.5.2 Ethical considerations

The generally slow rate of decline observed in patients with late onset SMA combined with provision of treatment within 52 weeks of those in the sham procedure group provides a strong ethical rationale for the design of the COAV101B12301 clinical study. In the natural history study described above (Coratti et al 2020b), 62% of patients who could sit but not walk at baseline showed stability (12-month changes within ± 2 HFMSE points), 25% showed decreased function (12-month changes > 2 HFMSE points), and 13% of patients showed improvements (12-month changes > 2 HFMSE points).

Ethical considerations for COAV101B12301 design include the following features.

- All eligible individuals enrolled in study COAV101B12301 will be offered IT administration of OAV101. Participants randomized to the sham procedure cohort may receive OAV101 after they complete the 52-week clinical trial assessment period. Although it is possible that a very small number of individuals could have elevated antiAAV9 antibodies that exclude them from receiving OAV101 in Treatment Period 2

(Week 52 + 1 day), the risk of natural infection resulting in elevated neutralizing antibodies in the 2 to 18 year old age range appears to increase slowly with age (Mimuro et al 2014). It is estimated that ≤ 5 participants who received the sham procedure would be excluded from receiving OAV101 treatment as a result of contracting a natural infection during Period 1.

- To improve treatment access during the study for participants, randomization is set at 3:2 rather than 1:1, which limits the number of participants in whom treatment is delayed and improves the probability that a participant would be in the OAV101 treatment group.

4.5.3 OAV101 risks

Evidence from the completed and ongoing clinical studies continue to demonstrate the efficacy of OAV101. Substantial clinical efficacy of OAV101 across multiple endpoints-survival, motor function, developmental motor milestones, and ventilatory and nutritional endpoints has been established and confirmed in First-in-Human and confirmatory studies. Long-term follow-up studies continue to support the durability of OAV101 efficacy, and patients continue to exhibit the achievement of additional milestones. Data spans pre-symptomatic and symptomatic patients and includes SMA Type 1 and Type 2 patients. The risk to participants in this trial will be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring and evaluation by an external Data Monitoring Committee (DMC). The safety profile of OAV101 is described in the Investigator's Brochure. The risks and benefits are derived from the following categories of clinical safety and efficacy data for the intravenous (IV) and intrathecal administration of OAV101 plus non-clinical data.

- Non-clinical toxicology and nonhuman primate studies
- Numerous clinical studies for the intravenous treatment of symptomatic and pre-symptomatic patients with SMA who have 1, 2 or 3 copies of the *SMN2* gene and bi-allelic *SMN1* gene deletions.
- Safety and clinically meaningful efficacy with intrathecal delivery of OAV101 was observed in the CL-102 clinical trial across an age range of 6 months to 5 years of age
- Long term observational follow-up studies of patients who were administered intravenous OAV101 in clinical trials
- United States (US) managed access program of patients treated with intravenous OAV101 (Zolgensma)
- Long-term registry of patients diagnosed with SMA, irrespective of type or treatment provided
- Post-marketing safety monitoring

A brief overview of the clinical data that defines the intravenous and intrathecal OAV101 risks are outlined below.

Clinical data overview for intravenous and intrathecal administration: As of 11-Jun-2020, based on individual case safety reports from all sources, the most common adverse events (25 or more reports) were CCI [redacted] On the basis of important identified and potential risks associated with OAV101, adverse events of special interest are summarized for the following categories. The

discussion of intrathecal OAV101 safety focuses on the 1.2 x 10^{14} vector genome dose selected for this clinical trial (COAV101B12301).

Each of the following is an important identified or important potential risk associated with OAV101:

- Hepatotoxicity
- Transient thrombocytopenia
- Cardiac adverse events
- Dorsal root ganglia toxicity
- Thrombotic microangiopathy
- Theoretical risk of tumorigenicity due to vector integration

Hepatotoxicity

Intravenous administration overview: Elevation in liver transaminases is observed with AAV gene therapy in humans (Verdera et al 2020). In OAV101 clinical trials elevations in liver transaminases have been reported. CCI [redacted]

As of June 2022, in the postmarketing setting, cases of acute liver failure have been reported, including 2 cases with a fatal outcome. In certain cases, patients required hospitalization, and exhibited signs and symptoms associated with liver dysfunction (e.g., jaundice, coagulopathy, elevated ammonia levels).

Intrathecal administration overview: CCI [redacted] With respect to the 1.2 x 10^{14} vector genome dose of intrathecal OAV101 selected for this clinical trial (COAV101B12301), the CL-102 open label trial included safety and efficacy evaluation of the 1.2 x 10^{14} vector genome dose of intrathecally administered OAV101 in 25 patients between 6 months and 5 years of age. CCI [redacted]

CCI [redacted]

Transient thrombocytopenia

Intravenous administration overview: CCI [redacted]

Intrathecal administration overview: CCI [redacted]

Cardiac adverse events

Intravenous administration overview: Cardiac toxicity has been identified as an important potential risk based on non-clinical toxicology data. The translatability of the observed findings to humans has not been verified. CCI

Intrathecal administration overview: CCI

Dorsal root ganglia toxicity

CCI Following intrathecal administration of OAV101 CCI findings in the nervous system CCI These findings were considered CCI nervous system findings CCI Further details of the OAV101-related CCI can be found in the Investigator's Brochure.

Intravenous and intrathecal OAV101 administration: CCI [redacted]

Thrombotic microangiopathy (TMA)

Intravenous administration overview: Thrombotic microangiopathy (TMA) is characterized by arteriole and capillary endothelial pathology and microvascular thrombosis. TMA presents clinically as a syndrome of thrombocytopenia, hemolytic anemia, and acute kidney injury. CCI [redacted]

Intrathecal administration overview: CCI [redacted]

Theoretical risk of tumorigenicity due to vector integration

There is a theoretical risk of tumorigenicity due to integration of AAV vector DNA into the genome. OAV101 (onasemnogene abeparvovec) is composed of a non-replicating AAV9 vector whose DNA persists largely in episomal form. Rare instances of random vector integration into human DNA are possible with recombinant AAV. The clinical relevance of individual integration events is unknown, but it is acknowledged that individual integration events could potentially contribute to a risk of tumorigenicity.

Risk of immunosuppression

All patients in the study will receive prophylaxis immunosuppression with prednisolone to mitigate safety risks associated with inflammation. The chronic use of corticosteroids may be associated with hypothalamic-pituitary-adrenal axis suppression, Cushing's syndrome and hyperglycemia which can be mitigated with adequate tapering. Increased susceptibility to new infections or exacerbation and dissemination of latent infections, as well as elevated blood pressure, salt and water retention, hypokalemia, and gastrointestinal perforation have been reported. Risks will be mitigated by close monitoring, and implementation of standard prophylaxis and tapering protocol (Table 6-2).

Risk of viral shedding

OAV101 DNA can be found in the blood, urine, saliva, and stool for up to a few weeks following injection. The risks associated with the shed vector are not known at this time; however, because the vector is non-pathogenic and cannot replicate, it is believed that the shed vector is unlikely to result in clinically significant adverse effect.

Risk of phlebotomy

Pain or bruising at the injection site may occur. Infections at the injection site are also possible. The World Health Organization (WHO) Guidelines for Drawing Blood and Best practices in Phlebotomy in pediatric patients (WHO 2010) will be followed.

Risks of lumbar puncture

Lumbar puncture risks can include headache, back pain, or bleeding near the puncture site that may need to be treated or may resolve on its own. Potential risks that are extremely rare include infection, nerve injury, and paralysis.

The risks are minimal in the context of one-time gene therapy providing potentially overall efficacy.

Risks of CCI

The test to measure CCI to determine CCI Thus, while the test can be utilized to measure CCI Therefore, the accuracy of results from this test has not been fully established. Furthermore, the benefit-risk of OAV101 in participants with CCI has not been determined.

4.5.4 OAV101-drug interactions

OAV101 is a gene replacement therapy product for one-time administration, which delivers a transgene construct expressing the SMN protein. Drug-drug interactions are not expected with OAV101.

4.5.5 Teratogenicity and associated risks

Women of child-bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the inclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

4.6 Rationale for Public Health Emergency mitigation procedures

During a public health emergency as declared by local or regional authorities i.e., pandemic, epidemic, or natural disaster, mitigation procedures to ensure participant safety and trial integrity may be implemented. Notification of the public health emergency as declared by local or regional authorities should be discussed among investigators and Novartis. All procedures adapted to the situation must be submitted, if required as per local regulations, through a protocol amendment for approval by local or regional Health Authorities and Ethics Committees prior to implementation of mitigation procedures.

5 Study Population

Inclusion and exclusion criteria should be assessed during the screening period to determine patient eligibility for the trial. This randomized, double-blind, sham-controlled study will test the clinical efficacy, safety, and tolerability over 52 weeks of a single, nominal dose (1.2×10^{14} vector genomes) of intrathecal OAV101 in patients with 5q SMA who are ≥ 2 to < 18 years of age at the time of screening. The 5q SMA study population genotype is characterized as harboring biallelic *SMN1* pathogenic variants. Approximately 125 patients aged ≥ 2 to < 18

years will be recruited consisting of ~65 patients between the ages of ≥ 2 to < 5 years and of ~60 patients between the ages of ≥ 5 to < 18 years. The ~125 participants enrolled to the trial are randomized in a 3:2 ratio to receive OAV101 by intrathecal lumbar puncture (LP) injection (n=~75) or to receive the sham procedure (n=~50).

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria.

1. Signed informed consent and assent (if applicable) must be obtained before any assessment is performed.
2. Diagnostic confirmation during screening period of 5q SMA.
3. The patient must be treatment naive (historical or current use) for all SMN-targeting therapies (e.g., risdiplam (Evrysdi) and nusinersen (Spinraza)).
4. ≥ 2 years and < 18 years of age at screening visit 1.
5. Onset of clinical signs and symptoms at ≥ 6 months of age.
6. Patient must have a complete HFMSE assessment with an available total score, as administered by qualified clinical evaluator during the screening period for trial eligibility.
7. Able to sit independently at screening, but has never had the ability to walk independently.
   - Definition of sitting independently: Child sits up straight with the head erect for at least 10 seconds without using arms or hands to balance body or support position (Wijnhoven et al 2004).
   - Definition of walking independently: The child is able to balance the body and control forward stepping movements without assistance (Wijnhoven et al 2004).
8. Estimated life expectancy > 2 years from screening, in the opinion of the Investigator.
9. Meets age-appropriate institutional criteria for use of anesthesia/sedation as assessed by the physician responsible for administering anesthesia/sedation.
10. Female participants who are sexually active or have reached menarche must have a negative pregnancy test at Screening. Those females who are sexually active must also agree to use highly effective methods of contraception (implants, injectables, oral contraceptives [hormonal], IUDs, total abstinence) as well or limit sexual activity to surgically sterilized or contraception-practicing partners during the trial and for 24 months after the administration of the investigational product. Female patients must agree to refrain from egg freezing and egg donation until 24 months after dosing.

    Note: In case of use of oral contraceptives, females should have been stable on the same pill for a minimum of 3 months before taking the study treatment. If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the informed consent form (ICF).
11. Males capable of fathering a child must agree to use barrier contraception (combination of a condom and spermicide) or be abstinent for 6 months after each OAV101 administration/sham procedure (i.e., Day 1 and Week 52 + 1 Day). In addition, male patients must agree to refrain from sperm donation during the trial and for 12 months after Treatment Period 2.
12. Must obtain bilateral radial and sural nerve SNAPs at Screening.

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study. Retesting of abnormal laboratory and other clinical parameters that could be transient or measurement error may be allowed up to two times based on judgement of the Principal Investigator in communication with the Sponsor Medical Monitor.

1. Excluding SMA, any medical condition considered clinically significant by the Investigator, including cardiomyopathy, hepatic dysfunction, kidney disorder, endocrine disorder including diabetes mellitus, gastrointestinal disorders, metabolic disorders, untreated B6 deficiency, severe respiratory compromise and significant brain abnormalities at either Screening or Baseline that, in the opinion of the investigator, would interfere with the overall interpretation of safety or efficacy of the study.
2. Anti-AAV9 antibody titer reported as elevated (reference to > 1:50 or a validated result consistent with being elevated) at Screening [redacted]
3. Clinically significant abnormalities in test results during screening period and/or during baseline period as determined by the investigator.
4. Participants will be excluded from the trial for inpatient surgery hospitalization, hospitalization for a pulmonary event, or hospitalization for nutritional support within 2 months prior to Screening and up to Day 1. In addition, patients will not be eligible for the trial if at Screening, inpatient major surgery is planned at any time during the 64-week study. Any other surgeries must not interfere with the ability of the patient to perform the study assessments.
5. Prior injury (e.g., upper or lower limb fracture) or surgical procedure which impacts the participant's ability to perform any of the outcome measure testing required in the protocol and from which the participant has not fully recovered or achieved a stable baseline upon entry into screening period.
6. Contraindications for lumbar puncture procedure, (including but not limited to cutaneous infection at the treatment site and signs or symptoms of increased intracranial pressure), active administration of any intrathecal therapy, presence of an implanted shunt for the drainage of CSF, presence of an implanted central nervous system (CNS) catheter, or any impediment to CSF access.
7. Presence of any of the following:
   - An active infectious process requiring systemic therapy intended to eliminate the infection within 30 days prior to dosing of OAV101 or the sham procedure
   - An active but untreated viral or bacterial infectious process within 30 days prior to dosing of OAV101 or the sham procedure
   - Febrile illness within 30 days prior to OAV101 administration or sham procedure
8. Administration of vaccines within 2 weeks prior to injection of OAV101 or sham procedure.
9. Clinical or radiological signs of aspiration within 30 days prior to Day 1.
10. Requiring invasive ventilation, awake noninvasive ventilation for > 6 hours during a 24-hour period, noninvasive ventilation for > 12 hours during a 24-hour period or requiring tracheostomy within 30 days prior to Day 1.

11. Awake hypoxemia (defined as O_2 saturation < 95% in room air) within 30 days prior to Day 1.

    NOTE: For altitudes > 1000 m, awake hypoxemia is defined as O_2 saturation < 92% in room air

    NOTE: For altitudes > 2500 m, awake hypoxemia is defined as O_2 saturation < 90% in room air
12. Hepatic dysfunction (i.e., ALT, TBL, GGT or GLDH, > ULN (i.e., CTCAE grade 1 or greater)) at Screening Visit 1.

    NOTE: In the absence of other liver laboratory abnormalities, isolated AST elevation is not considered exclusionary
13. Complications at screening that would interfere with motor efficacy assessments including but not limited to:
    - Presence of severe contractures (e.g., hip flexion contracture) which limits the participant's ability to be positioned in prone for HFMSE item administration
    - Scoliosis with a Cobb angle > 40 degrees in a sitting position, evident on x-ray examination at Screening
14. BMI < 3rd percentile if considered clinically significant by the investigator

    NOTE: BMI is based on the WHO Child Growth Standards (WHO 2022a) and WHO Growth reference data for 5-19 years (WHO 2022b).
15. History of untreated or uncorrected vitamin deficiencies which can produce sensory neuropathies such as pyridoxine deficiency (B6).
16. Concomitant use of any of the following medication categories within 90 days prior to study treatment (Day 1):
    - Ongoing systemic immunosuppressive therapy (e.g., corticosteroids (except for prophylactic use for OAV101 dosing), cyclosporine, tacrolimus, methotrexate, cyclophosphamide, intravenous immunoglobulin, rituximab), plasmapheresis, immunomodulators (e.g., adalimumab)
17. Inability to tolerate corticosteroids administered by mouth or gastrostomy tube.
18. Concurrent or previous participation in another investigational trial in which patient receives treatment within 30 days prior to screening, 5 half-lives of the drug, or until the expected pharmacodynamic effect has returned to baseline (e.g., biologics), whichever is longer.
    - NOTE: Participation in observational cohort studies or non-interventional studies in which the participant does not receive treatment or undergo procedures which may compromise this study data integrity may be allowed following Sponsor approval.
19. History of gene therapy, hematopoietic transplantation, or solid organ transplantation.
20. History of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes.
21. Deleted per Amendment #1
22. Any medication deemed by Principal Investigator to pose an unacceptable safety risk for gene therapy administration.
23. Surgery for scoliosis or hip fixation in the 12 months prior to Screening or planned within the next 64 weeks.

