Registry Information

Title	An International Observational Registry Study to Further Describe Long-term Safety and Effectiveness of Palovarotene in Patients with Fibrodysplasia Ossificans Progressiva (FOP)
Protocol version identifier	8.0
Date of last version of protocol	16 April 2025
Active substance	Palovarotene Pharmacotherapeutic group: other drugs for disorders of the musculoskeletal system, ATC code: M09AX11
Medicinal product	Palovarotene
Product reference	H004867
Procedure number	-
Sponsor	Ipsen Pharma SAS (EU)

Research question and objectives	The aim of the FOPal registry study is primarily to collect and assess real-world safety data on paediatric and adult participants with Fibrodysplasia Ossificans Progressiva (FOP) exposed to palovarotene and secondly to describe the effectiveness of palovarotene in exposed participants, including its effect on physical function. In addition, this study aims to descriptively compare key safety outcomes (i.e. flare-up episodes, growth and bone fractures) between exposed and unexposed participants. Primary objective: To collect and assess real-world safety data in participants with FOP exposed to palovarotene. Secondary objectives: *For participants with FOP exposed and unexposed to palovarotene:* • To describe the range of motion (ROM) as assessed by the Cumulative Analogue Joint Involvement Scale (CAJIS) for FOP; • To describe the use of assistive devices and adaptations for daily living; • To describe the physical function using age-appropriate forms of the Fibrodysplasia Ossificans Progressiva-Physical Function Questionnaire (FOP-PFQ); • To describe the parameters of lung function (observed and % predicted forced vital capacity (FVC), observed and % predicted forced expiratory volume in one second (FEV_1), absolute and % predicted FEV_1/FVC ratio, observed and % predicted diffusion capacity of the lung for carbon monoxide (DLCO)) at Baseline and over time; • To describe the physical and mental health (participants ≥15 years old) and overall quality of life (participants <15 years old) using age-appropriate forms of the Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health Scale; • To describe the flare-up frequency; • To describe any movement mobility change by body location and annually; • To describe the number of locations impacted by movement mobility change per participant annually; • To describe the movement mobility outcomes (change in extra bone growth and change in movement), causes and associated symptoms if preceded by a flare-up event by body location; • To describe the frequency, severity, outcome and descriptive details of any fractures (including bone fractures and vertebral fractures); • To describe the incidence of pregnancy. *For participants with FOP exposed to palovarotene who become pregnant while enrolled in FOPal:* • To describe pregnancy characteristics and outcomes; • To describe pregnancy-related adverse events (AEs) through the first year postpartum; • To describe birth and developmental outcomes through the infant(s)' first year of life.

	For growing children with FOP exposed and unexposed to palovarotene: • To describe linear height and knee height velocities until skeletal maturity or final adult height is reached; • To describe linear height z-scores until skeletal maturity or final adult height is reached; • To describe the difference between chronological age and bone age; • To describe the frequency, severity and descriptive details of premature physeal closure (PPC). *For participants with FOP exposed to palovarotene:* • To describe the use (dose and frequency) of palovarotene in the real-world setting.
Country(ies)/Site(s) of study	Exposed and unexposed participants will be recruited in countries/sites willing to participate and where palovarotene is registered/marketed.
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PROTOCOL SIGNATURES

Investigator Signature

I have read and agree to the study protocol CLIN-60120-453 entitled "An International Observational Registry Study to Further Describe Long-term Safety and Effectiveness of Palovarotene in Patients with Fibrodysplasia Ossificans Progressiva (FOP)". I am aware of my responsibilities as an investigator under the guidelines of Good Pharmacoepidemiology Practices (GPP), Good Pharmacovigilance Practices (GVP), any regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME: _____

TITLE: (Principal) Investigator: SIGNATURE: _____

DATE: _____

OFFICE: _____

Full investigational site contact details, including telephone numbers, will be documented in the Trial Master File.

On behalf of the sponsor:

NAME: PPD

TITLE: SIGNATURE: PPD

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2 LIST OF ABBREVIATIONS

ABBREVIATION	Wording Definition
ADR	Adverse Drug Reaction
ACVR1	Activin A Receptor Type 1
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALK2	Activin Receptor-like-kinase-2
BMP	Bone Morphogenetic Protein
CA	Competent Authorities
CAJIS	Cumulative Analogue Joint Involvement Scale
CI	Confidence Intervals
CIOMS	Council for International Organizations of Medical Sciences
CO	Carbon Monoxide
CT	Computed Tomography
DLCO	Diffusion Capacity of the Lung for Carbon Monoxide
eCRF	Electronic Case Report Form
EDD	Estimated Due Date
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FEV_1	Forced Expiratory Volume in one second
FOP	Fibrodysplasia Ossificans Progressiva
FOP-PFQ	Fibrodysplasia Ossificans Progressiva-Physical Function Questionnaire
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GMPC	Global Medical Publications and Communications
GP	General Practitioners
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HCP	Healthcare professional
HEENT	Head, eyes, ears, nose and throat
HO	Heterotopic Ossification

ICE	In Case of Emergency
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IPTW	Inverse Probability of Treatment Weighting
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
LAR	Legally Authorised Representative
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NHS	Natural History Study
NIS	Non-Interventional Study
OMIM	Online Mendelian Inheritance in Man
PBRER	Periodic Benefit-Risk Evaluation Report
PEP	Positive Expiratory Pressure
PI	Prescribing Information
PPC	Premature Physeal Closure
PROMIS	Patient-Reported Outcomes Measurement Information System
PS	Propensity Score
PSUR	Periodic Safety Update Report
PT	Preferred Term
QoL	Quality of Life
QPPV	Qualified Person Responsible for Pharmacovigilance
RARγ	Retinoic Acid Receptor Gamma
ROM	Range of Motion
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SMD	Standardised mean differences
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
SP	Service Provider

TEAE	Treatment-Emergent Adverse Event
TGF-β	Transforming Growth Factor Beta
WBCT	Whole Body Computed Tomography
WHODD	World Health Organization Drug Dictionary
wLME	Weighted Linear Mixed Effects

3 RESPONSIBLE PARTIES

A list of all investigators, including contact details, will be in a stand-alone document, available upon request.

4 ABSTRACT

Title	
Registry Study Title:	An International Observational Registry Study to Further Describe Long-term Safety and Effectiveness of Palovarotene in Patients with Fibrodysplasia Ossificans Progressiva (FOP)
Protocol Version N°:	8.0
Date of the Last Version of the Protocol:	16 April 2025
Author:	PPD

Rationale and Background

Fibrodysplasia ossificans progressiva (FOP; Online Mendelian Inheritance in Man (OMIM) #135100) is an ultra-rare genetic disorder, with an estimated prevalence of 1.36 per million individuals; however, the number of confirmed cases varies by country. FOP affects all races and there is no ethnic, sex-linked, or geographic predisposition. Median patient age at time of FOP diagnosis is 6.4 years.

Fibrodysplasia Ossificans Progressiva is caused by a spontaneous missense mutation in the activin A receptor type 1 *(ACVR1)*/activin receptor-like-kinase-2 (*ALK2*) gene, which encodes a receptor in the bone morphogenetic protein (BMP) signalling pathway. BMPs are extracellular ligands belonging to the TGF-β superfamily. Signal transduction studies show that receptor-regulated Smad proteins 1/5/8 are the immediate downstream molecules of BMP receptors and play a central role in BMP signal transduction.

Upon ligand binding to BMP receptors, there is a downstream activation of genes involved in the differentiation and activation of osteoblast and chondrocyte-like cells via phosphorylation of Smad proteins 1/5/8; this is regulated by the inhibitory factor FKBP12, which binds to the BMP type I receptor and stabilises the inactive form.

Most patients with FOP have classic FOP (~97%), but a minority are affected by non-classic FOP (~3%). In classic FOP, approximately 90% of patients carry the same specific *ACVR1/ALK2* pathogenic variant (c.617G>A; p.R206H) in the glycine and serine activation domain of the gene. In the presence of the pathogenic variant of the *ACVR1/ALK2* gene, FKBP12 binding is reduced, leading to enhanced BMP signalling. FOP diagnosis is clinical but requires genetic confirmation.

Patients with FOP experience sporadic and unpredictable episodes of soft-tissue swelling, pain, reduced movement, stiffness and fever, referred to as "flare-ups". Flare-ups appear spontaneously or after muscle fatigue, minor trauma, intramuscular injections or influenza-like viral illnesses and develop rapidly over several hours; these inciting events induce local inflammation, which is followed by recruitment of bone progenitor cells that differentiate into chondrocytes. Although some flare-ups regress spontaneously, many appear to lead to heterotopic ossification (HO), which transforms soft and connective tissues (including aponeuroses, fascia, ligaments, tendons and skeletal muscles) into heterotopic bone. Of patients with FOP, 95% manifest HO before reaching 15 years of age.

FOP is characterised by congenital malformation of the great toes and progressive HO in soft and connective tissues; it is a severely disabling HO disorder. Other clinical features observed in patients with FOP are shortened thumbs, cervical spine malformations, short broad femoral necks and proximal medial tibial osteochondromas. Typically, HO begins in the dorsal,

proximal, axial and cranial regions of the body (neck, shoulders and back) and progresses into ventral, caudal and distal regions (trunk and limbs). HO develops into ribbons, sheets and plates of extra bone throughout the body and across joints, thereby progressively restricting movement. Once ossification occurs, it is permanent; consequently, disability in FOP is cumulative, with most patients becoming immobilised and confined to a wheelchair by their third decade of life and requiring lifelong assistance in performing activities of daily living.

Fibrodysplasia Ossificans Progressiva is not only an extremely disabling disease but also a condition of considerably shortened lifespan. Morbidity associated with FOP includes fractures (due to the increased risk of falls, immobility and prednisone use), limb swelling, pressure sores, hearing impairment, gastrointestinal issues and pain. Patients with FOP reach a median survival of 56 (95% CI: 51; 60) years; death is often due to cardiorespiratory failure (as a result of respiratory insufficiency, which is usually caused by progressive restrictive chest-wall HO) or thrombosis.

Misdiagnosis and delayed diagnosis contribute to the accumulation of disability in patients with FOP. There is often a delay in the diagnosis of FOP because of lack of physician awareness and inadequate description in most medical textbooks. The median delay from onset of symptoms to the correct diagnosis is 1.1 years (range: <1 month to 49 years), after consultation with a median of six different healthcare professionals. FOP is misdiagnosed in up to 87% of individuals, with the most common incorrect diagnoses including cancer, aggressive juvenile fibromatosis, ankylosing spondylitis and bunions.

Until recently, there were no effective treatments to reduce the formation of heterotopic bone in FOP, with therapeutic approaches being limited to symptom management and flare-up prevention; consequently, as well as an imperative to improve early diagnosis and to reduce iatrogenic harm, there is a critical unmet need for definitive therapies for patients with FOP.

Palovarotene is being developed by Ipsen for the treatment of FOP. Palovarotene was first approved by Health Canada for the treatment of patients with FOP in adults and children aged 8 years and above for females and 10 years and above for males with FOP. Palovarotene is an orally bioavailable retinoic acid receptor gamma (RARγ) selective agonist.

Retinoic acid receptor gamma is a nuclear hormone receptor that has a role in regulating skeletal development and growth; it is expressed in chondrogenic cells and chondrocytes, where it operates as a transcriptional repressor. Activation of the retinoid signalling pathway and RARγ has been demonstrated to inhibit both chondrogenesis and HO. Given that chondrogenesis requires a decrease in retinoid signalling concurrent with upregulation of pro-chondrogenic pathways, including BMP signalling, RARγ agonists are likely to elicit anti-chondrogenic and anti-HO effects by maintaining retinoid signalling while reducing BMP signalling.

Retinoic acid receptor gamma agonists potently impede heterotopic endochondral ossification by inhibiting downstream effectors (namely Smad 1/5/8) of the mutated *ACVR1/ALK2* gene and by redirecting pre-chondrogenic mesenchymal stem cells from an osteoblast fate to a non-osseous soft-tissue fate.

The safety and efficacy of palovarotene in FOP have been evaluated in:

- Study PVO-1A-201 (complete): a randomised, double-blind, placebo-controlled, multicentre phase II study evaluating the efficacy (percentage of responders, defined by no or minimal new HO at flare-up site, compared with Baseline as assessed by plain radiographs) and safety of palovarotene. Participants experiencing a flare-up were enrolled in two cohorts for which the cohort data were pooled:

- patients ≥15 years were randomised 3:1 to palovarotene 10/5 mg (Weeks 1-2/3-6) or placebo;
- patients ≥6 years were randomised 3:3:2 to palovarotene 10/5 mg, palovarotene 5/2.5 mg (Weeks 1–2/3–6), or placebo.

• Study PVO-1A-202 (complete): an open-label extension of Study 201 collecting additional flare-up outcome data and evaluating the long-term efficacy (annualised change in new HO volume as assessed by low-dose whole body computed tomography (WBCT), excluding head, in Part C) and safety of palovarotene in participants with FOP, consisting of three parts:
  - Part A: participants experiencing another flare-up received palovarotene 10/5 mg (2/4 weeks) (or the weight-based equivalent for participants with <90% skeletal maturity);
  - Part B: participants ≥90% skeletally mature received chronic 5 mg daily treatment with increased dosing at the time of a flare-up to 20 mg for 4 weeks followed by 10 mg for 8 weeks (chronic/flare-up regimen), with continuation of treatment in 4-week increments for persistent symptoms; skeletally immature participants received palovarotene 20/10 mg (4/8 weeks) flare-up treatment or the weight-based equivalent;
  - Part C: the dosing regimens in Part B continued for up to an additional 48 months with the exception that participants with <90% skeletal maturity received palovarotene 5 mg (or the weight-based equivalent) daily in addition to 20/10 mg palovarotene or the weight- based equivalent for flare-ups;
  - Part D: a 2-year safety follow-up for skeletally immature children who stopped palovarotene for any reason.
• Study PVO-1A-301 (MOVE, complete): a 24-month (Part A) with 24-month extension (Part B), multicentre, single treatment arm, open-label phase III study evaluating the efficacy (annualised change in new HO volume as assessed by low-dose WBCT, excluding head) and safety of palovarotene in participants with FOP aged 4 years and older:
  - Participants received palovarotene 5 mg daily with increased dosing at the time of a flare-up or a substantial high-risk traumatic event likely to lead to a flare-up to 20 mg once daily for 4 weeks, followed by 10 mg once daily for 8 weeks (chronic/flare-up regimen), with flare-up treatment extension in 4-week increments for persistent symptoms. Anytime during flare-up treatment, the 12-week treatment restarted if the participant had another flare-up or a substantial high-risk traumatic event;
  - Doses were weight-adjusted for skeletally immature participants; <90% skeletal maturity (assessed by knee/wrist radiography every 6 months, or every 3 months in participants who received flare-up treatment since last assessment and/or had not achieved 100% skeletal maturity at last assessment);
  - In interim analyses (data cut-off of 28 February 2020 for final interim analysis), data were compared with untreated participants enrolled in a 3-year, longitudinal, non-interventional natural history study (NHS) conducted to further evaluate the disease characteristics, natural progression of FOP and the impact of flare-ups;
  - Part C: a 2-year safety follow-up for skeletally immature children who stopped palovarotene for any reason.