24. Positive for human immunodeficiency virus (HIV), hepatitis B, or hepatitis C, including latent infections that may be susceptible to reactivation due to corticosteroids

    Note: Other pathogens that may be endemic to specific regions/countries (e.g., human T-lymphotropic virus or mycobacterium tuberculosis) may be tested, as per investigator discretion and discussion with Sponsor.
25. Platelet count < LLN at screening.
26. Platelet transfusion within 1 month prior to screening and up to Day 1.
27. Clinically significant sensory abnormalities in the neurological examination at Screening.

6 Treatment

The investigational drug, OAV101, will be prepared by Novartis and supplied to the unblinded study-site pharmacist or equivalent per local practice. The pharmacist (or equivalently trained individual per local practice) will prepare the appropriate dosage (detailed instructions will be provided in the Pharmacy Manual). An unblinded interventional radiologist or qualified specialist (e.g., neurologist) will administer OAV101 (as described in the Pharmacy Manual). Strict blinding will be maintained once the participant leaves the procedure room.

6.1 Study treatment

For this study, the terms "investigational drug" or "study drug" refers to OAV101 administered as a single intrathecal dose of 1.2×10^{14} vector genomes. The term "study treatment" refers to OAV101 treatment or the sham procedure. The investigational drug OAV101 will be prepared and supplied by Novartis. See the Pharmacy Manual for OAV101 storage, preparation and administration procedures.

6.1.1 Investigational and control drugs

The biological product is a non-replicating recombinant AAV9 containing the cDNA of the human *SMN* gene under the control of the CMV enhancer/CB promoter. The AAV inverted terminal repeats (ITR) has been modified to promote intramolecular annealing of the transgene, thus forming a double-stranded transgene ready for transcription. This modified ITR, termed a "self-complementary" (sc) ITR, has been shown to significantly increase the speed of which the transgene is transcribed, and the resulting protein is produced. The biological product, called OAV101, expresses the human SMN protein in transduced cells.

Table 6-1 Investigational drug

Treatment Title	OAV101 (formerly AVXS-101)
Treatment Description	1.2×10^{14} vector genomes in [redacted] ml, one time
Type	biologic
Dose Formulation	solution
Route of administration	Intrathecal
Sourcing	Provided centrally by the sponsor or locally by designee
Packaging and Labeling	Study treatment will be provided in a single vial carton. Each vial carton will be labeled as required per country requirement.

6.1.2 Additional study treatments

No other treatment beyond investigational drug and prednisolone/placebo (described in Section 6.2) are included in this trial.

6.1.3 Treatment arms/group

Approximately 125 participants will be randomized to one of the following 2 treatment arms in a ratio of 3:2 (OAV101 : sham procedure):

- Group 1: OAV101 (1.2×10^{14} vector genomes)
- Group 2: sham procedure

[redacted]

6.1.4 Supply of study treatment

US and non-European Union (EU) countries where in-country depot is not required: Investigational Medicinal Product (IMP) is manufactured by the Sponsor and supplied to US or EU Contract Manufacturing Organization. The vials are packaged in a clinical carton (1 vial per carton) and shipped out of the US Contract Manufacturing Organization facility directly to sites. [redacted]

EU countries: IMP is manufactured by the Sponsor and supplied to EU Contract Manufacturing Organization. The vials are packaged in a clinical carton (1 vial per carton) and shipped out of the EU Contract Manufacturing Organization facility directly to the clinical sites. [redacted]

Ex-US non-EU countries where in-country depot is required: IMP is manufactured by the Sponsor, shipped to US or EU Contract Manufacturing Organization and supplied to in-country depot as needed. The vials are packaged in a clinical carton (1 vial per carton) and shipped out of the in-country depot directly to the clinical sites. [redacted]

6.1.5 Treatment duration

OAV101 is a one-time, single dose treatment for SMA. See study design for OAV101 dosing schedule (Section 3).

6.2 Other treatment(s)

In accordance with this protocol, all study participants randomized to the OAV101 treatment arm will receive immunomodulatory therapy with prednisolone and all participants randomized to the sham procedure arm will receive matching placebo by the unblinded pharmacist (or equivalent). The prednisolone oral liquid will be supplied by CCI [redacted]. The matching placebo will be supplied by CCI [redacted]. If the above prednisolone and placebo are not available, an equivalent corticosteroid and placebo will be provided by other manufacturers.

Immunomodulatory therapy is intended to mitigate safety risks associated with immune response to the AAV9 capsid that may occur after administration of OAV101.

Immune responses may lead to elevations in liver transaminases or elevations of Troponin I. Prior to initiation of the immunomodulatory regimen and prior to administration of OAV101/sham procedure, the participant must be checked for symptoms of active infection of any nature.

CCI [redacted] prednisolone/placebo dosing will be instituted according to the schedule below.

Table 6-2 Prednisolone Prophylaxis and Placebo Administration

Period	Dosing schedule	Dose
CCI [redacted]	CCI [redacted]	Prednisolone or placebo CCI [redacted]
CCI [redacted]	CCI [redacted]	Prednisolone or placebo CCI [redacted] CCI [redacted]
CCI [redacted]	CCI [redacted]	CCI [redacted]

Table 6-3 Additional study treatment

Treatment Title	CCI [redacted]	CCI [redacted]	CCI [redacted]	CCI [redacted]

Treatment Description	CCI	CCI	CCI	CCI
Dose Formulation	CCI	CCI	CCI	CCI
Unit Dose Strength(s)	CCI mg/ml	CCI	CCI mg/ml	CCI
Route of Administration	CCI	CCI	CCI	CCI
Use	Prophylactic therapy	Matching placebo for prophylactic therapy	Prophylactic therapy	Matching placebo for prophylactic therapy
Sourcing	Provided centrally by the sponsor or locally by designee	Provided centrally by the sponsor or locally by designee	Provided centrally by the sponsor or locally by designee	Provided centrally by the sponsor or locally by designee
Packaging and Labeling	Additional study treatment will be provided in a single bottle carton. Each bottle carton will be labeled as required per country requirement.	Additional study treatment will be provided in a single bottle carton. Each bottle carton will be labeled as required per country requirement.	Additional study treatment will be provided in a single bottle carton. Each bottle carton will be labeled as required per country requirement.	Additional study treatment will be provided in a single bottle carton. Each bottle carton will be labeled as required per country requirement.

6.2.1 Concomitant therapy

The Investigator should instruct the participant and his/her parents/caregivers to notify the study site about any new medications he/she takes after the participant was enrolled into the study. All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate CRFs.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication (Section 5.2 and Section 6.2.2). If in doubt, the Investigator should contact the Novartis medical monitor before enrollment of a participant or allowing a new medication to

be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

Participants are encouraged to follow all routinely scheduled immunizations, including vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as recommended by local health authorities and/or required by local site guidelines. Where feasible, the participant's vaccination schedule should be adjusted to accommodate concomitant corticosteroid administration prior to and following OAV101, specifically vaccinations should be withheld 2 weeks prior to OAV101 administration/sham procedure, and live vaccines should not be administered while receiving corticosteroids.

Prior medications excluded according to the criteria in Section 5.2 will be recorded within 90 days prior to Screening and all prior medications will be recorded on the eCRF at all visits prior to Baseline.

6.2.2 Prohibited medication

Except for concomitant medication allowed per protocol (see Section 6.2.1) and/or any nonexcluded medications which may be required to treat AEs, no medication other than study treatment will be allowed from the date the informed consent is signed until all of the study completion evaluations have been performed.

Concomitant use of any of the following medications are prohibited:

- Concomitant medication with the intent to treat SMA
- Any investigational medication other than OAV101
- Plasmapheresis and immunomodulators
- Use of intravenous immunoglobulins and vaccines 4 weeks after injection of OAV101 or sham procedure; unless required for treatment of Aes
- Live vaccines are prohibited while receiving corticosteroids. Participants are advised to complete all age-appropriate inoculations with live vaccines prior to enrolling in the study if possible.
- The use of immunosuppressive therapies, including but not limited to, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IVIG, rituximab, and adalimumab; unless required for treatment of Aes

Given the nature and profile of the treatment, i.e., gene therapy, there are no pharmacokinetic (PK)/pharmacodynamic (PD) drug interactions expected.

The Investigator should instruct the participant/caregiver to notify the study site about any new treatments the participant takes after the start of study treatment. All prohibited medications and significant non-drug therapies administered after the participant starts study treatment must be recorded in the eCRF.

6.3 Preparation and dispensation

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of prednisolone directly to a participant's home may be permitted (if allowed by

Local or Regional Health Authorities and Ethics Committees as appropriate). In the event the Investigator decides that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to supply the prednisolone even without performing an on-site visit, prednisolone will be dispatched from the site to the participant's home and remains under the accountability of the Investigator. In this case, regular phone calls or virtual contacts per schedule of assessment (Table 8-1) will occur between the site and the participant for instructional purposes, safety monitoring, drug accountability, investigation of any adverse events, ensuring participants continue to benefit from treatment and discussion of the participant´s health status until the participants can resume visits at the study site.

Study drug preparation

Study sites will be supplied with study drug in packaging as described under investigational and control drugs section.

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the participant by contacting the Interactive Response Technology (IRT) and obtaining the medication number(s).

OAV101 will arrive as outlined in the Pharmacy Manual. A single administration of OAV101 will be prepared by an appropriately trained unblinded pharmacist (or equivalent).

Preparation of OAV101 will be done aseptically under sterile conditions at the site per Pharmacy Manual and will be received ready for injection at the bedside.

The dose-delivery vessel will be delivered in the appropriate setting with immediate access to acute critical care management. The vessel will be delivered in accordance with the Pharmacy Manual. The investigational delivery system will be used in accordance with the Pharmacy Manual. Instructions for Use will be included in the Pharmacy Manual.

Study drug administration

OAV101

Participants will receive OAV101 injection under sterile conditions in an ICU patient room or other appropriate setting (e.g., interventional suite, operating room, dedicated procedure room) with immediate access to acute critical care management. Parents/caregivers must not be present in the procedure room to ensure blinding (See Section 6.5). Study drug will be administered in accordance with the Schedule of Assessments (Table 8-1).

Sites are instructed to refer to the Pharmacy Manual in the use of atraumatic needles, which has been shown to considerably reduce damage to the dura and consequently decrease the risk for CSF leakage after lumbar puncture (Rochwerg et al 2018, Nath et al 2018).

Sedation/anesthesia is required for all participants receiving OAV101 IT. Method and medications will be at the discretion of the local anesthesiologist but should incorporate a sufficient degree of sedation or anxiolysis to ensure analgesia and lack of movement for the procedure and post procedure Trendelenburg positioning placement. Participants will be placed in the Trendelenburg position, tilted head-down at 30° for 15 minutes following administration of OAV101 to enhance distribution to cervical and brain regions.

OAV101 will be administered under sterile conditions by an interventional radiologist or a qualified clinician in accordance with institutional guidelines. OAV101 will be delivered per standard of care for intrathecal delivery. In patients with medical complexities (e.g., scoliosis, spinal hardware, etc.) the use of image-guidance (e.g., fluoroscopy or ultrasound) is required to facilitate success of the procedure. For uncomplicated cases (e.g., a young child without scoliosis), the use of image- guidance is at the discretion of the proceduralist. Participants will be placed in the appropriate position and a spinal needle with stylet will be inserted by a lumbar puncture into the L3-L4 or L4-L5 (if needed, may be 1 segment above L3-L4 or 1 segment below L4-L5) interspinous space into the subarachnoid space, as detailed in the Pharmacy Manual. Subarachnoid cannulation will be confirmed with the flow of clear CSF from the needle hub. CCI [redacted] Dosing and administration of OAV101 is detailed in the Pharmacy Manual.

Sham procedure

The sham procedure will be performed in an ICU patient room or other appropriate setting (e.g., interventional suite, operating room, dedicated procedure room) with immediate access to acute critical care management. Parents/caregivers must not be present during the procedure to ensure blinding (See Section 6.5). The sham procedure will consist of a small needle prick on the lower back at the location where the LP injection is normally made. The needle will break the skin, but no needle insertion for lumbar puncture will occur. CCI [redacted] A detailed description of the sham procedure is provided in the Pharmacy Manual.

Post administration procedures

Following administration of gene replacement therapy/sham procedure, participants should return to an appropriate designated setting to ensure close monitoring of vital signs and Aes. Vital signs will be monitored as described under Vital Signs (Section 8.4.4). Participants should be maintained in an appropriate inpatient setting for 24 to 48 hours after the start of gene replacement therapy/sham procedure.

Participants will be kept in the ICU patient room or other appropriate setting (e.g., interventional suite, operating room, dedicated procedure room) with immediate access to acute critical care management for 24 to 48 hours for closer monitoring of mental status. During the inpatient stay, personnel are required to follow appropriate safety precautions as per institutional standards for infection control; standards may require personal protective equipment such as gowns, gloves, masks, glasses, and closed-toe shoes. Participants may be discharged from the hospital when the following criteria are met:

- Afebrile
- Absence of hypersensitivity reactions
- Absence of meningism
- Absence of abnormal laboratory values suggestive of possible CNS infection or complication

6.3.1 Handling of study treatment and other treatment

6.3.1.1 Handling of study treatment

Study treatment must be received by a designated unblinded person at the study site, handled and stored safely and properly and kept in a secured location to which only the designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified in the Pharmacy Manual.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization Quality Assurance. Please refer to procedures as outlined in the Pharmacy Manual.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The designated unblinded site personnel must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

At the conclusion of the study, and as appropriate during the course of the study, the designated site personnel will return a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

OAV101 will be stored in a locked, limited access room under the responsibility of the designated unblinded personnel (e.g., pharmacists) in accordance with local regulations, policies, and procedures. Control of storage conditions, especially control of temperature (e.g., refrigerated/freezer storage) and information on in-use stability and instructions for handling prepared OAV101 should be managed in accordance with the Pharmacy Manual.

Any quality issue noticed with the receipt or use of OAV101 (e.g., deficiency in condition, appearance, pertaining to documentation, labeling, expiration date, etc.) should be promptly reported to the Sponsor in accordance with procedures outlined in the Pharmacy Manual.

Under no circumstances will the Investigator supply OAV101 to a third party, allow OAV101 to be used other than as directed by this clinical trial protocol, or dispose of OAV101 in any other manner.

6.3.1.2 Handling of other treatment

The following non-study treatment has to be monitored specifically:

The designated site personnel must maintain an accurate record of the shipment and dispensing of prednisolone/placebo treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Participants/caregivers must be instructed to record the dose and date of prophylactic prednisolone/placebo taken/administered at home in the diary provided by Novartis and will be asked to return all unused study treatment and packaging at the end of the study or at the time of study discontinuation.

At the conclusion of the study, and as appropriate during the course of the study, the participant will return all unused prednisolone and matching placebo for accountability and reconciliation, which will be completed by designated site personnel and verified by the Novartis monitor. Upon completion of these tasks, drug can be destroyed at site according to institutional guidelines.

6.4 Participant numbering, treatment assignment, randomization

6.4.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is rescreened. The Participant No. consists of the Site Number (Site No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

The Investigator or designated staff will contact the IRT and provide the requested identifying information to register the participant. Once assigned, the Participant No. must not be reused for any other participant and the Participant No. for that individual must not be changed unless the participant is rescreened. The site should select the eCRF book with a matching Participant Number from the EDC system to enter data. If the participant fails to be treated for any reason, the IRT must be notified within 2 days that the participant was not treated. Rescreening is allowed for participants that were screen failures for a temporary reason. All eligibility criteria must be re-checked and met prior to enrollment of the participant into the study. A new Participant No. should be assigned for all rescreened participants.

A new ICF will need to be signed if the investigator chooses to rescreen the participant after a participant has screen failed, and the participant will be assigned a new Participant No.

6.4.2 Treatment assignment, randomization

At Screening Visit 3, all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact IRT after confirming that the participant fulfills all inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the participant.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by Novartis GCS using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis GCS using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

Randomization will CCI [redacted]

CCI [redacted]

The randomization scheme for participants will be reviewed and approved by a member of the Randomization Office.

6.4.2.1 Replacement policy

No participant replacement will be done for this study.

6.5 Treatment blinding

With the exception of designated unblinded site and Sponsor personnel, all other personnel, including participants, Investigator staff, clinical evaluators performing the assessments, and sponsor will remain blinded to the identity of the treatment from the time of randomization until database lock.