Safety data from the FOP clinical studies reflect exposure to palovarotene in a total of 164 participants, including 139 participants aged 8 years and above for females and 10 years and above for males (≥8/10 years; the target population for the FOPal registry study) for a mean duration of 94.1 weeks, to a maximum of 3.8 years. Participants received either:

- Chronic/flare-up regimen: 5 mg daily dose of palovarotene with a 20/10 mg dose for 12 weeks at the time of flare-up (4 weeks of 20 mg once daily followed by 10 mg once daily for 8 weeks);
- Flare-up regimen of either the 20/10 mg dose for 12 weeks, a 10/5 mg dose for 6 weeks (10 mg once daily for 2 weeks followed by 5 mg once daily for 4 weeks) or a 5/2.5 mg dose for 6 weeks (5 mg once daily for 2 weeks followed by 2.5 mg once daily for 4 weeks).

In palovarotene-exposed participants aged ≥8/10 years, the most commonly reported adverse reactions were in the *Skin and subcutaneous disorders* (97.8%), *Gastrointestinal disorders* (75.5%) and *Infections and infestations* (48.9%) System Organ Classes (SOC).

CCI

[redacted]

Participants <18 years with open epiphyses were assessed for growth during the clinical studies. PPC was identified in 27 of 102 participants (26%) <18 years of age and was more common in younger (<8/10 years: 14 of 25 participants, 56%) compared with older (≥8/10 to <14 years: 13 of 39 participants, 33%; and ≥14 to <18 years: 0 of 38 participants, 0%) participants. In participants who received only chronic dosing, PPC, when observed, typically occurred between 12 and 18 months. The higher proportion of younger participants with PPC is not unexpected given that pre-adolescent individuals are not expected to have physiologic growth plate closure. Thus, any narrowing, partial closure, or closure are likely to be assessed as premature by the clinician. However, the possibility that younger participants are predisposed to developing PPC or are more sensitive to the effects of palovarotene cannot be excluded.

Palovarotene treatment is currently indicated for children aged 8 years and above for females and 10 years and above for males (or as per the approved indication in locally approved label). However, children between the ages of 4 years and 8/10 years were included in the clinical studies and exposed to palovarotene. The safety profile for palovarotene in participants with

FOP was consistent across adult (≥18 years) and paediatric (≥8/10 to <18 years) age subgroups except for epiphyses premature fusion. Some mucocutaneous effects such as decubitus ulcers had a higher incidence in adult participants, which was consistent with disease burden, increasing disability and prolonged exposure to corticosteroids.

Radiological vertebral fractures (PT: Spinal fracture) were identified as a risk associated with palovarotene based on retrospective analyses performed on WBCT data in participants with FOP in the Phase 3 (MOVE) study.

No pregnancies were reported during the clinical development programme.

Ipsen will implement an observational, prospective and retrospective registry study, which is intended primarily to collect and assess real-world safety data on paediatric and adult participants with FOP exposed to palovarotene and secondly to describe the effectiveness of this treatment, including its effect on physical function. In addition, this study aims to descriptively compare key safety outcomes between participants with FOP exposed and unexposed to palovarotene.

Research Question and Objectives

The aim of the FOPal registry study is primarily to collect and assess real-world safety data on paediatric and adult participants with FOP exposed to palovarotene and secondly to describe the effectiveness of palovarotene in exposed participants, including its effect on physical function. In addition, this study aims to descriptively compare key safety outcomes (i.e. flare-up episodes, growth and bone fractures) between exposed and unexposed participants.

Primary objective:

To collect and assess real-world safety data in participants with FOP exposed to palovarotene.

Secondary objectives

For participants with FOP exposed and unexposed to palovarotene:

- To describe the range of motion (ROM) as assessed by the Cumulative Analogue Joint Involvement Scale (CAJIS) for FOP;
- To describe the use of assistive devices and adaptations for daily living;
- To describe the physical function using age-appropriate forms of the Fibrodysplasia Ossificans Progressiva-Physical Function Questionnaire (FOP-PFQ);
- To describe the parameters of lung function (observed and % predicted forced vital capacity (FVC), observed and % predicted forced expiratory volume in one second (FEV_1), absolute and % predicted FEV_1/FVC ratio, observed and % predicted diffusion capacity of the lung for carbon monoxide (DLCO)) at Baseline and over time;
- To describe the physical and mental health (participants ≥15 years old) and overall quality of life (QoL) (participants <15 years old) using age-appropriate forms of the Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health Scale;
- To describe the flare-up frequency;
- To describe any movement mobility change by body location and annually;
- To describe the number of locations impacted by movement mobility change per participant annually;
- To describe the movement mobility outcomes (change in extra bone growth and change in movement), causes and associated symptoms if preceded by a flare-up event by body

location;

- To describe the frequency, severity, outcome and descriptive details of any fracture (including bone fractures and vertebral fractures)
- To describe the incidence of pregnancy.

For participants with FOP exposed to palovarotene who become pregnant while enrolled in FOPal:

- To describe pregnancy characteristics and outcomes;
- To describe pregnancy-related AEs through the first year postpartum;
- To describe birth and developmental outcomes through the infant(s)' first year of life.

For growing children with FOP exposed and unexposed to palovarotene:

- To describe linear height and knee height velocities until skeletal maturity or final adult height is reached;
- To describe linear height z-scores until skeletal maturity or final adult height is reached;
- To describe the difference between chronological age and bone age;
- To describe the frequency, severity and descriptive details of PPC.

For participants with FOP exposed to palovarotene:

- To describe the use (dose and frequency) of palovarotene in the real-world setting.

Registry Study Design

FOPal is an observational, prospective and retrospective registry study designed to collect and assess real-world safety data on paediatric and adult participants with FOP exposed to palovarotene and secondly to describe the effectiveness of palovarotene in exposed participants, including its effect on physical function. Additionally, key safety outcomes (i.e. flare-up episodes, growth, and bone fractures) will be descriptively compared in participants with FOP exposed and unexposed to palovarotene enrolled in the FOPal registry.

Exposed and unexposed participants will be recruited in countries/sites willing to participate and where palovarotene is registered/marketed.

For exposed participants, the decision to prescribe palovarotene will be made prior to and independently of the decision to enrol the participants in the FOPal registry study. Palovarotene has to be prescribed by their treating physician, as per local label.

There will be a Study Steering Committee and a Publications Steering Committee. The Study Steering Committee should be composed of investigators, external clinical experts not directly involved in the registry and staff from the sponsor with the primary objective of assessing the study quality and conduct, as well as for the scientific quality of the final study report. The Publications Steering Committee should be composed of external experts (clinicians and scientists), patients and representatives of patient associations with the primary objective of driving publications.

Population

Paediatric and adult participants with FOP who are enrolled in the FOPal registry and have received at least one dose of palovarotene, prescribed as per local label, by their treating physician will be included in the palovarotene-exposed cohort.

Paediatric and adult participants with FOP who are enrolled in the FOPal registry and have never received palovarotene, will be included in the palovarotene-unexposed cohort.

Palovarotene-exposed cohort

Inclusion criteria:

To be included in the palovarotene-exposed cohort, the participants should fulfil all the following inclusion criteria:

(1) Paediatric (8 years to less than 18 years of age for girls and 10 years to less than 18 years of age for boys) and adult participants with FOP who have been prescribed palovarotene (prior to and independently of the decision to enrol the patient in the FOPal registry study) by their treating physician, as per local label;

(2) Signed informed consent as per local regulations must be obtained and maintained. Consent/assent from the participant should be obtained as appropriate before any registry study data collection is conducted. If applicable, parents or legally authorised representatives must give signed informed consent.

Exclusion criteria:

Participants will not be included in the palovarotene-exposed cohort if:

(1) Currently participating in any interventional clinical trial;

(2) Palovarotene is contraindicated as per the locally approved label (except for pregnant participants who have previously received and discontinued palovarotene at any time during the pregnancy and who will be included for safety follow-up).

Palovarotene-unexposed cohort

Inclusion criteria:

To be included in the palovarotene-unexposed cohort, the participants should fulfil all the following inclusion criteria:

(1) Paediatric (8 years to less than 18 years of age for girls and 10 years to less than 18 years of age for boys) and adult participants with FOP never treated with palovarotene;

(2) Signed informed consent as per local regulations must be obtained and maintained. Consent/assent from the participant should be obtained as appropriate before any registry study data collection is conducted. If applicable, parents or legally authorised representatives must give signed informed consent.

Exclusion criteria:

Participants will not be included in the palovarotene-unexposed cohort if:

(1) Currently participating in any interventional clinical trial;

(2) Previously received palovarotene, other synthetic oral retinoids, or any disease modifying therapy for the reduction of heterotopic ossification.

Variables

Participants will be followed in accordance with usual medical practice during their participation in the FOPal registry study. No additional assessments or tests will be required by this protocol. As this is an observational registry study, if some assessments are not routinely performed by the investigator, they will not complete the corresponding sections in the electronic Case Report Form (eCRF).

Relevant data collected as part of routine medical care will be captured in the eCRF by the investigator. These data will be transmitted to the sponsor for analysis. Data transmitted will be pseudonymised and will be identified by a participant number.

Data will be collected at the Baseline Visit and at each Follow-up Visit (scheduled as per routine clinical practice*).

**Follow-up Visits are recommended every 6 months, or as per local label.*

The Baseline Visit should ideally be a clinic visit but all visits can be performed by either telephone/video contact or by clinic visit as per the investigator's judgement.

The investigator must ensure that the participant receives appropriate medical follow-up and this should be properly documented in the participant's medical records and eCRFs regarding:

- AEs or their sequelae (any AE, based on the investigator's opinion, not only those assessed as related) that persist after the date of palovarotene discontinuation for exposed participants.
- Medical events of special interest (growth outcomes, including PPC, and fractures) for unexposed participants for the entire study duration.

The FOPal registry captures individual participants' data including demographics and baseline characteristics, FOP history, treatment information, body height and weight, safety variables, effectiveness variables and treatment variables.

Endpoints

Primary safety endpoints are:

- Incidence and description of all treatment-emergent adverse events (TEAEs), whether or not they are considered as related to palovarotene;
- Incidence and description of all serious TEAEs, whether or not they are considered as related to palovarotene;
- Incidence and description of all nonserious TEAEs whether or not they are considered as related to palovarotene;
- Incidence and description of all serious and nonserious treatment-related TEAEs.

Secondary endpoints are:

For participants with FOP exposed and unexposed to palovarotene:

- Raw values and change from Baseline in CAJIS total score at each Follow-up Visit;
- Raw values and shift from Baseline in use of assistive devices and adaptations for daily living at each Follow-up Visit;
- Raw values and change from Baseline in % of worst score for total score, upper extremities subscore and mobility subscore using age-appropriate forms of the FOP-PFQ at each Follow-up Visit;
- Raw values and change from Baseline in observed and % predicted FVC at each Follow-up Visit;
- Raw values and change from Baseline in observed and % predicted FEV_1 at each Follow-up Visit;
- Raw values and change from Baseline in absolute and % predicted FEV_1/FVC ratio at each Follow-up Visit;
- Raw values and change from Baseline in observed and % predicted DLCO at each Follow-up Visit;
- Raw values and change from Baseline in physical and mental function (mean global physical and mental health score converted into T-scores) for participants ≥15 years old and overall QoL (mean total score converted into T-scores) for participants <15 years old using age-appropriate forms of PROMIS Global Health Scale at each Follow-up Visit;

- Annualised frequency of flare-ups, categorised by overall occurrence;
- Number of locations impacted by movement mobility change per participant, annually and change from Baseline;
- Any movement mobility change (better movement/the same movement/slightly worse movement/moderately worse movement/severely worse movement) by body location and annually;
- Evolution of locations impacted by movement mobility change (how many times a location is impacted) per body location, annually and change from baseline;
- Movement mobility outcomes (change in extra bone growth and change in movement), causes, associated symptoms if preceded by a flare-up event by body location;
- Frequency, severity, outcome and descriptive characteristics of any fractures, overall and at each Follow-up Visit, categorised by location;
- Annualised frequency and descriptive characteristics of bone fractures, categorised by overall occurrence and location;
- Incidence of pregnancy.

For participants with FOP exposed to palovarotene who become pregnant while enrolled in FOPal:

- Pregnancy characteristics and outcomes;
- Pregnancy-related AEs through the first year postpartum;
- Birth and developmental outcomes through the infant(s)' first year of life.

For growing children with FOP exposed and unexposed to palovarotene:

- Raw values and change from Baseline in linear height and knee height velocity at each Follow-up Visit until skeletal maturity or final adult height is reached;
- Baseline linear height z-scores and change from Baseline at each Follow-up Visit until skeletal maturity or final adult height is reached;
- Mean difference between chronological age and bone age at each Follow-up Visit;
- Frequency, severity and descriptive details of PPC overall and at each Follow-up Visit.

For participants with FOP exposed to palovarotene:

- Mean dose/year for chronic treatment;
- Mean dose/cycle for flare-up treatment.

Data Sources

Source data includes any data collected as part of routine medical care which will be captured in an eCRF by the investigator and transmitted to the sponsor for analysis. The patient-reported questionnaires (FOP-PFQ, PROMIS Global Health Scale and FOP assistive devices assessment) will be completed directly by the participant on paper.

Registry Study Size

The FOPal registry study aims to enrol a minimum of 67 participants with FOP treated with palovarotene and 33 participants with FOP not treated with palovarotene. Approximately half of the participants in each cohort (exposed and unexposed) will be paediatric (8 years to less than 18 years of age for girls and 10 years to less than 18 years of age for boys).

Data Analysis

Analyses will be primarily descriptive.

Descriptive summary statistics will include mean, standard deviation, 95% confidence intervals (CI) of the mean/median, median, minimum, maximum, or frequency counts of the data collected. Percentages will be based on the number of non-missing observations.