Treatment Period 1 (Screening/Baseline through Week 52)

Randomization: After eligibility for the trial has been determined and informed consent has been obtained, study participants will be randomly assigned using central randomization in a 3:2 ratio (OAV101: sham procedure). Randomization data will be kept strictly confidential until the time of the primary analyses which will occur once the last participant completes Week 52, and will not be accessible by anyone else involved in the study with the following exceptions of unblinded study staff listed below. At this time, treatment assignments will be unblinded to designated sponsor personnel and a full analysis of all efficacy and safety data will be conducted.

Parents and key study personnel (e.g, outcome assessors) must not be present during the procedure to ensure blinding.

The following personnel will be unblinded to the identity of the treatment from the time of randomization:

- IRT personnel who require access to unblinded data
- For the purpose of DMC support, an independent analysis team (Unblinded Statistician/ Statistical Programmer/ Data Analyst)

Sites:

- Unblinded site pharmacist (or equivalent)
- Designated site physician (e.g., Interventional Radiologist) whose role is to perform the sham procedure (i.e., needle prick) or to administer OAV101.
- Designated Procedure Room staff required during the sham procedure or during OAV101 administration

Sponsor:

- Global Clinical Supply management
- Designated Clinical Research Monitors (CRAs)
- Novartis Scientific Monitor
- Unblinded Medical Monitor
- Other designated personnel

Treatment and Follow-up Period 1 blinding

Blinding of Treatment Allocation: The identity of ancillary study treatment (prednisolone and matching placebo) will be concealed by identical packaging, labeling, schedule of administration and appearance.

Unblinding may occur in the event of participant emergencies. The Principal Investigator and Novartis will assess whether the participant whose treatment code has been broken should be withdrawn from the study prematurely (e.g., will not proceed into Treatment Period 2).

If a participant has been randomized to OAV101 administration, the unblinded pharmacist (or equivalent) will prepare a single intrathecal dose of OAV101. The prepared dose will be delivered to the location of the procedure. Participants will be adequately sedated (following institutional guidelines) for lumbar puncture to avoid any awareness of the procedure. A qualified interventional radiologist or specialist (e.g., neurologist) who is unblinded to study treatment will perform the intrathecal administration of OAV101 or the sham procedure. Any study personnel involved with patient treatment or evaluation (e.g., Principal Investigator, study coordinator, site clinical evaluator) cannot be present at the time of the procedure. Parents/caregivers must not be present in the procedure room. Treatment assignment will remain blinded to all patients, site and Novartis personnel (unless otherwise specified), and will similarly be blinded to post-treatment anti-AAV9 antibody results. The pharmacist (or equivalent) and the clinician administering the procedure will be specifically instructed not to discuss any details regarding patient dosing with members of the study team (including the Principal Investigator, study coordinator, and site clinical evaluator) involved in the care or evaluation of the patients.

Prednisolone and placebo prednisolone administration and blinding: Prednisolone administration is required at the time of OAV101 dosing to suppress the immune response. For those participants receiving OAV101, prednisolone will be given CCI [redacted] In order to mimic the prednisolone prophylaxis in the OAV101 treatment group and preserve blinding, the sham procedure group will receive a placebo formulation that is identical in packaging, labeling, schedule of administration, appearance, taste, and odor.

Post-administration follow-up and blinding: The Principal Investigator, physical therapists and any other clinical evaluators will be blinded at all times. In order to limit any potential bias, the HFMSE and RULM assessors (i.e., physical therapists or equivalent) should not have access to any study-related data, other than the data for the assessment(s) which they will administer. Unblinded site personnel will be responsible for performing the OAV101 dosing/sham procedure and may also assess subject safety and AEs within the 2 to 3 days following the study

treatment administration (i.e., during the in-hospitalization period). The unblinded personnel must not be involved in any other aspect of the study, other than the responsibilities detailed in the Pharmacy Manual, and must not divulge the subject's treatment assignment. The blinded personnel will be responsible for all other aspects of the study.

Treatment and Follow-up Period 2 blinding

Anti-AAV9 antibody results CCI [redacted] will be supplied to designated unblinded Novartis personnel. Designated unblinded Novartis personnel will communicate to the investigator when a participant (who received sham procedure in Period 1) has an anti-AAV9 antibody titer reported as elevated (reference to > 1:50 or a validated result consistent with being elevated) (Table 6-4). Novartis GCS will issue OAV101 only if anti-AAV9 antibody titer is not reported as elevated.

At the Week 52 + 1 Day visit, all eligible participants who received the sham procedure in Treatment Period 1 (Day 1) will receive a lumbar puncture and the administration of OAV101 1.2 and all eligible participants who received OAV101 in Period 1 will receive the sham procedure. Blinding will be maintained in the same manner described above for Treatment Period 1. Participants will be followed until Week 64 for efficacy and safety. A small number of control patients (estimated as ≤ 5) may not receive OAV101 treatment at Week 52 due to elevated AAV9 antibodies and would be unblinded. Sham-procedure participants who do not continue to Treatment Period 2 will be captured on the eCRF disposition page.

The DMC responsible for assessments on the safety and overall risk to benefit ratio of the study conduct will have access to the results with aggregated treatment assignment (Section 10.4.1). An independent team of statisticians and programmers, not otherwise involved in the conduct of the study, will be responsible for the timely coordination and delivery of the data to the DMC on a regular basis and will have access to the aggregated treatment assignment and patient level data as requested.

Table 6-4 Blinding and unblinding plan

Role	Time or Event		
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)
Participants	B	B	UI
Site staff	B	B	UI
Unblinded site staff (see text for details)	B	UI	UI
Drug Supply and Randomization Office	UI	UI	UI
Unblinded sponsor staff (see text for details)	B	UI	UI
Statistician/statistical programmer/data analysts	B	B	UI
Independent committees used for assessing interim results	B	UI	UI
All other sponsor staff not identified above	B	B	UI
B Remains blinded UI Allowed to be unblinded on individual patient level			

6.6 Dose escalation and dose modification

Not applicable. OAV101 is a recombinant AAV9 gene therapy which is administered once.

6.7 Additional treatment guidance

Not applicable.

6.7.1 Treatment compliance

OAV101 will be administered as a one-time intrathecal injection. If dose is not fully completed, the site personnel will need to reflect total volume administered as well as the date and time of administration in the CRF. The investigator must promote compliance with the administration of prednisolone or placebo by instructing the participant/caregiver to administer as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant/caregiver must also be instructed to record the dose and date of prednisolone/placebo taken/administered at home in a diary provided by Novartis and to contact the investigator if he/she is unable for any reason to administer as prescribed. Compliance will be assessed by the investigator and/or study personnel using information provided by the participant/caregiver in the diary. This information should be captured in the source document at each visit. All prednisolone/placebo dispensed and returned must be recorded in the Drug Accountability Log.

6.7.2 Recommended treatment of adverse events

The Investigator will use his/her medical judgement in accordance with standard of care to treat adverse events. Medication and/or intervention used to medically manage Aes must be recorded on the appropriate CRF. At present there is insufficient information to provide specific recommendations regarding treatment of AEs other than prednisolone used to dampen the immune reaction directed against OAV101 (Table 6-2).

6.7.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to treat the participant safely. Most often, knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The Investigator will provide:

- protocol number
- participant number

In addition, oral and written information to the participant must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that unblinding can be performed at any time.

It is important to note that the decision to discontinue a treated participant from the study does not automatically preclude inclusion in the long-term follow-up study.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation) IRB/Independent Ethics Committee (IEC)-approved informed consent.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her level of understanding.

Informed consent and assent, if applicable, must be obtained before conducting any study–specific procedures (e.g., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Novartis will provide to Investigators, in a separate document, a proposed informed consent and assent forms that complies with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Good Clinical Practice (GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the Investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about known side effects regarding the investigational treatment can be found in the Investigator's Brochure. This information will be included in the participant informed consent and should be discussed with the caregiver(s)/parent(s)/legal guardian and/or participant upon obtaining consent and also during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between Investigator's Brochure updates will be communicated as appropriate, for example, via an Investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the caregiver(s)/parent(s) and/or participant.

The following informed consents are included in this study:

- Global Model Informed Consent Form to be signed by the participant once he/she turns 18 years of age (to the extent possible and in accordance with local IRB requirements).
- Global Model Parent Legal Guardian ICF
- Global Model Child Assent Form
- Global Model Adolescent Assent Form
- Global Pregnancy Follow-up Model ICF for Pregnant Participant
- Global Pregnancy Follow-up Model ICF for Pregnant Partner of Male Participants

Women of child-bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the

study and agree that in order to participate in the study they must adhere to the contraception requirements.

Male participants must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, the Investigator may conduct the informed consent discussion remotely (e.g., telephone, videoconference) if allowable by a local Health Authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g., the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists type and timing of all assessments. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who discontinue from the study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit if they agree as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, the AE and concomitant medications not previously reported must be recorded on the CRF.

The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the Investigator as the situation dictates. If allowable by a local Health Authority, national and local regulations and depending on operational capabilities, phone calls, virtual contacts (e.g., tele consultation) or visits by site staff/ off-site healthcare professional(s) staff to the participant´s home, can replace certain protocol assessments, for the duration of the disruption until it is safe for the participant to visit the site again. If the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

Table 8-1 Assessment Schedule

Period	Screening			Baseline	Treatment Period 1			Follow-up Period 1											
Visit Name	**Visit 1[1]**	**Visit 2**	**Visit 3**	**Baseline Visit[2]**	**Day 1**	**Day 2**	**Optional Day 3**	**WK 1**	**WK 2**	**WK 3**	**WK 4**	**WK 6**	**WK 8**	**WK 10**	**WK 12**	**WK 16**	**WK 20**	**WK 24**	**WK 28**	**WK 32**
Days	**-60 +15**	**-21 ±7**	**-14 ±7**	**-1**	**1**	**2**	**3**	**8 ±2**	**15 ±2**	**22 ±2**	**29 ±2**	**43 ±2**	**57 ±2**	**71 ±2**	**85 ±7**	**113 ±7**	**141 ±7**	**169 ±7**	**197 ±7**	**225 ±7**
Inclusion / Exclusion criteria	X	X		X																
OAV101 IT administration/sham procedure					X[3]															
IRT contact	X	X		X																
IRT randomization			X																	
Informed consent/assent	X																			
Information to be collected on screening failures	X	X		X																
Demography	X																			
Medical history/current medical conditions	X																			
Independent Sitting Assessment	X																			
Prior medications	X	X		X	X															
Concomitant medications and therapies					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Head circumference for patients <= 3 years of age	X			X							X				X					X
Head circumference for patients > 3 years of age	X			X																

Period	Screening			Baseline	Treatment Period 1			Follow-up Period 1											
Visit Name	**Visit 1[1]**	**Visit 2**	**Visit 3**	**Baseline Visit[2]**	**Day 1**	**Day 2**	**Optional Day 3**	**WK 1**	**WK 2**	**WK 3**	**WK 4**	**WK 6**	**WK 8**	**WK 10**	**WK 12**	**WK 16**	**WK 20**	**WK 24**	**WK 28**	**WK 32**
Days	**-60 +15**	**-21 ±7**	**-14 ±7**	**-1**	**1**	**2**	**3**	**8 ±2**	**15 ±2**	**22 ±2**	**29 ±2**	**43 ±2**	**57 ±2**	**71 ±2**	**85 ±7**	**113 ±7**	**141 ±7**	**169 ±7**	**197 ±7**	**225 ±7**
Vital Signs	X	X		X	X[4]	X[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BMI	X			X							X		X		X			X		
Body Weight	X	X		X	X	X		X			X		X		X	X	X	X	X	X
Body Height (Segmental by Tibial Length)	X			X							X		X		X			X		
Neurological Examination	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	S			S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Chest X-ray	X																			
Spinal X-Ray for Scoliosis Assessment	X[6]																			
Prophylactic prednisolone/placebo				X[7]	X	X	X	X	X	X	X	X	X							
Adverse events/SAEs	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI																				
Hammersmith Functional Motor Scale Expanded (HFMSE)	X	X		X							X		X		X	X	X	X	X	X
Revised Upper Limb Model (RULM)	X	X		X							X		X		X	X	X	X	X	X
CCI																				
Ventilatory support	X			X																

Period	Screening			Baseline	Treatment Period 1			Follow-up Period 1											
Visit Name	**Visit 1[1]**	**Visit 2**	**Visit 3**	**Baseline Visit[2]**	**Day 1**	**Day 2**	**Optional Day 3**	**WK 1**	**WK 2**	**WK 3**	**WK 4**	**WK 6**	**WK 8**	**WK 10**	**WK 12**	**WK 16**	**WK 20**	**WK 24**	**WK 28**	**WK 32**
Days	**-60 +15**	**-21 ±7**	**-14 ±7**	**-1**	**1**	**2**	**3**	**8 ±2**	**15 ±2**	**22 ±2**	**29 ±2**	**43 ±2**	**57 ±2**	**71 ±2**	**85 ±7**	**113 ±7**	**141 ±7**	**169 ±7**	**197 ±7**	**225 ±7**
CCI [redacted]																				
BLOOD: Serum beta-human chorionic gonadotropin pregnancy test (Quantitative). Female participants only[11]		X																		
URINE beta-human chorionic gonadotropin pregnancy test (Qualitative). Female participants only[12]	S			S							S		S		S	S	S	S	S	S
Hepatitis Panel[13]	X																			
HIV Screen (Antigen/Antibody)	X																			
Hematology	X			X		X[14]		X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry	X			X				X	X	X	X	X	X	X	X	X	X	X	X	X

Period	Screening			Baseline	Treatment Period 1			Follow-up Period 1											
Visit Name	**Visit 1[1]**	**Visit 2**	**Visit 3**	**Baseline Visit[2]**	**Day 1**	**Day 2**	**Optional Day 3**	**WK 1**	**WK 2**	**WK 3**	**WK 4**	**WK 6**	**WK 8**	**WK 10**	**WK 12**	**WK 16**	**WK 20**	**WK 24**	**WK 28**	**WK 32**
Days	**-60 +15**	**-21 ±7**	**-14 ±7**	**-1**	**1**	**2**	**3**	**8 ±2**	**15 ±2**	**22 ±2**	**29 ±2**	**43 ±2**	**57 ±2**	**71 ±2**	**85 ±7**	**113 ±7**	**141 ±7**	**169 ±7**	**197 ±7**	**225 ±7**
Troponin I	X							X			X		X		X			X		
Coagulation Panel	X			X[14]																
Urinalysis	X			X				X												
5q SMA Genetic Testing (SMN1 and SMN2)	X																			
CCI																				

Period	Screening			Baseline	Treatment Period 1			Follow-up Period 1											
Visit Name	**Visit 1[1]**	**Visit 2**	**Visit 3**	**Baseline Visit[2]**	**Day 1**	**Day 2**	**Optional Day 3**	**WK 1**	**WK 2**	**WK 3**	**WK 4**	**WK 6**	**WK 8**	**WK 10**	**WK 12**	**WK 16**	**WK 20**	**WK 24**	**WK 28**	**WK 32**
Days	**-60 +15**	**-21 ±7**	**-14 ±7**	**-1**	**1**	**2**	**3**	**8 ±2**	**15 ±2**	**22 ±2**	**29 ±2**	**43 ±2**	**57 ±2**	**71 ±2**	**85 ±7**	**113 ±7**	**141 ±7**	**169 ±7**	**197 ±7**	**225 ±7**
CCI																				
Electrocardiogram (ECG)	X			X				X			X		X		X			X		
Echocardiogram	X							X			X		X		X			X		
Sensory Nerve Action Potential (SNAP)/Electrophysiology	X	X[20]																		
Study completion information																				

Period	Follow-up Period 1						Treatment Period 2			Follow-up Period 2							
Visit Name	**WK 36**	**WK 40**	**WK 44**	**WK 48**	**WK 50**	**WK 52[2]**	**WK 52+1 Day**	**WK 52+2 Days**	**Optional WK 52+3 Days**	**WK 53**	**WK 54**	**WK 55**	**WK 56**	**WK 58**	**WK 60**	**WK 62**	**WK 64/EOS[21]**
Days	**253 ±7**	**281 ±7**	**309 ±7**	**337 ±7**	**351 ±2**	**365 ±7**	**366**	**367**	**368**	**372 ±2**	**379 ±2**	**386 ±2**	**393 ±2**	**407 ±2**	**421 ±2**	**435 ±2**	**449 ±3**
Inclusion / Exclusion criteria				X		X											
OAV101 IT administration/sham procedure							X[22]										
IRT contact					X	X											X
IRT randomization																	