Missing data will not be replaced but will be summarised in all relevant tables.

Subgroup analyses will be performed by age group and gender. Additional subgroup analysis may be conducted as required.

To descriptively compare the key safety outcomes, the Safety Exposed Population will be matched with the Safety Unexposed Population. To minimise potential selection bias resulting from differences between these two cohorts, the propensity score (PS) method will be used. Estimates and 95% confidence intervals (CI) will be reported.

Milestones

Up to 11 years of FOPal study duration, with an enrolment period of maximum 10 years from first participant, first visit and a minimum of 1 year of data collected for participants who are enrolled within that period.

Participant enrolment will start from the date of commercial palovarotene availability in the given country for exposed participants, and once the investigational site has been activated for all participants.

Start of data collection: Q4 2024 (in Canada).

Planned end of data collection: Q4 2035.


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6 MILESTONES

Milestone	Planned date
Start of data collection	Once palovarotene is reimbursed/participants have access to commercial product and the first site is activated to enrol. Q4 2024 (in Canada)
End of data collection	Up to 11 years following start of data collection. Planned Q4 2035
Interim report	As required, for publication purposes.
Final report of registry study results	Planned January 2037

7 RATIONALE AND BACKGROUND

7.1 Disease Background

Fibrodysplasia ossificans progressive (FOP; Online Mendelian Inheritance in Man (OMIM) #135100) is an ultra-rare genetic disorder, with an estimated prevalence of 1.36 per million individuals [1]; however, the number of confirmed cases varies by country [2, 3]. FOP affects all races and there is no ethnic, sex-linked or geographic predisposition [4, 5]. Median patient age at time of FOP diagnosis is 6.4 years [1].

FOP is caused by a spontaneous missense mutation in the activin A receptor type 1 *(ACVR1)*/activin receptor-like-kinase-2 (*ALK2*) gene, which encodes a receptor in the bone morphogenetic protein (BMP) signalling pathway [4, 5]. BMPs are extracellular ligands belonging to the TGF-β superfamily [6, 7]. Signal transduction studies show that receptor-regulated Smad proteins 1/5/8 are the immediate downstream molecules of BMP receptors and play a central role in BMP signal transduction [6, 7].

Upon ligand binding to BMP receptors, there is a downstream activation of genes involved in the differentiation and activation of osteoblast and chondrocyte-like cells via phosphorylation of Smad proteins 1/5/8 [6, 7]; this is regulated by the inhibitory factor FKBP12, which binds to the BMP type I receptor and stabilises the inactive form [6, 7].

Most patients with FOP have classic FOP (~97%), but a minority are affected by non-classic FOP (~3%) [5]. In classic FOP, approximately 90% of patients carry the same specific *ACVR1/ALK2* pathogenic variant (c.617G>A; p.R206H) in the glycine and serine activation domain of the gene [8-15]. In the presence of the pathogenic variant of the *ACVR1/ALK2* gene, FKBP12 binding is reduced, leading to enhanced BMP signalling [7]. FOP diagnosis is clinical but requires genetic confirmation [4, 16].

Patients with FOP experience sporadic and unpredictable episodes of soft-tissue swelling, pain, reduced movement, stiffness and fever, referred to as “flare-ups” [4, 16–18]. Flare-ups appear spontaneously or after muscle fatigue, minor trauma, intramuscular injections or influenza-like viral illnesses and develop rapidly over several hours [17]; these inciting events induce local inflammation, which is followed by recruitment of bone progenitor cells that differentiate into chondrocytes [19]. Although some flare-ups regress spontaneously, many appear to lead to heterotopic ossification (HO), which transforms soft and connective tissues (including aponeuroses, fascia, ligaments, tendons and skeletal muscles) into heterotopic bone [4, 17]. Of patients with FOP, 95% manifest HO before reaching 15 years of age [20].

Fibrodysplasia ossificans progressive is characterised by congenital malformation of the great toes and progressive HO in soft and connective tissues; it is a severely disabling HO disorder [1, 18]. Other clinical features observed in patients with FOP are shortened thumbs, cervical spine malformations, short broad femoral necks and proximal medial tibial osteochondromas [4, 9]. Typically, HO begins in the dorsal, proximal, axial and cranial regions of the body (neck, shoulders and back) and progresses into ventral, caudal and distal regions (trunk and limbs) [8]. HO develops into ribbons, sheets and plates of extra bone throughout the body and across joints, thereby progressively restricting movement [1]. Once ossification occurs, it is permanent; consequently, disability in FOP is cumulative, with most patients becoming immobilised and confined to a wheelchair by their third decade of life and requiring lifelong assistance in performing activities of daily living [1, 4, 21–23].

Fibrodysplasia ossificans progressive is not only an extremely disabling disease but also a condition of considerably shortened lifespan [24]. Morbidity associated with FOP includes fractures (due to the increased risk of falls, immobility and prednisone use), limb swelling, pressure sores, hearing impairment, gastrointestinal issues [25] and pain [26]. Patients with FOP

reach a median survival of 56 (95% CI: 51; 60) years; death is often due to cardiorespiratory failure (as a result of respiratory insufficiency, which is usually caused by progressive restrictive chest-wall HO) or thrombosis [1, 4, 16, 24].

Misdiagnosis and delayed diagnosis contribute to the accumulation of disability in patients with FOP. There is often a delay in the diagnosis of FOP because of lack of physician awareness and inadequate description in most medical textbooks [4, 27]. The median delay from onset of symptoms to the correct diagnosis is 1.1 years (range: <1 month to 49 years), after consultation with a median of six different healthcare professionals [27]. FOP is misdiagnosed in up to 87% of individuals, with the most common incorrect diagnoses including cancer, aggressive juvenile fibromatosis, ankylosing spondylitis and bunions [4, 27].

Until recently, there were no effective treatments to reduce the formation of heterotopic bone in FOP, with therapeutic approaches being limited to symptom management and flare-up prevention [17, 28]; consequently, as well as an imperative to improve early diagnosis and to reduce iatrogenic harm, there is a critical unmet need for definitive therapies for patients with FOP [27, 29].

7.2 Treatment Background

Palovarotene is being developed by Ipsen for the treatment of FOP. Palovarotene was first approved by Health Canada for the treatment of patients with FOP in adults and children aged 8 years and above for females and 10 years and above for males with FOP. Palovarotene is an orally bioavailable retinoic acid receptor gamma (RARγ) selective agonist.

Retinoic acid receptor gamma is a nuclear hormone receptor that has a role in regulating skeletal development and growth; it is expressed in chondrogenic cells and chondrocytes [30], where it operates as a transcriptional repressor [31]. Activation of the retinoid signalling pathway and RARγ has been demonstrated to inhibit both chondrogenesis and HO [29]. Given that chondrogenesis requires a decrease in retinoid signalling concurrent with upregulation of pro-chondrogenic pathways, including BMP signalling [32, 33], RARγ agonists are likely to elicit anti-chondrogenic and anti-HO effects by maintaining retinoid signalling while reducing BMP signalling [19].

Retinoic acid receptor gamma agonists potently impede heterotopic endochondral ossification by inhibiting downstream effectors (namely Smad 1/5/8) of the mutated *ACVR1/ALK2* gene and by redirecting pre-chondrogenic mesenchymal stem cells from an osteoblast fate to a non-osseous soft-tissue fate [19, 34].

7.3 Safety and Efficacy of Palovarotene

The safety and efficacy of palovarotene in FOP have been evaluated in:

- Study PVO-1A-201 (complete): a randomised, double-blind, placebo-controlled, multicentre phase II study evaluating the efficacy (percentage of responders, defined by no or minimal new HO at flare-up site, compared with Baseline as assessed by plain radiographs) and safety of palovarotene. Participants experiencing a flare-up were enrolled in two cohorts for which the cohort data were pooled:
  - patients ≥15 years were randomised 3:1 to palovarotene 10/5 mg (Weeks 1-2/3-6) or placebo;
  - patients ≥6 years were randomised 3:3:2 to palovarotene 10/5 mg, palovarotene 5/2.5 mg (Weeks 1–2/3–6), or placebo.
- Study PVO-1A-202 (complete): an open-label extension of Study 201 collecting additional flare-up outcome data and evaluating the long-term efficacy (annualised change in new HO volume as assessed by low-dose whole body computed tomography

(WBCT), excluding head, in Part C) and safety of palovarotene in participants with FOP, consisting of three parts:

- Part A: participants experiencing another flare-up received palovarotene 10/5 mg (2/4 weeks) (or the weight-based equivalent for participants with <90% skeletal maturity);
- Part B: participants ≥90% skeletally mature received chronic 5 mg daily treatment with increased dosing at the time of a flare-up to 20 mg for 4 weeks followed by 10 mg for 8 weeks (chronic/flare-up regimen), with continuation of treatment in 4-week increments for persistent symptoms; skeletally immature participants received palovarotene 20/10 mg (4/8 weeks) flare-up treatment or the weight-based equivalent;
- Part C: the dosing regimens in Part B continued for up to an additional 48 months with the exception that participants with <90% skeletal maturity received palovarotene 5 mg (or the weight-based equivalent) daily in addition to 20/10 mg palovarotene or the weight- based equivalent for flare-ups;
- Part D: a 2-year safety follow-up for skeletally immature children who stopped palovarotene for any reason.

• Study PVO-1A-301 (MOVE, complete): a 24-month (Part A) with 24-month extension (Part B), multicentre, single treatment arm, open-label phase III study currently evaluating the efficacy (annualised change in new HO volume as assessed by low-dose WBCT, excluding head) and safety of palovarotene in participants with FOP aged 4 years and older:

- Participants received palovarotene 5 mg daily with increased dosing at the time of a flare-up or a substantial high-risk traumatic event likely to lead to a flare-up to 20 mg once daily for 4 weeks, followed by 10 mg once daily for 8 weeks (chronic/flare-up regimen), with flare-up treatment extension in 4-week increments for persistent symptoms. Anytime during flare-up treatment, the 12- week treatment restarted if the participant had another flare-up or a substantial high-risk traumatic event;
- Doses were weight-adjusted for skeletally immature participants; <90% skeletal maturity (assessed by knee/wrist radiography every 6 months, or every 3 months in participants who received flare-up treatment since last assessment and/or had not achieved 100% skeletal maturity at last assessment);
- In interim analyses (data cut-off of 28 February 2020 for final interim analysis), data were compared with untreated participants enrolled in a 3-year, longitudinal, non-interventional natural history study (NHS) conducted to further evaluate the disease characteristics, natural progression of FOP and the impact of flare-ups;
- Part C: a 2-year safety follow-up for skeletally immature children who stopped palovarotene for any reason.

7.3.1 Safety Profile of Palovarotene

Safety data from the FOP clinical studies reflect exposure to palovarotene in a total of 164 participants, including 139 participants aged 8 years and above for females and 10 years and above for males (≥8/10 years; the target population for the FOPal registry study) for a mean duration of 94.1 weeks, to a maximum of 3.8 years. Participants received either:

- Chronic/flare-up regimen 5 mg daily dose of palovarotene with a 20/10 mg dose for 12 weeks at the time of flare-up (4 weeks of 20 mg once daily followed by 10 mg once daily for 8 weeks);
- Flare-up regimen of either the 20/10 mg dose for 12 weeks, a 10/5 mg dose for 6 weeks (10 mg once daily for 2 weeks followed by 5 mg once daily for 4 weeks) or a 5/2.5 mg dose for 6 weeks (5 mg once daily for 2 weeks followed by 2.5 mg once daily for 4 weeks).

In palovarotene-exposed participants aged ≥8/10 years, the most commonly reported adverse reactions were in the *Skin and subcutaneous disorders* (97.8%), *Gastrointestinal disorders* (75.5%) and *Infections and infestations* (48.9%) System Organ Classes (SOC).

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Participants <18 years with open epiphyses were assessed for growth during the clinical studies. PPC was identified in 27 of 102 participants (26%) <18 years of age and was more common in younger (<8/10 years: 14 of 25 participants, 56%) compared with older (≥8/10 to <14 years: 13 of 39 participants, 33%; and ≥14 to <18 years: 0 of 38 participants, 0%) participants. In participants who received only chronic dosing, PPC, when observed, typically occurred between 12 and 18 months. The higher proportion of younger participants with PPC is not unexpected given that pre-adolescent individuals are not expected to have physiological growth plate closure. Thus, any narrowing, partial closure, or closure are likely to be assessed as premature by the clinician. However, the possibility that younger participants are predisposed to developing PPC or are more sensitive to the effects of palovarotene cannot be excluded.

Palovarotene treatment is currently indicated for children aged 8 years and above for females and 10 years and above for males (or as per the approved indication in locally approved label). However, children between the ages of 4 years and 8/10 years were included in the clinical studies and exposed to palovarotene. The safety profile for palovarotene in participants with

FOP was consistent across adult (≥18 years) and paediatric (≥8/10 to <18 years) age subgroups except for epiphyses premature fusion. Some mucocutaneous effects such as decubitus ulcers had a higher incidence in adult participants, which was consistent with disease burden, increasing disability and prolonged exposure to corticosteroids.

Radiological vertebral fractures (PT: Spinal fracture) were identified as a risk associated with palovarotene based on retrospective analyses performed on WBCT data in participants with FOP in the Phase 3 (MOVE) study.

No pregnancies were reported during the clinical development programme.

7.3.2 Efficacy of Palovarotene

The phase III study, PVO-1A-301, evaluated the efficacy and safety of the chronic/flare-up palovarotene treatment regimen in reducing new HO as compared with data from the NHS, Study PVO-1A-001. The NHS was an international, 3-year, longitudinal, non-interventional study in 114 participants with FOP with R206H mutation; 98 participants provided at least one post-baseline assessment. All WBCT images from treated participants in Study PVO-1A-301 and untreated participants in the NHS were read in a manner blinded to study origination. Of the 107 participants enrolled in Study PVO-1A-301, 99 had the R206H mutation and 8 had other FOP mutations. Of the 99 with the R206H mutation, 97 had at least one post-baseline HO volume measurement and were included in the Full Analysis Set. The treatment groups assessed in the chronic/flare-up regimen were well matched for baseline demographics.

The median age (range) of participants in the overall population in the palovarotene group (N=99) and in the untreated group (N=111) was 13 (4, 61) and 15 (4, 56) years, respectively. There were more male than female participants in both the palovarotene (53.5% and 46.5%, respectively) and untreated (54.1% and 45.9%, respectively) groups.