Period	Follow-up Period 1						Treatment Period 2			Follow-up Period 2							
Visit Name	**WK 36**	**WK 40**	**WK 44**	**WK 48**	**WK 50**	**WK 52[2]**	**WK 52+1 Day**	**WK 52+2 Days**	**Optional WK 52+3 Days**	**WK 53**	**WK 54**	**WK 55**	**WK 56**	**WK 58**	**WK 60**	**WK 62**	**WK 64/EOS[21]**
Days	**253 ±7**	**281 ±7**	**309 ±7**	**337 ±7**	**351 ±2**	**365 ±7**	**366**	**367**	**368**	**372 ±2**	**379 ±2**	**386 ±2**	**393 ±2**	**407 ±2**	**421 ±2**	**435 ±2**	**449 ±3**
Informed consent/assent																	
Information to be collected on screening failures																	
Demography																	
Medical history/current medical conditions																	
Independent Sitting Assessment																	
Prior medications																	
Concomitant medications and therapies	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Head circumference for patients <= 3 years of age						X											
Head circumference for patients > 3 years of age																	
Vital Signs	X	X	X	X		X[23]	X	X	X	X	X	X	X	X	X	X	X
BMI	X			X		X							X		X		X
Body Weight	X	X	X	X		X	X	X		X			X		X		X
Body Height (Segmental by Tibial Length)	X			X		X							X		X		X
Neurological Examination	X	X	X	X		X[23]	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	S	S	S	S		S[23]	S	S	S	S	S	S	S	S	S	S	S
Chest X-ray				X													
Spinal X-Ray for Scoliosis Assessment																	

Period	Follow-up Period 1						Treatment Period 2			Follow-up Period 2							
Visit Name	**WK 36**	**WK 40**	**WK 44**	**WK 48**	**WK 50**	**WK 52[2]**	**WK 52+1 Day**	**WK 52+2 Days**	**Optional WK 52+3 Days**	**WK 53**	**WK 54**	**WK 55**	**WK 56**	**WK 58**	**WK 60**	**WK 62**	**WK 64/EOS[21]**
Days	**253 ±7**	**281 ±7**	**309 ±7**	**337 ±7**	**351 ±2**	**365 ±7**	**366**	**367**	**368**	**372 ±2**	**379 ±2**	**386 ±2**	**393 ±2**	**407 ±2**	**421 ±2**	**435 ±2**	**449 ±3**
Prophylactic prednisolone/placebo						X[7]	X	X	X	X	X	X	X	X	X		
Adverse events/SAEs	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
CCI																	
Hammersmith Functional Motor Scale Expanded (HFMSE)	X	X	X	X		X							X		X		X
Revised Upper Limb Model (RULM)	X	X	X	X		X							X		X		X
CCI																	
Ventilatory support				X		X											
CCI																	
BLOOD: Serum beta-human chorionic gonadotropin pregnancy test				X													

Period	Follow-up Period 1						Treatment Period 2			Follow-up Period 2							
Visit Name	**WK 36**	**WK 40**	**WK 44**	**WK 48**	**WK 50**	**WK 52[2]**	**WK 52+1 Day**	**WK 52+2 Days**	**Optional WK 52+3 Days**	**WK 53**	**WK 54**	**WK 55**	**WK 56**	**WK 58**	**WK 60**	**WK 62**	**WK 64/EOS[21]**
Days	**253 ±7**	**281 ±7**	**309 ±7**	**337 ±7**	**351 ±2**	**365 ±7**	**366**	**367**	**368**	**372 ±2**	**379 ±2**	**386 ±2**	**393 ±2**	**407 ±2**	**421 ±2**	**435 ±2**	**449 ±3**
(Quantitative). Female participants only[11]																	
URINE beta-human chorionic gonadotropin pregnancy test (Qualitative). Female participants only[12]	S	S	S			S							S		S		S
Hepatitis Panel[13]				X													
HIV Screen (Antigen/Antibody)				X													
Hematology	X	X	X	X		X		X[14]		X	X	X	X	X	X	X	X
Clinical Chemistry	X	X	X	X		X				X	X	X	X	X	X	X	X
Troponin I				X						X			X		X		X
Coagulation Panel				X		X[14,23]											
Urinalysis				X		X				X							
5q SMA Genetic Testing (*SMN1* and *SMN2*)																	
CCI																	

Period	Follow-up Period 1						Treatment Period 2			Follow-up Period 2							
Visit Name	WK 36	WK 40	WK 44	WK 48	WK 50	WK 52[2]	WK 52+1 Day	WK 52+2 Days	Optional WK 52+3 Days	WK 53	WK 54	WK 55	WK 56	WK 58	WK 60	WK 62	WK 64/EOS[21]
Days	253 ±7	281 ±7	309 ±7	337 ±7	351 ±2	365 ±7	366	367	368	372 ±2	379 ±2	386 ±2	393 ±2	407 ±2	421 ±2	435 ±2	449 ±3
CCI																	
Electrocardiogram (ECG)				X		X				X			X		X		X
Echocardiogram				X						X			X		X		X
Sensory Nerve Action Potential (SNAP)/Electrophysiology																	
Study completion information						X											X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor

[S] Assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database

[1] The assessments for Screening Visit 1 can be conducted over more than 1 visit, as close to the original visit date as possible

[2] Assessments for the Baseline Visit and Week 52 Visit can be conducted over more than 1 day, as close to the original visit date as possible. Clinical and laboratory results must be consistent with institutional guidelines for lumbar puncture before proceeding with OAV101 dosing/sham procedure.

[3] Patients will be hospitalized for inpatient OAV101administration/sham procedure on Day 1 (or on Day -1 as per local standard of care). In-patient observation will continue on Day 2 and Day 3 (optional), i.e., 24 to 48 hours post-study treatment If study treatment visit on Day 1 is not possible due to a national emergency or other

Period	Follow-up Period 1						Treatment Period 2			Follow-up Period 2							
Visit Name	WK 36	WK 40	WK 44	WK 48	WK 50	WK 52[2]	WK 52+1 Day	WK 52+2 Days	Optional WK 52+3 Days	WK 53	WK 54	WK 55	WK 56	WK 58	WK 60	WK 62	WK 64/EOS[21]
Days	253 ±7	281 ±7	309 ±7	337 ±7	351 ±2	365 ±7	366	367	368	372 ±2	379 ±2	386 ±2	393 ±2	407 ±2	421 ±2	435 ±2	449 ±3

unforeseen reason, extensions to the visit window may be discussed with the Sponsor.

[4] Vital signs, with the exception of blood pressure, will be recorded pre-study treatment (OAV101 dosing/sham procedure) and then monitored every 15 (± 5) minutes for the first 1 hour, every 30 (± 10) minutes until 2 hours, every 2 hours (± 15 minutes) until 8 hours, and every 4 hours (± 30 minutes) until 16 hours. Blood pressure will be recorded pre-study treatment and every 8 hours (± 2 hours) through 16 hours

[5] Vital signs should be performed 20-24 hours post OAV101 dosing/sham procedure

[6] Re-screening: Participants who screen failed and have study-specific spine films available, may use these spine films at re-screening with sponsor approval. The data from the study-specific spine films should be entered in the eCRF

[7] Prophylactic prednisolone/placebo must be administered CCI

[8] CCI

[9] CCI

[10] CCI

[11] Female participants who are sexually active or have reached menarche must have a negative pregnancy test at Screening. A negative urine pregnancy test may be used for eligibility but should be confirmed with blood test prior to the Baseline visit.

[12] Female participants who are sexually active or have reached menarche.

[13] Hepatitis panel includes Hepatitis C antibody, Hepatitis B surface antigen (HbsAG), and Hepatitis B core antibody

[14] To be performed by local lab. For platelets, further close monitoring should be performed locally as needed, particularly in the first two weeks following infusion.

[15]To be performed by Sponsor-designated lab

[16] CCI

[17] CCI

[18] CCI

CCI

[20] SNAP is not performed at Screening Visit 2 if a SNAP score was obtained at Screening Visit 1

[21] If discontinuation, all efforts should be made to complete the End of Study (EOS) assessments prior to study discontinuation.

[22] Patients will be hospitalized for inpatient OAV101administration/sham procedure on Week 52 +1 Day (or on Week 52 as per local standard of care). In-patient

Period	Follow-up Period 1						Treatment Period 2			Follow-up Period 2							
Visit Name	WK 36	WK 40	WK 44	WK 48	WK 50	WK 52[2]	WK 52+1 Day	WK 52+2 Days	Optional WK 52+3 Days	WK 53	WK 54	WK 55	WK 56	WK 58	WK 60	WK 62	WK 64/EOS[21]
Days	253 ±7	281 ±7	309 ±7	337 ±7	351 ±2	365 ±7	366	367	368	372 ±2	379 ±2	386 ±2	393 ±2	407 ±2	421 ±2	435 ±2	449 ±3

observation will continue on Week 52 +2 Days and Week 52 +3 Days (optional), i.e., 24 to 48 hours post-study treatment. If study treatment visit on Week 52 + 1 Day is not possible due to a national emergency or other unforeseen reason, extensions to the visit window may be discussed with the Sponsor.

[23] Vital signs, neurological examination, physical examination, and coagulation will be performed within 2 days prior to the OAV101 dosing/sham procedure

[24] CCI [redacted]

[25] CCI [redacted]

8.1 Screening

Screening

Written informed consent must be obtained prior to any screening procedures. Please refer to Section 7 for the Informed Consent procedures. After informed consent is collected, the participant must be registered in IRT, eligibility reviewed and, once eligible, study treatment pre-ordered. Assessments that confirm participant eligibility and randomization into the study will occur at Screening Visit 1 and 2 (Table 8-1).

Given the potentially long duration of the study visits, sites may provide comfort items (e.g., playbooks, toys, teddy bears, and/or some form of media) that would not impact or interfere with study procedures and assessments, in order to promote compliance, and as per local guidelines and regulations.

The exact sequence of screening assessments is at the discretion of the Site. It is recommended to obtain the anti-AAV9 antibody screening results first for timely completion of the eligibility assessment.

Re-screening: It is permissible to re-screen a potential participant if the participant fails the initial screening (screen failure); however, each case must be discussed and agreed with the Sponsor on a case-by-case basis. Re-screening should not be performed in order to avoid the eligibility criteria or for any reason that would place the participant at safety risk. Re-screened participants will need to be re-consented and a new Participant Number will be assigned. Re-screening tests should be repeated as per inclusion/exclusion requirements and rescreening should be documented in medical records.

8.1.1 Inclusion and exclusion criteria

The Investigator must ensure that all participants being considered for the study meet the inclusion and do not meet any exclusion criteria. No additional exclusions should be applied by the Investigator, in order that the study population will be representative of all eligible participants. Participant selection is to be established by checking through all inclusion/exclusion criteria at screening. A relevant record must be stored with the source documentation at the study site. Deviation from any entry criterion excludes a participant from enrollment into the study. The Investigator or his/her deputy must promote compliance to inclusion/exclusion criteria for the duration of the study.

8.1.2 Information to be collected on screening failures

Ineligible participants

Participants who sign an informed consent form and subsequently found to be ineligible prior to enrollment will be considered as screen failures. The reason for screen failure should be entered on the applicable CRF. CRFs pertaining to demography, informed consent, withdraw of consent (if applicable), inclusion/exclusion criteria, SMA diagnosis, anti-AAV9 antibody, 5q SMA genetic testing, and death (if applicable) should also be completed for screen failure participants. The anti-AAV9 antibody and 5q SMA genetic testing results will be collected in the appropriate Novartis database. No other data will be entered into the clinical database for

participants who are screen failures, unless the participant experienced a SAE during the screening period (see SAE section for reporting details) or protocol-related AE. Data and samples collected from participants prior to screen failure may still be analyzed.

Failure due to temporary conditions

Participants who fail eligibility during the screening process for a temporary or transient condition (e.g., viral illness, concomitant medication, or laboratory values, etc.) may be rescreened. When all inclusion and exclusion criteria will have to be reverified, a new participant number will be assigned. A participant initially excluded for a condition no longer exclusionary upon a protocol amendment may also be re-screened.

8.1.3 Prior medications

Prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system.

8.1.4 Medical history and current medical conditions

Relevant medical history, hospitalizations, and current medical conditions will be recorded on the eCRF until signature of the informed consent. Where possible, diagnoses and not symptoms will be recorded. Any event or change in the participant's condition or health status occurring *prior to* informed consent will be reported in the Relevant medical history / Current medical conditions section of the eCRF. Medical history will be coded using the Medical dictionary for regulatory activities (MedDRA) and the number and percentage of participants with each history by preferred term presented, including the presence of scoliosis and presence of contractures.

SMA HISTORY

SMA history may include the following:

- Type of *SMN1* pathogenic variants on each allele (e.g., deletion, point mutation)
- *SMN2* gene copy number
- Age at SMA symptom onset
- Date at SMA diagnosis
- Highest motor function achieved
- Type and frequency of physical therapy
- Number of hospitalizations for pneumonia with or without respiratory failure
- Familial history of SMA, including parent carriers and affected sibling(s)

8.1.5 Screening laboratory testing

Laboratory testing performed during the Screening/Baseline period is described in Table 8-1.

8.1.6 Virus serology

The administration of an AAV vector has the risk of causing immune-mediated hepatotoxicity. For participants who have HIV or positive serology for hepatitis B or C, administration of the AAV vector may represent an unreasonable risk; therefore, negative serology testing must be

confirmed at screening, prior to treatment. These samples will be collected in accordance with Table 8-1 and shipped in accordance with the laboratory manual provided by the central laboratory.

Other pathogens that may be endemic to specific regions/countries (e.g., human T-lymphotropic virus or mycobacterium tuberculosis) may also be tested, as per investigator discretion and discussion with sponsor.

8.1.7 Ventilatory support

Ventilatory support assessment will be performed by a pulmonologist (or appropriate individual as per standard institutional practice) and conducted as specified in Table 8-1. Prior to study entry, the Investigator or designee will review and document ventilator usage during the 2 weeks prior to screening

8.1.8 Radiological evaluations

Radiological examinations are performed to assess participants for disease complications in accordance with Inclusion/Exclusion criteria (Section 5).

8.1.8.1 Chest X-Ray

Standard posterior to anterior (PA) and lateral chest X-ray will be performed at Screening Visit 1 and at Week 48.

8.1.8.2 Scoliosis assessment

Spine films will be performed in two planes in a sitting position to assess scoliosis and pelvic obliquity. The following data is recorded for each participant (Fujak et al 2013).

- Scoliosis shape (C-shape or S-Shape)
- Levels involved (Cervical, Thoracic, and/or Lumbar)
- Cobb angle
- Pelvic obliquity, if available (Osebold et al 1982)

Re-screening: Participants who screen failed and have study-specific spine films available, may use these spine films at re-screening with sponsor approval. The data from the study-specific spine films should be entered in the eCRF.

8.1.9 Independent sitting assessment

The ability to sit independently for at least 10 seconds will be assessed at Screening, in accordance with the inclusion criteria (Section 5.1).

8.2 Participant demographics/other baseline characteristics

Demographics (including age, sex, race, and ethnicity)/medical history/current medical conditions (until date of signature of informed consent) will be captured in the eCRF. Participant race and ethnicity data are collected and analyzed to identify variations in safety or efficacy profile of the treatment due to these factors. In addition, these data are necessary to assess the diversity of the study population as required by Health Authorities. Country–specific

regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

All prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start of the study must be documented. See the protocol Section 6.2.1 Concomitant Therapy for further details on what information must be recorded on the appropriate page of the eCRF.

8.3 Efficacy

The efficacy assessments described below have been selected in order to evaluate the effect of OAV101 on SMA. The primary and secondary efficacy assessments (HFMSE and RULM) are chosen based on their acceptability to health authorities, extensive validation and clinical use, Novartis study experience (AVXS-101-CL-102 open-label trial), and proof of utility for efficacy assessment in other trials (Mercuri et al 2018b). The assessments described for the exploratory endpoints (Section 8.3.3) are chosen to augment understanding of clinical meaningfulness of OAV101 treatment.

8.3.1 Primary and secondary efficacy assessments

Primary and secondary endpoints rely on data collected by trained and qualified site clinical evaluators (physical therapist, occupational therapist, or national equivalent) using the HFMSE and the RULM over a 52-week period after OAV101 administration/sham procedure. Select HFMSE and RULM administrations may be observed during the assessment through videoconference (or recorded and reviewed) by an external trainer to provide initial and/or ongoing clinical evaluator feedback on assessment administration. Given the global nature of COAV101B12301, recordings for later review require compliance with local regulations and laws.

8.3.1.1 Hammersmith Functional Motor Scale Expanded (HFMSE)

Background

The HFMSE was devised for use in children with SMA Type 2 and Type 3 to give objective information on motor ability and clinical progression (Glanzman et al 2011) and has been used in a double blinded clinical trial of Type 2 SMA to demonstrate efficacy of SMN-targeting therapy (Mercuri et al 2018b). The HFMSE (2019 edition) assessment will be administered by the qualified site clinical evaluator (e.g., licensed physical or occupational therapist, or national equivalent) in accordance with the Schedule of Assessments (Table 8-1). The same clinical evaluator should administer the HFMSE for a given participant throughout the study (i.e., every visit). The HFMSE is a SMA-specific 33-item questionnaire that is easily administered by clinical evaluators in a short period of time, requires minimal equipment, and is designed to factor in patient fatigue. Each motor skill item is scored on a 3-point Likert scale from 0 (no response) to 2 (full response), with a total score range of 0 to 66. A higher score indicates a higher ability level. A Phase 1 study of nusinersen reaffirmed that the HFMSE is sensitive to change, with a 3-point change in score considered clinically meaningful and indicates that a child improved on at least 2 HFMSE motor skills. The HFMSE has well-established psychometric properties. Evaluation of inter-rater reliability and test-retest reliability demonstrated that these functional assessments can be performed reliably in a multicenter clinical trial with rigorous initial, annual, and periodic retraining and support to ensure standardization. The HFMSE administration in OAV101B12301 will occur as follows.

Completion of Assessment

- Obtaining a complete HFMSE assessment that is a true representation of the participant's motor ability is critical in order to appropriately investigate OAV101 efficacy. The completeness of the HFMSE assessment has been considered in Type 2 SMA motor assessment analyses, thus allowing for fair and valid assessment of motor abilities (Mercuri et al 2019, Coratti et al 2020b). Every effort should be made to administer all scale items appropriately following scale criteria. In the event that an item is not able to be administered, a 'Cannot Test' (CNT) is marked for that item. To ensure the patient's true motor ability is being represented, rescheduling of the assessment administration is warranted when any factor significantly impedes the participant's ability to perform the motor assessment which includes behavior issues (e.g., tantrums, inconsolable), refusal to participate in testing, transient pain, fractures, intercurrent surgery, or recent pneumonia or other infections. CCI [redacted] Study specific requirements around HFMSE administration requirements are outlined below. Based on prior experience in the open label AVXS-101-CL-102 clinical trial of intrathecal OAV101, very few incomplete assessments are anticipated.

Contractures: It is important to note that contractures alone do not exclude participants from being scored on the HFMSE. The impact of contractures on some assessment items needs to be established, therefore the therapist should indicate "limited by contracture". However, participants with severe contractures, which limit their ability to be positioned in prone during Screening, are not eligible (exclusion criterion 13).

HFMSE at Screening

- In order to assess trial eligibility, an HFMSE assessment with total score must be obtained during the Screening period (Section 5.1).
- Two HFMSE assessments are performed during the screening period. Although two complete HFMSE assessments is preferred at Screening, a minimum of one assessment with total score must be obtained.
- Rescheduling of the assessment administration within the screening window is required if an HFMSE assessment with a total score is unable to be obtained.

HFMSE assessment at baseline and post-OAV101 administration/sham procedure to Week 64 (End of Study)

- HFMSE is administered at each visit specified in the Schedule of Assessments (Table 8-1).

HFMSE assessment CCI [redacted]

8.3.1.2 Revised Upper Limb Model (RULM)

Background

RULM is a validated, SMA-specific assessment that measures motor performance in the upper limbs from childhood through adulthood in ambulatory and never ambulatory individuals with SMA, and weaker individuals who have a floor effect or very low score on the Hammersmith Functional Motor Scale (HFMS) (Mazzone et al 2017). The revised version of the test consists of 19 scorable items: 18 items scored on a 0 (unable) to 2 (full achievement) scale, and one item that is scored from 0 (unable) to 1 (able). These item scores are summed to give a total score ranging from 0 to 37 points with lower scores reflecting poorer ability. The RULM consists of upper limb performance items that are reflective of reachable space and activities of daily living (i.e., raise a can to mouth as if drinking, take a coin and place it in a box, and remove the lid of a container). The test is performed unilaterally using the limb preferred by the patient. The RULM is quickly administered and suitable for use in multicenter settings. Evaluation of inter-rater reliability and test-retest reliability demonstrated that these functional assessments can be performed reliably in a multicenter clinical trial with rigorous initial, annual, and periodic retraining and support to ensure standardization. The RULM will be administered by a site clinical evaluator (e.g., licensed physical or occupational therapist, or national equivalent) in accordance with the Schedule of Assessments.

The RULM was a critical motor assessment that contributed to risdiplam approval by the Food and Drug Administration (FDA) in the SUNFISH trial which included 2 to 25 year old Type 2 and Type 3 SMA patients (EVRYSDI Prescribing Information 2020, Genentech 2021). The RULM was used in the CHERISH clinical trial of nusinersen which included Type 2 and 3 SMA in 2 to 12 year olds (Mercuri et al 2018b). In the CHERISH study, the least squares mean analysis of the RULM data versus controls showed 3.7 point difference (95% CI = 2.3 – 5.0). Since the RULM was a secondary endpoint in the CHERISH trial and a hierarchical end point analysis was performed, a p-value was not calculated since a prior endpoint did not reach statistical significance. Like the HFMSE, the RULM has been successfully implemented in clinical trials that assess efficacy of SMN-targeting therapies. RULM administration is recommended for assessment of patients > 2 years of age with the ability to sit by the SMArtCare-project (Pechmann et al 2019, Schorling et al 2020).

Completion of Assessment

Obtaining a complete RULM assessment at a visit that is a true representation of the participant's motor ability is critical in order to appropriately investigate OAV101 efficacy. Every effort should be made to administer all scale items appropriately following scale criteria. In the event that an item is not able to be administered a 'Cannot Test' (CNT) is marked for that item. To ensure the patient's true motor ability is being represented, rescheduling of the assessment administration is warranted when any factor significantly impedes the participant's ability to perform the motor assessment which includes behavior issues (e.g., tantrums, inconsolable), refusal to participate in testing, transient pain, fractures, intercurrent surgery, or recent pneumonia or other infections. CCI [redacted] Study specific requirements around RULM administration requirements are outlined below. Ensuring completeness of the assessment is an approach to ensure that data

representative of the participant's motor function is used for analysis (Pera et al 2019). Of note, test participation refusals are uncommon among individuals performing the RULM, even in younger children (Mazzone et al 2017).

RULM at Screening

- Two RULM assessment are performed during the screening period. Although two complete RULM assessments is preferred at Screening, a minimum of one assessment with total score should be obtained.

RULM assessment at baseline and post-OAV101 administration/sham procedure to Week 64 (End of Study),

- RULM is administered at visits as specified in the Schedule of Assessments (Table 8-1).

RULM assessment CCI

CCI

8.3.2 Appropriateness of efficacy assessments

Efficacy assessments in this study are standard for this indication and participant population. The rationale and support for HFMSE and RULM use for efficacy assessment are described in Section 4.1, Section 8.3.1.1, and Section 8.3.1.2.

8.3.3 Exploratory assessments

8.3.3.1 CCI

CCI

8.3.3.2 CCI

CCI

[redacted]

8.3.3.3 CCI

CCI

[redacted]

8.3.3.4 CCI

CCI

8.3.3.5 CCI

CCI

CCI

8.3.3.6 CCI

CCI

8.3.3.7 CCI

CCI

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed (Table 8-1). Safety parameters include demographics/medical history, physical and neurological examinations, vital signs, height and weight measurements, 12-lead ECGs, echocardiograms, laboratory assessments, and AE monitoring. For details on AE collection and reporting, refer to Section 10.1.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again. If participants cannot visit the site for safety lab assessments through central labs, home-nursing may be deployed using central lab kits or local lab collection may be used and results will be entered in the eCRF.

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected unless otherwise specified. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to Investigators in the Laboratory Manual.

For countries where regulatory requirements do not permit Point of Care Testing for urinalysis (i.e., use of dipstick) the analysis will be performed at the central laboratory.

8.4.1.1 Urinalysis

Dipstick measurements for protein, blood, and WBC/leukocytes will be performed. If dipstick measurement results are positive (abnormal), a urine sample will be sent to the central laboratory for microscopic evaluation in accordance with the Laboratory Manual.

8.4.1.2 Hematology

Hematology analysis will include a complete blood count with differential and platelet count. Samples will be collected and shipped in accordance with the laboratory manual provided by the central laboratory. Blood samples for hematology analysis will be collected as specified in the Table 8-1.

Hematology analysis will include the following at all trial visits:

- Hematocrit
- Hemoglobin
- MCH
- MCHC
- MCV
- Platelets
- Red blood cells
- White blood cells
- Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands)

Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, were observed in OAV101 clinical studies with intravenous administration. In most cases, the lowest platelet value occurred the first week following OAV101 administration. Platelet counts should be obtained before OAV101/sham administration and should be closely monitored in the first two weeks following treatment on a regular basis afterwards as specified in Table 8-1, until any abnormal platelet counts return to baseline.

Hematology analyses are required prior to discharge on Day 2 and Week 52+2 Days. These tests will be performed as per investigational site standard procedures at the local laboratory. As determined by the Investigator, further hematology tests should be done in the first two weeks following OAV101 administration as per investigational site standard procedures at the local laboratory. Local labs should be entered on the respective eCRF page.

Investigators will receive hematology results from all other study visits from the central laboratory.

8.4.1.3 Coagulation panel

Coagulation testing will include prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT). Coagulation testing is required to be done locally to confirm that there are no clinically significant abnormal results prior to OAV101 dosing/sham procedure (both Treatment Period 1 and 2).

8.4.1.4 Clinical chemistry

Samples will be collected and shipped in accordance with the laboratory manual provided by the central laboratory. Blood samples for chemistry analysis will be collected as specified in the Assessment Schedule (Table 8-1). Clinical chemistry may be evaluated in the non-fasted state.

If immediate/same-day chemistry analyses are required during Treatment Period 1 or Treatment Period 2, as determined by Investigator, tests will be performed as per investigational site standard procedures at the local laboratory. **If liver aminotransferase elevations occur post OAV101 administration/sham procedure, the process outlined in Section 10.3.1 should be followed.**

Chemistry analysis will include the following analytes:

- Albumin
- Alkaline phosphatase (ALP)
- Alanine aminotransferase
- Aspartate aminotransferase
- GGT
- Lactate Dehydrogenase (LDH)
- Glutamate dehydrogenase
- Bicarbonate
- Calcium
- Phosphorus
- Chloride

- Sodium
- Potassium
- Creatinine
- Creatine kinase
- Total Bilirubin (NOTE: If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated)
- Direct Bilirubin
- Indirect Bilirubin
- Blood urea nitrogen
- Glucose

Troponin I will be collected as specified in the Schedule of Assessments (Table 8-1).

CCI [redacted]

8.4.1.5 BLOOD: Serum beta-human chorionic gonadotropin pregnancy test (Quantitative). Female participants only

Blood beta-human chorionic gonadotropin (beta-hCG) testing (Quantitative) will be performed at screening visit 2 and at the Week 48 visit. Serum beta-hCG testing will be performed on females of childbearing potential (See Section 8.4.2).

8.4.1.6 URINE beta-human chorionic gonadotropin pregnancy test (Qualitative). Female participants only

All female participants who are sexually active or have reached menarche will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements. The cultural differences as well as standard of care approaches across participating countries must be taken into account in order to appropriately manage contraception and pregnancy considerations.

Urine human chorionic gonadotropin (hCG) dipstick testing will be performed on females of child-bearing potential. First-morning urine is the preferred specimen; however, any specimen is suitable for testing.

8.4.2 Pregnancy testing

For female participants who are sexually active or have reached menarche, quantitative beta-human chorionic gonadotropin testing in blood for pregnancy is required at screening visit 2 and at the Week 48 visit. For all female participants meeting this definition of child-bearing potential, qualitative beta-human chorionic gonadotropin in urine will be performed at monthly intervals during the trial. Note that a positive urine test should be confirmed with a serum pregnancy test. The cultural differences across participating countries need to be taken into account and it is acceptable to have both options simultaneously in the protocol to allow for cultural differences between participating countries. In case of a positive test, the participant

must contact the investigator immediately. In this fashion, the pregnancy discussion will become an additional point at each visit, serving to increase compliance with contraception.

*Additional pregnancy testing may be performed if requested per local requirements.

8.4.3 Clinical safety evaluations

8.4.3.1 Neurological examination

A complete neurological examination is performed at visits specified in Table 8-1, with attention to exam features and patient symptoms consistent with a sensory neuronopathy. The neurological exam should include detailed, age-appropriate sensory testing (such as examination of proprioceptive, vibratory, tactile and pain sensation) at each visit. An age-appropriate sensory exam is important for sensory neuronopathy detection.

Any clinically significant abnormal finding should be recorded as an AE. The neurological examination should only be recorded as abnormal if there are abnormalities in the sensory examination.

Further clinical evaluation of sensory abnormalities will include nerve conduction studies per local standard of care including but not limited to sural sensory nerve action potential (SNAP).

8.4.3.2 Physical examination

Physical examinations will be conducted by the investigator or designee as specified in Table 8-1.

A complete review of systems is performed at the time of each physical examination. Physical examinations will include each system: head, eyes, ears, nose and throat (HEENT), lungs/thorax, cardiovascular, abdomen, musculoskeletal, neurologic, dermatologic, lymphatic, and genitourinary.

Physical examination data will be captured on source documentation.

8.4.4 Vital signs

Vital sign parameters include blood pressure, respiratory rate, pulse, temperature, and pulse oximetry.

Vital signs will be obtained as specified in the Table 8-1. On Day 1 and Week 52+1 Day (OAV101 administration or sham procedure), vital signs, with the exception of blood pressure, will be recorded pre-dose and then monitored every 15 (± 5) minutes for the first 1 hour, every 30 (± 10) minutes until 2 hours, every 2 hours (± 15 minutes) until 8 hours, and every 4 hours (± 30 minutes) until 16 hours. Blood pressure will be recorded pre-dose and every 8 hours (± 2 hours) through 16 hours.

8.4.5 Electrophysiology

Electrophysiology assessments are performed in conjunction with patient history and neurological examination to monitor for sensory neuronopathy.

8.4.5.1 Sensory nerve action potential (SNAP)/electrophysiology

BACKGROUND

The sensory nerve action potential (SNAP) provides information on the sensory nerve axon and its pathway from the distal receptors in the skin to the dorsal root ganglia. The SNAP represents the sum of single nerve fiber action potentials.

PERFORMANCE

Although electrophysiology (SNAP assessment) is performed at Screening and at post-treatment visits when there are sensory abnormalities in the neurological examination detailed investigations for a sensory neuronopathy can be initiated based on the clinical judgement at any time during the study.

Orthodromic or antidromic SNAPs are acceptable depending on the institutional protocol. Sensory nerve conduction studies to assess SNAPs will be performed for all study patients at Screening. The SNAP will be scored as "Present" or "Absent" or "Unable to obtain".

Pre-treatment: SNAP must be performed for all participants at Screening Visit 1. If the SNAP is scored as "Unable to obtain" at Screening Visit 1, then SNAP must be performed at Screening Visit 2. Bilateral radial and sural nerve SNAPs must be obtained at one of the two screening visits for trial eligibility. Rescheduling is warranted when any factor impedes the ability to obtain SNAP data.

If the SNAP is scored as "Absent" at any one of the pre-treatment visits, the clinician must assess whether the absent SNAP is supported by any clinically significant sensory abnormal finding(s) in the neurological examination.