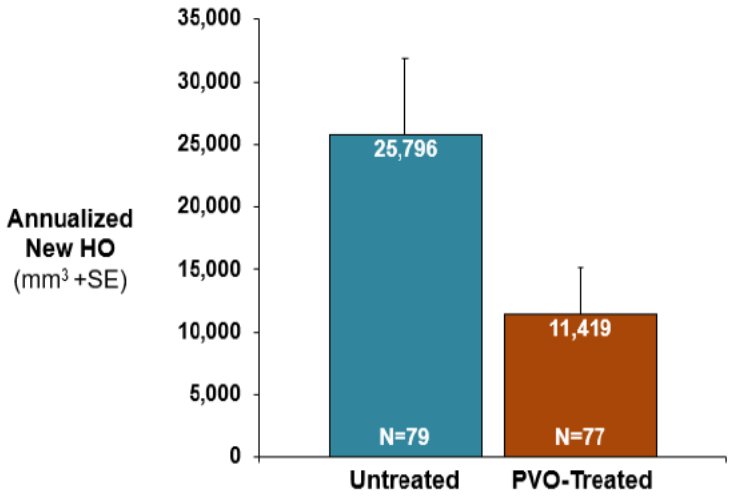
Post-hoc analyses showed that mean annualised new HO volume in the overall population was 60% lower in participants receiving the chronic/flare-up palovarotene regimen (9427 mm^3) versus untreated participants from the NHS (23 720 mm^3).

The weighted linear mixed effects (wLME) analysis showed 54% lower fitted mean annualised new HO volume in palovarotene-treated participants (9367 mm^3) versus untreated participants in the NHS (20 273 mm^3) yielding 2-sided nominal p-value p=0.0392.

The median age (range) of participants in the target ≥8/10 years population in the palovarotene group (N=79) and in the untreated group (N=88) was 14 (8, 61) and 18 (9, 56) years, respectively. There were more male than female participants in both the palovarotene (54.4% and 45.6%, respectively) and untreated (51.1% and 48.9%, respectively) groups.

The mean annualised new HO volume in the target ≥8/10 years population in palovarotene-treated and untreated participants is shown in Figure 1 . Results were similar to the overall population, with the mean annualised new HO volume in palovarotene-treated participants (11 419 mm^3) 56% lower than that observed in untreated participants (25 796 mm^3). The wLME analysis showed 49% lower fitted mean annualised new HO volume in palovarotene-treated participants (11 033 mm^3) versus untreated participants in the NHS (21 476 mm^3), yielding 2-sided nominal p-value p=0.1124.

Figure 1 Mean Annualised New HO Volume in Study PVO-1A-301 (≥8/10 years)



HO=heterotopic ossification; SE=standard error.

Note: Figure summarises mean observed annualised new HO.

7.4 Registry Study Rationale

Ipsen will implement an observational, prospective and retrospective registry study, which is intended primarily to collect and assess real-world safety data on paediatric and adult participants with FOP exposed to palovarotene and secondly to describe the effectiveness of this treatment, including its effect on physical function. In addition, this study aims to descriptively compare key safety outcomes between participants with FOP exposed and unexposed to palovarotene enrolled in the FOPal registry.

8 RESEARCH QUESTION AND OBJECTIVES

8.1 Research Question

The aim of the FOPal registry study is primarily to collect and assess real-world safety data on paediatric and adult participants with FOP exposed to palovarotene and secondly to describe the effectiveness of palovarotene in exposed participants, including its effect on physical function. In addition, this study aims to descriptively compare key safety outcomes (i.e. flare-up episodes, growth and bone fractures) between exposed and unexposed participants.

8.2 Objectives

8.2.1 Primary Objective

To collect and assess real-world safety data in participants with FOP exposed to palovarotene.

8.2.2 Secondary Objectives

For participants with FOP exposed and unexposed to palovarotene:

- To describe the range of motion (ROM) as assessed by the Cumulative Analogue Joint Involvement Scale (CAJIS) for FOP;
- To describe the use of assistive devices and adaptations for daily living;
- To describe the physical function using age-appropriate forms of the Fibrodysplasia Ossificans Progressiva-Physical Function Questionnaire (FOP-PFQ);
- To describe the parameters of lung function (observed and % predicted forced vital capacity (FVC), observed and % predicted forced expiratory volume in one second (FEV_1), absolute and % predicted FEV_1/FVC ratio, observed and % predicted diffusion capacity of the lung for carbon monoxide (DLCO)) at Baseline and over time;
- To describe the physical and mental health (participants ≥15 years old) and overall quality of life (QoL) (participants <15 years old) using age-appropriate forms of the Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health Scale;
- To describe the flare-up frequency;
- To describe any movement mobility change by body location and annually;
- To describe the number of locations impacted by movement mobility change per participant annually;
- To describe the movement mobility outcomes (change in extra bone growth and change in movement), causes and associated symptoms if preceded by a flare-up event by body location;
- To describe the frequency, severity, outcome and descriptive details of any fractures (including bone fracture and vertebral fractures).
- To describe the incidence of pregnancy.

For participants with FOP exposed to palovarotene who become pregnant while enrolled in FOPal:

- To describe pregnancy characteristics and outcomes;
- To describe pregnancy-related AEs through the first year postpartum;
- To describe birth and developmental outcomes through the infant(s)' first year of life.

For growing children with FOP exposed and unexposed to palovarotene:

- To describe linear height and knee height velocities until skeletal maturity or final adult height is reached;
- To describe linear height z-scores until skeletal maturity or final adult height is reached;
- To describe the difference between chronological age and bone age;
- To describe the frequency, severity and descriptive details of PPC.

For participants with FOP exposed to palovarotene:

- To describe the use (dose and frequency) of palovarotene in the real-world setting.