Post-treatment: Post-treatment, SNAP is performed if there are sensory abnormalities in the neurological examination. A complete neurological examination is performed at visits specified in Table 8-1, with attention to exam features and patient symptoms consistent with a sensory neuronopathy (refer to Section 8.4.3.1).

Any patient with new post-treatment sensory symptoms with or without loss of a SNAP will receive a comprehensive assessment of the differential diagnosis. The differential diagnosis should include a careful assessment for sensory neuronopathy (sensory ganglionopathy). CSF testing and MRI imaging of brain, spinal cord, and dorsal root ganglia is encouraged. Sensory ganglionopathies are usually associated with diffuse SNAP abnormalities but may be patchy early, with upper limb involved before lower limb.

TECHNICAL REQUIREMENTS

Performance of sensory nerve action potentials (SNAPs) should comply with professional society standards (Stålberg et al 2019, AANEM 2020).

SNAP is a conduction study commonly used to evaluate suspected peripheral neuropathies.

Nerve conduction study is a test commonly used to evaluate the function, especially the ability of electrical conduction by the motor and sensory nerves of human body. It is evaluated by performing sural SNAP. The sural SNAP is obtained by electrically stimulating sensory fibers. Results will be entered in the eCRF.

8.4.6 Anthropometry

Complications associated with SMA (e.g., scoliosis and contractures) are considered in the determination of height, weight, and BMI.

8.4.6.1 Body height (segmental by tibial length)

Direct measurement of recumbent length or height may be challenging in children and adolescents with physical disabilities due to joint contractures, muscular weakness, scoliosis, or poor cooperation. Since patients in the trial are never ambulatory, use the tibial length for segmental height assessment in all participants (Preedy 2012, Samson-Fang and Bell 2013, Mokhy et al 2020). Tibial length measurement does not require specialized equipment, is not impacted on by knee and ankle contractures and the landmarks are relatively easy to palpate.

- Use a flexible tape measure that does not stretch.
- Tibial length is the distance from the superomedial edge of the tibia to the inferior edge of the medial malleolus.
- The measurement should be conducted with the child in a seated position facing the observer with the left ankle or calf resting on the right knee so that the medial aspect of the tibia faces upwards. Measurements are recorded in centimeters (cm).

Use the following equation for both males and females to estimate height in males and females who are ≥ 2 to ≤ 12 years of age (Stevenson Equation).

- Height = (3.26 × TL) + 30.8
  - TL=Tibial length

Use the following equations for males and females to estimate height in males and females who are > 12 years of age (Gauld Equation).

- Males: Height = (2.758 × TL) + (1.717 × A) + 21.818
- Females: Height = (2.771 × TL) + (1.457 × A) + 37.748
  - TL = Tibial length (cm)
  - A = age in years to one decimal place (e.g. 5.3 years)

The height calculation is necessary to calculate BMI, an eligibility criterion that must be assessed at screening. The height calculation should be checked by an additional study staff to ensure accuracy.

8.4.6.2 Body weight

The Centers for Disease Control and Prevention (CDC) procedure for weight measurement is recommended (CDC Anthropometry 2020).

Weight measurement for all trial participants should be performed as follows:

- Remove shoes and heavy clothes. Weights taken with shoes on will be considered invalid. A thin set of clothes or examination gown is permitted.
- Disposable undergarments (e.g., diapers) should be dry.
- All medical appliances must be removed (e.g., ankle foot orthosis; thoraco-lumbar-sacral orthosis).

- Use appropriately calibrated digital scale as recommended by the CDC (CDC Anthropometry 2020).
- Values are recorded in kilograms (kg) to two decimal places (e.g., 15.25 kg).
- Participants who cannot stand alone on the scale will be weighed with the assistance of an adult (or per local standard of care). In order to obtain the patient weight, the adult weight is subtracted from the total weight of the patient+adult.

8.4.6.3 BMI

BMI is a person's weight in kilograms divided by the square of height in meters. The CDC BMI calculator for children and teens (age range 2 to 19 years) can be used to determine eligibility (CDC BMI Calculator 2020).

Alternatively, the following equation may be used to calculate BMI:

- $BMI = W / H^2$
- W = weight in kilograms (kg) to decimal places (e.g., 15.25 kg)
- H = height in meters (m) to two decimal places (e.g., 0.92 m) (Section 8.4.6.1)

8.4.6.4 Head circumference for patients > 3 years of age

Refer to CDC guidelines for head circumference measurement (CDC Anthropometry 2020). Serial measurements are not required on children > 3 years of age.

8.4.6.5 Head circumference for patients <= 3 years of age

Refer to CDC guidelines for head circumference measurement (CDC Anthropometry 2020). Head circumference measurements will be taken in children ≤ 3 years of age in accordance with the Schedule of Assessments (Table 8-1).

8.4.7 Echocardiogram

A standard transthoracic ECHO will be performed at times indicated in the Schedule of Assessments (Table 8-1) and interpreted locally by a cardiologist or a designee for immediate safety evaluation. The ECHOs will also be collected for centralized review by a cardiologist.

8.4.8 Electrocardiogram

Full details of all procedures relating to the ECG collection and reporting will be contained in the technical manual which is provided to the site by the core laboratory.

In the event that a clinically significant ECG abnormality is identified at the site (e.g., severe arrhythmia, conduction abnormality of QTcF > 500 ms), a copy of the assessment is sent to the core laboratory for expedited review if applicable, and the ECG is repeated to confirm the diagnosis. If the patient is hemodynamically compromised, the investigator or a medically qualified person must initiate appropriate safety procedures without delay (e.g., cardioversion).

ECGs must be recorded (after 10 minutes rest in the supine position to ensure a stable baseline / according to the ECG investigator manual). The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood

sampling (Figure 8-1). The Fridericia QT correction formula (QTcF) must be used for clinical decisions, e.g., at the Screening and Baseline visits(s) to assess eligibility. The investigator must calculate QTcF if it is not auto-calculated by the ECG machine. Triplicate 12-lead ECGs are to be recorded approximately 2 minutes apart. The mean QTcF value for each visit will be calculated from the triplicate ECGs for each participant. For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. ECG safety monitoring, or a review process, should be in place for clinically significant ECG findings, at Baseline, before administration of treatment and during the study.

Additional unscheduled safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated.

Clinically significant abnormalities must be recorded on the relevant section of the CRFs as either medical history/current medical conditions or Aes as appropriate.

Figure 8-1 Timing of study procedures

HFMSE and RULM are recommended to be performed first, prior to all other assessments, if possible.

8.4.9 Appropriateness of safety measurements

Safety assessments such as Aes, clinical laboratory assessments, ECGs, and vital signs are standard for this indication/participant population.

8.5 Additional assessments

No additional tests will be performed on participants entered into this study.

8.5.1 Clinical Outcome Assessments (COAs)

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, COA data may be collected remotely (e.g., web portal, telephone interviews) depending on local regulations, technical capabilities, and following any applicable training in the required process.

Clinician Reported Outcomes (ClinRO)

The impact of OAV101 on ClinROs will be assessed by the following measures in order to understand clinically meaningful aspects of motor improvements.

- Hammersmith Functional Motor Scale Expanded (2019 version) (Section 8.3.1.1)

- Revised Upper Limb Module (16-Dec-2014) (Section 8.3.1.2)

[redacted]

Data will be captured through the use of an eCOA device, as provided to sites by selected third-party vendor.

[redacted]

8.5.2 [redacted]

Collection and/or analysis of samples may not be performed in countries where it is not feasible (e.g., due to regulatory restrictions, not possible to export samples, and/or assay(s) not available in local countries).

[redacted] These specimens will be used to identify and/or verify potential markers that may be predictive of disease activity, disease course and/or clinical response to treatment. [redacted]

While the goal of the [redacted] assessments is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a collection, or not perform or discontinue an analysis [redacted]

CCI [redacted]

DNA samples (Required)

Eligibility requires genetic testing confirmation of a molecular diagnosis of 5q SMA. CCI [redacted]

8.5.2.1 CCI [redacted]

CCI [redacted]

8.5.3 CCI [redacted]

CCI [redacted]

8.5.3.1 CCI [redacted]

CCI [redacted]

8.5.3.2 Anti-AAV9 antibody testing (BLOOD)

CCI

CCI

8.5.3.3 CCI

8.5.4 CCI

CCI

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

Since this is a single dose trial of gene therapy, discontinuation of study treatment is not possible since the vector transduces patient cells resides as episomal concatemers in the host cell nucleus. Participants who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see 'Withdrawal of Informed Consent' section). Where possible, they should return for the assessments indicated in the Assessment Schedule. If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person

pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

In the event of study discontinuation, the EOS Visit should be completed (refer to Section 8). At a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments/medications
- Aes, including SAEs

The investigator must also contact the IRT to register the participant's discontinuation from study participation.

9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops any protocol-required assessments or follow-up, for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 8).

If a participant's anti-AAV9 antibody titer test result is reported as elevated (reference to > 1:50 CCI discontinuation from the study will occur after the participant completes the End of follow-up Period 1 (Week 52). No further treatment or follow-up will occur (refer to Table 8-1 and Section 3). This does not apply to participants administered OAV101 in Period 1.

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from the study or withdraw consent (or exercise other participants' data privacy rights), the Investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g., dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.2 Withdrawal of informed consent/Opposition to use data/biological samples

Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a participant:

- Explicitly requests to stop use of their data

  and

- No longer wishes to receive study treatment prior to OAV101 administration in Treatment Period 1 or Treatment Period 2

  and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be as per local regulations (e.g., in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the participant, collect follow-up data (e.g., to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definition of these terms.

In this situation, the Investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/exercise data/privacy rights and record this information. The investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/exercise data/privacy rights should be made as detailed in the assessment table (refer to Section 8).

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

9.3 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their last study visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

9.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination (but not limited to):

1. Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
2. Decision based on recommendations from applicable board(s) after review of safety and efficacy data
3. Discontinuation of study drug development
4. Regulatory Authority recommendation

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment: The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The Investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial. The

Principal Investigator or designee will contact the study participant and/or the caregiver and provide instructions for returning to the Independent Treatment Site, or the Local Study Site, as appropriate. Every effort will be made to complete all end of study visit assessments for all treated study participants in the case of early study termination by the sponsor.

10 Safety monitoring, reporting and committees

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product. A treatment-emergent adverse event is defined as any event not present prior to the initiation of the treatment or any event already present that worsens in either intensity or frequency following exposure to the treatment.

The Investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of AEs must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

Adverse events will be assessed as follows:

1. Severity grade
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e., progression of the study indication) the assessment of causality will usually be ‘Not suspected.’ The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates or ongoing)

4. Whether it constitutes an SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment
6. Its outcome (i.e., recovery status or whether it was fatal)

All adverse events must be treated appropriately.

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued through the end of study visit. If prednisolone treatment is required after the end of study visit (Week 64), AE monitoring will continue for 30 days after the last dose of prednisolone.

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent (e.g., continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about known adverse drug reactions for the investigational drug can be found in the Investigator''s Brochure.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

10.1.2 Adverse events of special interest

On the basis of important identified or potential risks associated with OAV101, AESIs are determined and categorized as follows. These will be summarized based using Standardized MedDRA terminology:

- Hepatotoxicity
- Transient thrombocytopenia
- Thrombotic microangiopathy
- Cardiac adverse events
- Dorsal root ganglia toxicity
- New malignancies

10.2 Data collection

Designated Investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 Code of Federal Regulations (CFR) Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the Investigator staff.

The Investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the Investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

10.2.1 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of an SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines 2003).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the participant's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in hospital admission
- is medically significant, e.g., defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately

life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines 2003).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction. All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.2.2 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days after the last study visit if there are post-treatment follow-up visits with no required procedures must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded on the electronic SAE form with paper backup; all applicable sections of the form must be completed in order to provide a clinically thorough report.

SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Clinical Trial Regulation 536/2014 (if submitted under EU CTR or) Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period after the last study visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

Treatment-emergent elevations in AST or ALT (>3x ULN) in combination with total bilirubin >2x ULN or jaundice in the absence of cholestasis (defined as ALP < 2 ULN) or other causes of hyperbilirubinemia can be an indicator of severe drug induced liver injury (Hy's Law). For this reason, a potential Hy's Law case requires expedited reporting, and will be handled as a serious unexpected adverse event (assessing it as medically significant in the absence of any other seriousness criteria). It must be reported as an SAE to the sponsor promptly (i.e., even before all other possible causes of liver injury have been excluded). Reporting should include all available information, especially that needed for evaluating the diagnosis, severity and likelihood that the study treatment caused the reaction. For patient monitoring and to better understand potential etiologies, the investigator must initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

10.2.3 Pregnancy reporting

If a female trial participant becomes pregnant, the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Risks to the fetus of recombinant AAV gene therapy to the fetus are unknown. Since there is a difference in risks between the treatment groups, all pregnancy cases must be unblinded. The investigator will break the study blind for that participant and inform the participant which treatment she was on. This applies also when pregnancy occurs in partners of male participants.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship of OAV101 to any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

If a female partner of a male trial participant who took study treatment in this study becomes pregnant, pregnancy outcomes should be collected. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

NOTE: Payment for all aspects of obstetrical care, child or related care will be the participant's responsibility.

10.2.4 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

- Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol
- Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE. Study treatment errors and uses outside of what is foreseen in the protocol, misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness. For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.3 Additional Safety Monitoring

10.3.1 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of OAV101, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Appendix 2, Section 16.2.1 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every hepatotoxicity event defined in Section 16.2.1 should be followed up by the Investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-1 and Table 16-2.

If elevated, repeat liver chemistry tests (i.e., ALT, AST, TBL, PT/INR, ALP, and G-GT) will be performed within 48-72 hours to confirm elevation. These liver chemistry repeats should be performed. At a local laboratory to monitor the safety of the participant. Any local liver chemistry tests should have results recorded on the appropriate CRF.

If the initial elevation is confirmed, follow-up requirements will be performed based on the liver laboratory trigger, and per Table 16-1 and Table 16-2:

- Hospitalization of the participant, if appropriate
- Causality assessment of the liver event
- Thorough investigation and follow-up of the liver event, which may include:
  - Based on Investigator's discretion: serology tests, laboratory tests for other causes of hepatitis, including viral hepatitis, imaging such as abdominal ultrasound/Fibroscan (i.e., elastography), and pathology assessments
  - Obtaining a more detailed history of signs and symptoms and prior or concurrent diseases

- Obtaining a history of concomitant drug use, including nonprescription medications (e.g., acetaminophen); and herbal and dietary supplement preparations
- Exclusion of underlying liver disease
- Pediatric gastroenterology or hepatology consultations, if appropriate

All follow-up information and procedures performed must be recorded as appropriate in the CRF.

10.3.2 CCI

CCI [redacted] will be administered by an individual who has received training and certification in its administration. CCI [redacted]

CCI [redacted]

In addition, all life-threatening events must be reported as SAEs. CCI [redacted]

10.3.3 Post-mortem data collection

In the event of a fatal outcome, autopsy, where possible, an autopsy will be requested for any participant who receives gene replacement therapy. The autopsy will be performed by the clinical site local pathologist, hospital, or other applicable location. Autopsy should be performed per local standard of care and with particular attention to CNS, dorsal root ganglia, liver, kidneys, heart, and skeletal muscle. Instructions to be followed for sample collection, processing and shipment are available in the Autopsy and Tissue/Organ Collection Manual.

Declining autopsy will not prevent patients from participating in the trial.

Final autopsy report will be stored in the eTMF.

10.3.4 CCI [redacted]

In the event a participant undergoes a CCI [redacted] should be performed as per local standard of care and local regulations. CCI [redacted] should be collected and sent CCI [redacted]

These additionally obtained CCI [redacted]

Participants/participants' parents/guardians will be asked to provide additional consent CCI [redacted]

10.4 Committees

10.4.1 Data Monitoring Committee

This study will include a data monitoring committee which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess at defined intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify, or terminate a trial.

Specific details regarding composition, responsibilities, data monitoring, and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

11 Data Collection and Database management

11.1 Database management and quality control

Novartis personnel (or designated Contract Research Organisation (CRO)) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes and data about all study treatment(s) dispensed to the participant will be tracked using an IRT. The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.2 Site monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e., electronic CRFs (eCRFs)) with the Investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by the CRAs.

The Investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the participant's file. The Investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

12.1 Analysis sets

The Intent to Treat Analysis Set (ITT) comprises all randomized participants, regardless of whether they were dosed with study treatment (OAV101) or who underwent sham procedure during Treatment Period 1. Participants will be analyzed according to the treatment/procedure they have been assigned to.

The Full Analysis Set (FAS) comprises all randomized participants who were dosed with study treatment (OAV101) or who underwent sham procedure during Treatment Period 1. Participants will be analyzed according to the treatment/procedure they have been assigned to.

As per the protocol, participant randomization occurs approximately 2 weeks prior to when treatment administration/sham procedure is planned to occur. There is a possibility that a participant is randomized but subsequently becomes ineligible for the trial during this time and ultimately would not be dosed with study treatment/undergo the sham procedure or contribute to the post-treatment study assessments. In order to account for this possibility, the FAS will exclude participants who were randomized but were not dosed with study treatment/did not undergo sham procedure.

The Active Treatment Period 2 Set (ATP2) comprises all participants who were dosed with study treatment (OAV101) or who underwent sham procedure during Treatment Period 2.

The Safety Set includes all participants who were dosed with study treatment (OAV101) or who underwent sham procedure. Participants will be analyzed according to the study treatment/procedure received.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively by treatment group for the FAS and the Safety Set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 2^{5t}h and 7^{5t}h percentiles may also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by treatment group and overall.

12.3 Treatments

The Safety Set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 2^{5th} and 7^{5th} percentiles, minimum, and maximum will be presented.

The details pertaining to the administration of study treatment will be summarized by means of descriptive statistics using the Safety Set.

Concomitant medications and significant non-drug therapies prior to and after the administration of the study treatment will be summarized according to the ATC classification system, by treatment group.

12.4 Analysis supporting primary objectives

The primary objective of the study is described in Table 2-1. Efficacy analyses will use the FAS unless otherwise specified.

The primary analysis will be performed after all participants have completed Week 52 or discontinued prior to Week 52. A final analysis will be performed after all participants have

completed Week 64 (or discontinued prior to Week 64). Formal testing of the primary endpoint with full alpha level will be performed at the primary analysis time point.

12.4.1 Definition of primary endpoint(s)

The primary endpoint of the study is the change from Baseline in HFMSE total score at the end of Follow-up Period 1 in the overall study population (≥ 2 to < 18 year age group).

CCI [redacted] Refer to Section 8.3.1 for details pertaining to the completion of assessments.

12.4.2 Statistical model, hypothesis, and method of analysis

The aim is to estimate the treatment effect of intrathecal OAV101 compared to the sham procedure, for the target population on the primary endpoint. The justification of the corresponding primary estimand are detailed in Section 2.1.

The statistical hypothesis for the primary endpoint being tested is that there is no difference in the change from Baseline in HFMSE total score at the end of Follow-up Period 1 in the OAV101 treatment group compared to the sham procedure group.

Let p_j denote the change from Baseline in HFMSE total score at the end of Follow-up Period 1 for treatments j, j = 0, 1 where:

0 corresponds to sham procedure

1 corresponds to OAV101

In statistical terms, H_0: $p_1 = p_0$, H_A: $p_1 \neq p_0$, i.e.,:

H_0: OAV101 is not different from sham procedure with respect to the change from Baseline in HFMSE total score at the end of Follow-up Period 1.

H_A: OAV101 is different from sham procedure with respect to the change from Baseline in HFMSE total score at the end of Follow-up Period 1.

The primary efficacy endpoint variable will be analyzed using a mixed model with repeated measurements (MMRM) with the observed change from Baseline in HFMSE total score at all post-Baseline visits (through the end of Follow-up Period 1) as the dependent variable. The fixed effects will include treatment, scheduled visit, treatment by visit interaction, CCI [redacted] An unstructured covariance matrix will be used. LSMs for each treatment group, standard errors, associated 95% confidence intervals (CIs), difference of LSMs compared to sham procedure group, the associated 95% CI for the difference, as well as the two-sided p-values will be tabulated by visit and treatment. The null hypothesis will be rejected if the two-sided p-value for the LSM difference between the OAV101 arm and the sham procedure arm at the end of Follow-up Period 1 is less than the alpha level dictated by the sequential testing procedure (Figure 12-1).

The detailed testing strategy including the primary efficacy endpoint is provided in Section 12.5.

12.4.3 Handling of intercurrent events of primary estimand

The primary analyses will account for intercurrent events as explained in the following:

- **Study discontinuation due to reasons other than death:** It is assumed that participants discontinuing the study prior to Week 52 would follow the same trend as participants who continued and remained in the study for the full 52 weeks. Data collected up to the point of discontinuation will be included in the MMRM (hypothetical strategy).
- **Use of prohibited concomitant medications not for the intent to treat SMA:** Assessments collected while/after receiving prohibited concomitant medications will be included in the analyses (Treatment policy strategy).
- **Use of prohibited concomitant medications for the intent to treat SMA (i.e. nusinersen, risdiplam):** Assessments collected while/after receiving prohibited concomitant medications will not be included in the analyses. Only data collected up to the point of initiating a prohibited medication for the intent to treat SMA will be included in the MMRM and the data collected after the initiation of prohibited medication for the intent to treat SMA will be considered as missing (Hypothetical strategy).
- **Study discontinuation due to death:** The worst HFMSE score will be imputed for participants who discontinue the study due to death, and this imputed score will be utilized in the analysis. The "worst score" refers to the worst (lowest) HFMSE score collected for the participant who had the death event throughout the trial (considering both the baseline and post-baseline period). It is anticipated that this intercurrent event is unlikely to occur during this study.

12.4.4 Handling of missing values not related to intercurrent event

The primary analysis method, MMRM, implicitly imputes missing data under a missing at random assumption.

12.4.5 Sensitivity analyses

In order to assess the potential impact of excluding participants from the primary analysis who are randomized into the study but did not receive treatment, the primary efficacy analysis will be repeated using the ITT Set. The same analysis methodology as described for the primary analysis of the primary efficacy endpoint (i.e. MMRM) will be applied for this sensitivity analysis.

A sensitivity analysis using multiple imputation approach will also be performed for the primary estimand, to assess the robustness of the estimation in the presence of deviations from the assumptions specified in the primary analysis. Additional details will be provided in the statistical analysis plan (SAP).

12.4.6 Supplementary analysis

No supplementary analysis is planned.

12.5 Analysis supporting secondary objectives

The secondary objectives are described in Table 2-1. Secondary efficacy analyses will use the FAS.

12.5.1 Efficacy and/or pharmacodynamic endpoint(s)

The secondary endpoint analyses are as follows:

1. Change from Baseline in HFMSE total score at the end of Follow-up Period 1 for participants aged ≥ 2 to < 5 years
2. Achievement of at least a 3-point improvement from baseline in HFMSE total score at the end of Follow-up Period 1 (responders) for participants in the overall study population
3. Achievement of at least a 3-point improvement from baseline in HFMSE total score at the end of Follow-up Period 1 in the ≥ 2 to < 5 years age group
4. Change from Baseline in RULM total score at the end of Follow-up Period 1 for participants aged ≥ 2 to < 18 years
5. Change from Baseline in RULM total score at the end of Follow-up Period 1 for participants aged ≥ 2 to < 5 years

The continuous secondary endpoints of change from baseline in HFMSE and RULM scores in the younger age group or the whole study population will be analyzed in a similar manner to how the primary endpoint will be analyzed.

The dichotomous endpoint (proportion of responders, defined as participants who achieve at least a 3-point improvement from baseline in HFMSE total score at the end of Follow-up Period 1) will be analyzed by Generalized Linear Mixed Effects Model including treatment, CCI [redacted] The model will include the link=logistic function.

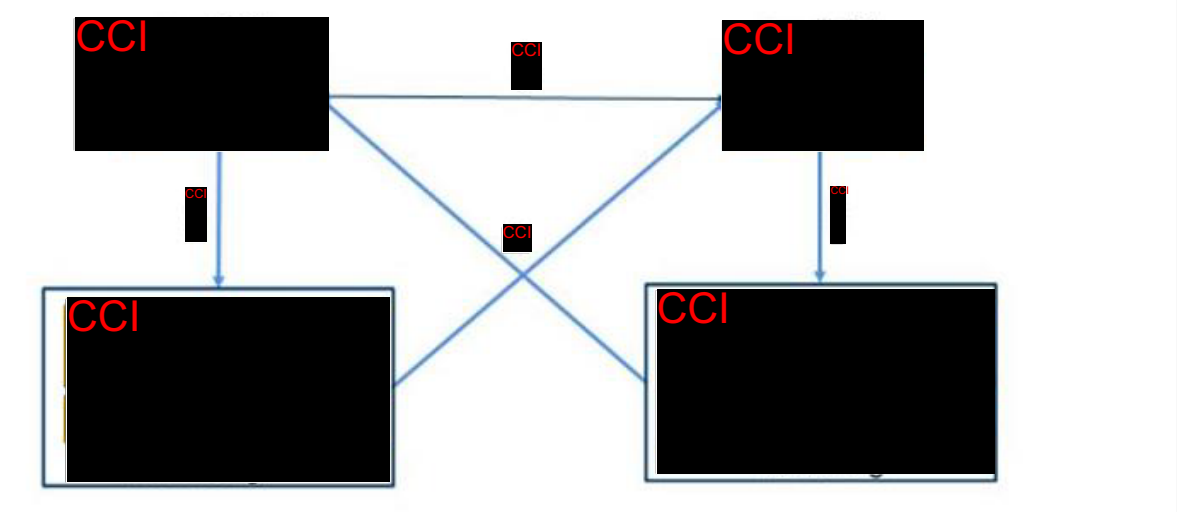
CCI [redacted] Refer to Section 8.3.1 for details pertaining to the completion of assessments.

Testing Procedure

CCI [redacted]

CCI

Figure 12-1 CCI



12.5.2 Safety endpoints

For all safety analyses, the Safety Set will be used. All listings and tables will be presented by treatment group.

Safety summaries (tables, figures) will include only data from the post-treatment period with the exception of baseline data, which will also be summarized where appropriate (e.g., change from baseline summaries). In addition, a separate summary for deaths occurring post-treatment will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date on or after the date of dose administration (treatmentemergent AEs).

The on-treatment period lasts from the date of administration of study treatment to completion of the study at Week 64.

Adverse events

All information obtained on adverse events will be listed by treatment group and participant.

The number (and percentage) of participants with treatment emergent adverse events (events with an onset after the dose of study medication or events which were present prior to start of double-blind treatment but increased in severity, changed from being not suspected to being suspected of study drug relationship, or developed into SAEs after the start of the treatment period) will be summarized in the following ways:

- by treatment group, primary system organ class and preferred term.
- by treatment group, primary system organ class, preferred term and maximum severity.

- by treatment group, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related adverse events, deaths, serious adverse events, and other significant adverse events leading to discontinuation.

The number (and proportion) of participants with AESIs will be summarized by treatment.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be summarized by treatment and visit/time.

12-lead ECG

All ECG data will be summarized by treatment and visit/time.

PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each participant during the study.

Categorical analysis of QT/QTc interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from Baseline will be presented.

Echocardiogram

All echocardiogram data will be summarized by treatment and visit/time. Additionally, the following will be summarized:

- Number and percentage of participants with intracardiac thrombi
- Number and percentage of participants with low cardiac function

These parameters are defined as follows:

Intracardiac thrombi: Post-baseline ECHO result of thrombus present (response of Yes)

Low cardiac function: Post-baseline ECHO results of LVEF < 56% or LVFS < 28%

Clinical laboratory evaluations

All laboratory data will be summarized by treatment and visit/time. Shift tables using the low/normal/high classification as well as CTCAE grades will be used to compare baseline to the worst on-treatment value.

CCI [redacted]

CCI [redacted]

12.6 Analysis of exploratory endpoints

The exploratory objectives are described in Table 2-1.

The full list of exploratory endpoints to be included in the CSR and detailed analysis methods will be detailed in the study SAP.

12.6.1 CCI

CCI [redacted] Additional data, from other clinical trials, are often needed to confirm associations. Alternatively, if the number of participants enrolled in the study is too small to complete proper statistical analyses, the data may be combined, as appropriate, with those from other studies to enlarge the dataset for analysis.

Data generated on hypothesis-free platforms will be reported separately (e.g., CSR addendum).

12.6.2 CCI

CCI [redacted], will be tabulated with descriptive statistics by visit and treatment. Additional exploratory analyses and their results, if applicable, will be included CCI [redacted]

12.6.3 CCI

CCI [redacted]

CCI [redacted]

12.7 Interim analyses

No formal interim analysis is planned for this trial.

12.8 Sample size calculation

The sample size calculation is primarily based on the primary variable, change from Baseline in HFMSE total score.

12.8.1 CCI

CCI

Assuming a true treatment difference in the change from Baseline in HFMSE of 3 points and a standard deviation of 5 points, a sample size of 125 participants (75 in the OAV101 treatment group and 50 in the sham procedure group) provides approximately 90% power that the primary analysis will be statistically significant at the two-sided 5% alpha level assuming a minimal number of participants prematurely withdraw from the study prior to Week 52. In addition, assuming a larger treatment difference in the change from Baseline in HFMSE total score of 5 points and the same standard deviation as anticipated in the overall study population (5 points) in the ≥ 2 to < 5 years old group, a sample size of 65 participants (39 in the OAV101 treatment group and 26 in the sham procedure group) could achieve > 95% power in this younger age group.

12.8.2 Secondary endpoint(s)

Sample size considerations were primarily based on the primary endpoint.

Because this is the first OAV101 clinical trial to include the RULM assessment, there are no historical data available upon which to base sample size calculations on.

In the AVXS-101-CL-102-IT clinical trial, the HFMSE responder endpoint was defined as the achievement of improvement in HFMSE of ≥ 3 points at any post baseline time point (through Month 12): 11/12 (91.7%) patients treated with OAV101 achieved response, compared to 2/15 (13.3%) patients in the PNCR group. For the current study, the responder endpoint is defined as the achievement of improvement in HFMSE of ≥ 3 points at the end of follow-up period 1 (and will be based on the average of the HFMSE scores at Month 11 and Month 12). Applying this same definition to the AVXS-101-CL-102-IT data, 9/12 (75%) patients treated with OAV101 achieved response. For PNCR, HFMSE was assessed less frequently (the last 2 time points of relevance were Month 9 and Month 12). Considering just the PNCR patients with HFMSE data at Month 9 and/or Month 12, then based on the average of these 2 scores or based on the single available score, 2/15 (13%) achieved response. The power to detect a significant difference in the ≥ 2 to < 5 year age group in this study, assuming a response rate of 75% for OAV101 and 13% for sham and alpha=0.05, would be > 99% with the planned sample size of N=65 patients (39 in OAV101, 26 in sham).

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last participant last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g., Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial Investigator meetings.

Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.

Summary results of primary and secondary endpoints will be disclosed based upon global Last Participant Last Visit (LPLV) date, since multinational studies are locked and reported based upon the global LPLV.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

13.5 Participant engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants at the timepoints indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Thank you letter
- Plain language trial summary–- after CSR publication

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

References are available upon request

AANEM Professional Practice Committee (2020) Establishing standards for acceptable waveforms in nerve conduction studies. Muscle Nerve; 61:280-7.

CCI [redacted]

Aragon-Gawinska K, Daron A, Ulinici A, et al (2020) Sitting in patients with spinal muscular atrophy type 1 treated with nusinersen. Dev Med Child Neurol; 62:310-14.

Arenas J, Diaz V, Liras G, et al (1988) Activities of creatine kinase and its isoenzymes in serum in various skeletal muscle disorders. Clin Chem; 34 (12):2460-2.

Bernal S, Alías L, Barceló MJ, et al (2010) The c.859G>C variant in the SMN2 gene is associated with types II and III SMA and originates from a common ancestor. J Med Genet; 47:640-2.

Burghes AHM, Beattie CE (2009) Spinal muscular atrophy: why do low levels of survival motor neuron protein make motor neurons sick? Nat Rev Neurosci; 10:597-609.

CDC Anthropometry Procedures (2020) (Internet) Available from: <https://.n.cdc.gov/nchs/data/nhanes/2019-2020/manuals/2020-Anthropometry-Procedures-Manual-508.pdf> (Accessed 24-March-2021).

CDC BMI Calculator (2020) (Internet) Available from: <https://.cdc.gov/healthyweight/bmi/calculator.html> (Accessed 24-Mar-2021).

Calucho M, Bernal S, Alías L, et al (2018) Correlation between SMA type and SMN2 copy number revisited: An analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. Neuromuscul Disord; 28:208-15.

Coratti G, Lucibello S, Pera MC, et al (2020a) Gain and loss of abilities in type II SMA: A 12-month natural history study. Neuromuscul Disord; 30(9):765-71.

Coratti G, Pera MC, Lucibello S, et al (2020b) Age and baseline values predict 12 and 24-month functional changes in type 2 SMA. Neuromuscul Disord; 30(9):756-64.

Coratti G, Pera MC, Montes J, et al (2021) Different trajectories in upper limb and gross motor function in spinal muscular atrophy. Muscle Nerve: 64(5):552-9.

EVRYSDI Prescribing Information (2020) (Internet) Available from: <https://.accessdata.fda.gov/drugsatfda_docs/label/2020/213535s000lbl.pdf> (Accessed 04-April-2021).

Farrar MA, Vucic S, Johnston HM, et al (2013) Pathophysiological insights derived by natural history and motor function of spinal muscular atrophy. J Pediatr; 162(1):155-9.

CCI [redacted]

CCI [redacted]

Fleming S, Thompson M, Stevens R, et al (2011) Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet; 377:1011-8.

Flynn JT, Kaelber DC, Baker-Smith CM, et al (2017) Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. Pediatrics. 140(3):e20171904.

Fujak A, Raab W, Schuh A, et al (2013) Natural course of scoliosis in proximal spinal muscular atrophy type II and IIIa: descriptive clinical study with retrospective data collection of 126 patients. BMC Musculoskelet Disord; 14:283.

Genentech (2021) Sunfish Study (Internet) Available from: <https://.evrysdi-hcp.com/study-results/later-onset-results.html> (Accessed 15-March-2021).

Glanzman AM, O'Hagen JM, McDermott MP, et al (2011) Validation of the Expanded Hammersmith Functional Motor Scale in spinal muscular atrophy type II and III. J Child Neurol; 26(12):1499-507.

Glascock J, Sampson J, Connolly AM, et al (2020) Revised Recommendations for the Treatment of Infants Diagnosed with Spinal Muscular Atrophy Via Newborn Screening Who Have 4 Copies of SMN2. J Neuromuscul Dis; 7(2):97-100.

Glascock J, Sampson J, Haidet-Phillips A, et al (2018) Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening. J Neuromuscul Dis; 5:145-58.

CCI [redacted]

Hatfield MK, Handrich SJ, Willis JA, et al (2008) Blood patch rates after lumbar puncture with Whitacre versus Quincke 22- and 20-gauge spinal needles. Am J Roentgenol; 190:1686-9.

Hirschmann J, Sedlmayr B, Zierk J, et al (2017) Evaluation of an Interactive Visualization Tool for the Interpretation of Pediatric Laboratory Test Results. Studies in Health Technology Informatics; 243:207-11.

Hudry E, Vandenberghe LH (2019) Therapeutic AAV Gene Transfer to the Nervous System: A Clinical Reality. Neuron; 101(5):839-62

ICH-E2D Guidelines (2003) Post-approval safety data management: definitions and standards for expedited reporting (Internet) Available from: <https://.database.ich.org/sites/default/files/E2D_Guideline.pdf> (Accessed 24-March-2021).

Kaufmann P, McDermott MP, Darras BT, et al (2012) Prospective cohort study of spinal muscular atrophy types 2 and 3. Neurology; 79:1889-97.

Kolb SJ, Kissel JT (2011) Spinal muscular atrophy: a timely review. Arch Neurol; 68(8):979-84.

Krosschell KJ, Maczulski JA, Crawford TO, et al (2006) A modified Hammersmith functional motor scale for use in multi-center research on spinal muscular atrophy. Neuromuscul Disord; 16:417-26.

Krosschell KJ, Scott CB, Maczulski JA, et al (2011) Reliability of the Modified Hammersmith Functional Motor Scale in young children with spinal muscular atrophy. Muscle Nerve; 44:246-51.

Le TT, McGovern VL, Alwine IE, et al (2011) Temporal requirement for high SMN expression in SMA mice. Hum Mol Genet; 20(18):3578-91.

Lefebvre S, Bürglen L, Reboullet S, et al (1995) Identification and characterization of a spinal muscular atrophy-determining gene. Cell; 80:155-65.

Main M, Kairon H, Mercuri E, et al (2003) The Hammersmith functional motor scale for children with spinal muscular atrophy: a scale to test ability and monitor progress in children with limited ambulation. Eur J Paediatr Neurol; 7:155-9.

CCI [redacted]

Mazzone ES, Mayhew A, Montes J, et al (2017) Revised upper limb module for spinal muscular atrophy: Development of a new module. Muscle Nerve; 55:869-74.

McCormack MC, Bascom R, Brandt M, et al (2021) Electronic Health Records and Pulmonary Function Data: Developing an Interoperability Roadmap. An Official American Thoracic Society Workshop Report. Ann Am Thorac Soc; 18(1): e1-11.

Mercuri E, Bertini E, Iannaccone ST (2012) Childhood spinal muscular atrophy: controversies and challenges. Lancet Neurol; 11:443-52.

Mercuri E, Darras BT, Chiriboga CA, et al (2018b) Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. N Engl J Med; 378(7):625-35.

Mercuri E, Finkel RS, Muntoni F, et al (2018a) Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord; 28:103-15.

Mercuri E, Lucibello S, Pera MC, et al (2019) Long-term progression in type II spinal muscular atrophy: A retrospective observational study. Neurology; 93(13):e1241-47.

Mercuri E, Messina S, Battini R, et al (2006) Reliability of the Hammersmith functional motor scale for spinal muscular atrophy in a multicentric study. Neuromuscul Disord; 16:93-8.

Mimuro J, Mizukami H, Shima M, et al (2014) The prevalence of neutralizing antibodies against adeno-associated virus capsids is reduced in young Japanese individuals. J Med Virol; 86:1990-7.

Mokhy MS, Jamaluddin R, Ismail AR, et al (2020) Anthropometry Measurements to Determine Nutritional Status Among Cerebral Palsy Children: A Scoping Review. Mal J Med Health Sci; 16(SUPP6):213-218.

Monani UR, Lorson CL, Parsons DW, et al (1999) A single nucleotide difference that alters splicing patterns distinguishes the SMA gene SMN1 from the copy gene SMN2. Hum Mol Genet; 8(7):1177-83.

Nath S, Koziarz A, Badhiwala JH, et al (2018) Atraumatic versus conventional lumbar puncture needles: a systematic review and meta-analysis. Lancet; 391:1197-204.

National High Blood Pressure Education Program Working Group (2004) The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics; 114(suppl 2):555-76.

O'Hagen JM, Glanzman AM, McDermott MP, et al (2007) An expanded version of the Hammersmith Functional Motor Scale for SMA II and III patients. Neuromuscul Disord; 17:693-7.

Osebold WR, Mayfield JK, Winter RB et al (1982) Surgical treatment of paralytic scoliosis associated with myelomeningocele. J Bone Joint Surg Am. 64(6):841-56.

Pane M, Coratti G, Sansone VA, et al (2019) Nusinersen in type 1 spinal muscular atrophy: Twelve-month real-world data. Ann Neurol; 86(3):443-51.

Pechmann A, König K, Bernert G, et al (2019) SMArtCARE - A platform to collect real-life outcome data of patients with spinal muscular atrophy. Orphanet J Rare Dis; 14:18.

Pechmann A, Langer T, Schorling D, et al (2018) Evaluation of Children with SMA Type 1 Under Treatment with Nusinersen within the Expanded Access Program in Germany. J Neuromuscul Dis; 5:135-43.

Pellizzoni L, Kataoka N, Charroux B, et al (1998) A novel function for SMN, the spinal muscular atrophy disease gene product, in pre-mRNA splicing. Cell; 95:615-24.

Pera MC, Coratti G, Mazzone ES, et al (2019) Revised upper limb module for spinal muscular atrophy: 12 month changes. Muscle Nerve; 59:426-30.

CCI [redacted]

Preedy VR (eds) (2012) Handbook of Anthropometry; Physical Measures of human Form in Health and Disease (Internet) Available from: https://.springer.com/gp/book/9781441917874 (Accessed 22-Mar-2021)

Ramsey D, Scoto M, Mayhew A, et al (2017) Revised Hammersmith Scale for spinal muscular atrophy: A SMA specific clinical outcome assessment tool. pLoS One; 12(2): e0172346.

Riessland M, Kaczmarek A, Schneider S, et al (2017) Neurocalcin Delta Suppression Protects against Spinal Muscular Atrophy in Humans and across Species by Restoring Impaired Endocytosis. Am J Hum Genet; 100:297-315.

Rochette CF, Gilbert N, Simard LR (2001) SMN gene duplication and the emergence of the SMN2 gene occurred in distinct hominids: SMN2 is unique to Homo sapiens. Hum Genet; 108:255-66.

Rochwerg B, Almenawer SA, Siemieniuk RAC, et al (2018) Atraumatic (pencil-point) versus conventional needles for lumbar puncture: a clinical practice guideline. BMJ; 361:k1920.

Samson-Fang L, Bell KL (2013) Assessment of growth and nutrition in children with cerebral palsy. Eur J Clin Nutr; 67:S5-8.

Schorling DC, Pechmann A, Kirschner J (2020) Advances in Treatment of Spinal Muscular Atrophy - New Phenotypes, New Challenges, New Implications for Care. J Neuromuscul Dis; 7:1-13.

Stålberg E, van Dijk H, Falck B, et al (2019) Standards for quantification of EMG and neurography. Clin Neurophysiol; 130:1688-729.

CCI [redacted]

Sugarman EA, Nagan N, Zhu H, et al (2012) Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. Eur J Hum Genet; 20:27-32.

Swoboda KJ, Prior TW, Scott CB, et al (2005) Natural history of denervation in SMA: relation to age, SMN2 copy number, and function. Ann Neurol; 57(5):704-12.

van den Akker E, van der Vlugt CJB, Bleijs DA, et al (2013) Environmental risk assessment of replication competent viral vectors applied in clinical trials: potential effects of inserted sequences. Curr Gene Ther; 13(6):395-412.

Verdera HC, Kuranda K, Mingozzi F (2020) AAV Vector Immunogenicity in Humans: A Long Journey to Successful Gene Transfer. Mol Ther; 28(3):723-46.

WHO (2010) WHO guidelines on drawing blood: best practices in phlebotomy. (Internet) Avaiable from: <https://.euro.who.int/__data/assets/pdf_file/0005/268790/WHO-guidelines-on-drawing-blood-best-practices-in-phlebotomy-Eng.pdf p. 1-109> (Accessed 07-July-2021)

WHO (2022a) Body mass index-for-age (BMI-for-age) (Internet) Avaiable from: <https://www.who.int/toolkits/child-growth-standards/standards/body-mass-index-for-age-bmi-for-age> (Accessed 17-February-2022)

WHO (2022b) BMI-for-age (5-19 years) (Internet) Available from: <https://www.who.int/tools/growth-reference-data-for-5to19-years/indicators/bmi-for-age> (Accessed 17-February-2022).

Wijnhoven TM, de Onis M, Onyango AW, et al (2004) Assessment of gross motor development in the WHO Multicentre Growth Reference Study. Food Nutr Bull; 25(1 suppl 1):S37-S45.

16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

Clinically relevant laboratory abnormalities

Age-appropriate, normal laboratory values and clinical measurements should be used in pediatric population. Laboratory tests are commonly interpreted in relation to established reference intervals. These limits serve to differentiate between normal and pathological findings, and to gauge the severity of any abnormal increases or decreases. As far as laboratory parameters are known to characteristically vary with age, pediatric test results are usually interpreted in relation to these physiological dynamics. Reference intervals for pediatric patients have been calculated by partitioning data from a healthy reference population into age groups, so that the corresponding subset-specific percentiles would form step functions of age (Hirschmann et al 2017).

Vital signs

Within vital signs data, height and weight are commonly collected along with heart rate, respiratory rate, and blood pressure. The exam and vital sign data can be interpreted only with a thorough understanding of normal values. In pediatrics, normal respiratory rate, heart rate, and blood pressure have age-specific norms (Fleming et al 2011, Flynn et al 2017). The full list of clinically relevant vital signs will be included in the CSR and detailed summary methods will be specified in the Statistical Analysis Plan.

16.2 Appendix 2: Liver laboratory triggers & follow-up monitoring requirements

16.2.1 Liver laboratory triggers

Liver laboratory triggers which require follow-up monitoring include:

- ALT > 3 × ULN
- TBL > 1.5 × ULN (in the absence of known Gilbert's syndrome)
- Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated (direct) fraction] without notable increase in ALP to > 2 × ULN)

16.2.2 Follow up requirements for liver laboratory triggers – ALT and AST, with and without TBL

Table 16-1 Follow-up requirements for liver laboratory triggers – ALT and AST, with and without TBL

ALT	TBL	Liver Symptoms	Actions/Follow-up Monitoring
ALT > 3 x ULN	· Normal · For participants with Gilbert's syndrome: No change in baseline TBL	None	· Review compliance with immunomodulatory therapy (Section 6.2) · Measure ALT, AST, TBL, fractionated bilirubin (direct and indirect), INR, and GLDH within 48-72 hours · Follow-up for symptoms
ALT > 5 x ULN	· Normal · For participants with Gilbert's syndrome: No change in baseline TBL	With or without symptoms	· Review compliance with immunomodulatory therapy (Section 6.2) · Measure ALT, AST, TBL, fractionated bilirubin (direct and indirect), INR, albumin, CK, and GLDH within 48 - 72 hours · Follow-up for symptoms · Initiate close monitoring (hospitalization when appropriate) and workup for competing etiologies[a] · Exclude underlying liver disease · Obtain detailed history of concomitant medications (e.g. acetaminophen) · Consult pediatric gastroenterologist[b]
ALT or AST > 3 x ULN	· TBL > 2 x ULN (or INR > 1.5) · For participants with Gilbert's syndrome: Doubling of direct bilirubin	With or without symptoms	
ALT > 3 x ULN	Normal or elevated	Severe fatigue, nausea, vomiting, and/or right upper quadrant pain	

[a] Work-up for competing etiologies may include (but not limited to) viral hepatitis panel (IgM anti-HAV; HBsAg, IgM anti-HBc, hepatitis B virus (HBV) DNA, hepatitis C virus (HCV) ribonucleic acid (RNA), anti-HCV, IgM & IgG, hepatitis E virus (HEV) RNA, anti-HEV, viral panel (CMV, EBV, HSV), autoimmune hepatitis (ANA, anti-smooth muscle antibody (ASMA) titers)
[b] Consider appropriate imaging and liver biopsy in consultation with a pediatric gastroenterologist

16.2.3 Follow up requirements for liver laboratory triggers - isolated hyperbilirubinemia

Table 16-2 Follow-up requirements for liver laboratory triggers - isolated hyperbilirubinemia

Criteria Total Bilirubin (isolated)	Actions required	Follow-up monitoring
>1.5 – 3.0 x ULN	· Repeat LFTs within 48-72 hours	· Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline
> 3 – 10 x ULN (in the absence of known Gilbert's syndrome)	· Repeat LFTs within 48-72 hours · Hospitalize if clinically appropriate · Establish causality · Record the AE and contributing factors (e.g. concomitant medications, medical history, labs) in the appropriate CRF	· Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline (ALT, AST, TBL, Alb, PT/INR) · Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	· Hospitalize the participant · Establish causality · Record the AE and contributing factors (e.g. concomitant medications, medical history, laboratory evaluations) in the appropriate CRF	· ALT, AST, TBL, Alb, PT/INR, until resolution (frequency at investigator discretion)
LFT(s) = liver function test Based on investigator's discretion, investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, pediatric gastroenterologist's or hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.		

16.2.4 Prednisolone dosing

Prednisolone dosing

- CCI [redacted]
- CCI [redacted] (as defined in Section 16.2.1), refer to the follow-up requirements specified in Table 16-1 and Table 16-2.
- Live vaccines are prohibited while receiving corticosteroids. Participants are advised to complete all age-appropriate inoculations with live vaccines prior to enrolling in the study if possible.
- CCI [redacted]