9 RESEARCH METHODS

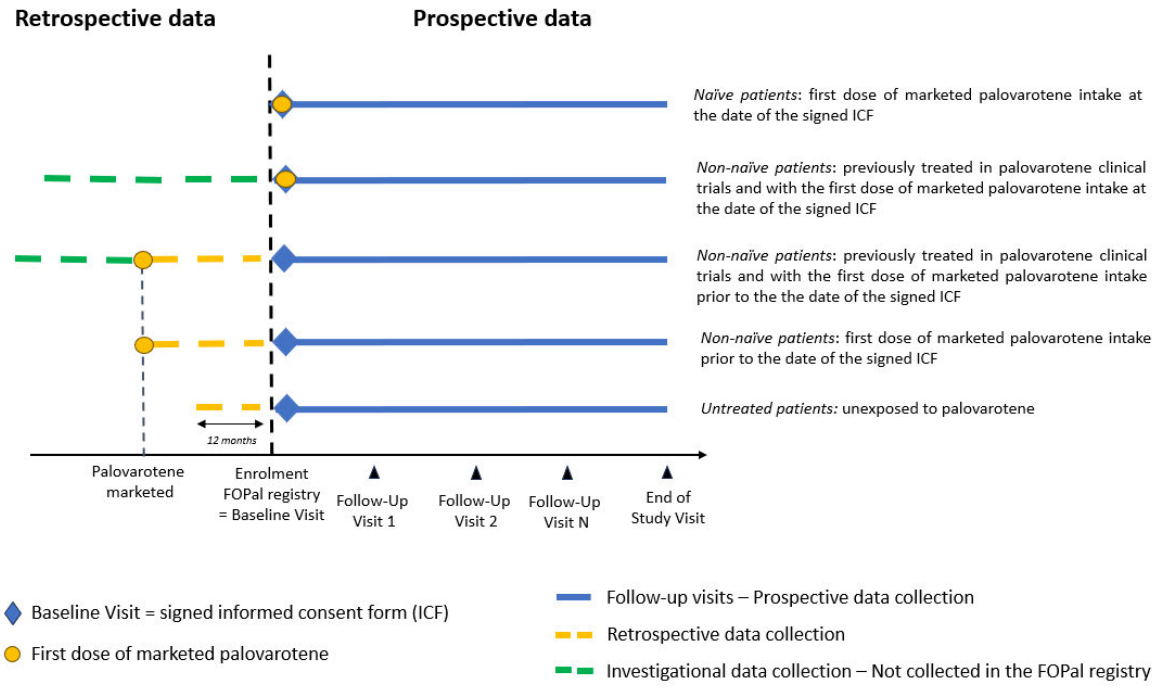
9.1 Registry Study Design

FOPal is an observational, prospective and retrospective registry study designed to collect and assess real-world safety data on paediatric and adult participants with FOP exposed to palovarotene and secondly to describe the effectiveness of palovarotene in exposed participants. Additionally, key safety outcomes (i.e. flare-up episodes, growth and bone fractures) will be descriptively compared in participants with FOP exposed and unexposed to palovarotene enrolled in the FOPal registry.

Exposed and unexposed participants will be recruited in countries/sites willing to participate and where palovarotene is registered/marketed. For exposed participants, the decision to prescribe palovarotene will be made prior to and independently of the decision to enrol the patient in the FOPal registry study.

Participants who started palovarotene treatment before the implementation of the registry study in their country may also be enrolled. All participants who received at least one dose of palovarotene treatment before enrolling in the registry study (i.e. signing the informed consent) will be considered non-naïve. In such context, some data will be collected retrospectively from the first dose of marketed palovarotene intake. A schematic representation of the different data collection scenarios is shown Figure 2.

Figure 2 Schematic representation of the different scenarios applied for prospective and retrospective data collection from participants enrolled in the FOPal registry



The schedule of assessments in Table 2 and Table 3 describes the type of data collected for exposed naïve and non-naïve participants, respectively, from the first dose of marketed palovarotene intake. The schedule of assessments in Table 4 describes the type of data collected for unexposed participants from up to 12 months before the ICF signature. The details are described in the Section 9.2.7.

As this is a non-interventional, observational registry study designed to collect and assess real-world data, exposed participants will receive palovarotene as prescribed by their treating physician, as per local label. Palovarotene will be supplied to the participant according to usual practice, not by the sponsor.

In addition, participants will be treated in accordance with usual medical practice during their participation in the FOPal registry study. No additional assessments or tests will be required by this protocol. All relevant data collected as part of routine medical care will be captured using the electronic Case Report Form (eCRF) by the investigator (patient-reported questionnaires will be completed directly by the participant on paper and returned to the site for data entry into the eCRF) and transmitted to the sponsor. If some assessments are not routinely performed by the investigator, they will not complete the corresponding sections in the eCRF.

The FOPal registry study will collect data at Baseline and at each Follow-up Visit. Follow-up Visits are scheduled as per routine clinical practice (recommended every 6 months).

The duration of the FOPal registry study is up to 11 years, with an enrolment period of maximum 10 years from first participant, first visit, and a minimum of 1 year of data collected for participants who are enrolled within that period.

The primary objective of the FOPal registry study is to collect and assess real-world safety data in participants with FOP exposed to palovarotene, to permit the description and incidence of all treatment-emergent adverse events (TEAEs), serious TEAEs and nonserious TEAEs, whether or not they are considered related to palovarotene and all serious and nonserious treatment-related TEAEs.

Secondary objectives include collecting real-world data to describe the effectiveness of palovarotene on ROM, use of assistive devices and adaptations for daily living, physical function, lung function and physical and mental health (or overall QoL in participants <15 years old). Specifically, any movement mobility change, the number of impacted locations and the movement mobility outcomes will also be described, as well as the use of palovarotene (dose, frequency) in the real-world setting. Incidence of pregnancy, outcomes of pregnancies, AEs related to pregnancy through the first year postpartum and birth and developmental outcomes through the infant(s)' first year of life will be described.

There will be a Study Steering Committee and a Publications Steering Committee. The Study Steering Committee should be composed of investigators, external clinical experts not directly involved in the registry and staff from the sponsor with the primary objective of assessing the study quality and conduct, as well as for the scientific quality of the final study report. The Publications Steering Committee should be composed of external experts (clinicians and scientists), patients and representatives of patient associations with the primary objective of driving publications.

9.2 Setting

Paediatric and adult participants with FOP who are enrolled in the FOPal registry and have received at least one dose of palovarotene, prescribed as per local label, by their treating physician will be included in the palovarotene-exposed cohort. Paediatric and adult participants with FOP who are enrolled in the FOPal registry and have never received palovarotene, will be included in the palovarotene-unexposed cohort.

Individuals who do not meet the criteria for participation in the FOPal registry study (screen failure) or who withdraw their consent may be rescreened. Rescreened participants should be assigned a new participant number. The informed consent process is described in Section 9.13.

9.2.1 Palovarotene-exposed Cohort

9.2.1.1 Inclusion Criteria

To be included in the palovarotene-exposed cohort, the participants should fulfil all the following inclusion criteria:

(1) Paediatric (8 years to less than 18 years of age for girls and 10 years to less than 18 years of age for boys) and adult participants with FOP who have been prescribed palovarotene (prior to and independently of the decision to enrol the patient in the FOPal registry study) by their treating physician, as per local label;

(2) Signed informed consent as per local regulations must be obtained and maintained. Consent/assent from the participant should be obtained as appropriate before any registry study data collection is conducted. If applicable, parents or legally authorised representatives must give signed informed consent.

9.2.1.2 Exclusion Criteria

Participants will not be included in the palovarotene-exposed cohort if:

(1) Currently participating in any interventional clinical trial;

(2) Palovarotene is contraindicated as per the locally approved label (except for pregnant participants who have previously received and discontinued palovarotene at any time during the pregnancy and who will be included for safety follow-up).

9.2.2 Palovarotene-unexposed Cohort

9.2.2.1 Inclusion Criteria

To be included in the palovarotene-unexposed cohort, the participants should fulfil all the following inclusion criteria:

(1) Paediatric (8 years to less than 18 years of age for girls and 10 years to less than 18 years of age for boys) and adult participants with FOP untreated with palovarotene;

(2) Signed informed consent as per local regulations must be obtained and maintained. Consent/assent from the participant should be obtained as appropriate before any registry study data collection is conducted. If applicable, parents or legally authorised representatives must give signed informed consent.

9.2.2.2 Exclusion Criteria

Participants will not be included in the palovarotene-unexposed cohort if:

(1) Currently participating in any interventional clinical trial;

(2) Previously received palovarotene, other synthetic oral retinoids, or any disease modifying therapy for the reduction of heterotopic ossification.

9.2.3 Registry Study Population

Paediatric and adult participants with FOP who are enrolled in the FOPal registry and have received at least one dose of palovarotene, prescribed, as per local label, by their treating physician will be included in the palovarotene-exposed cohort. Participants never treated with palovarotene will be included in the palovarotene-unexposed cohort.

To be enrolled, participants must comply with all the inclusion criteria (Section 9.2.1.1 and Section 9.2.2.1 for the palovarotene-exposed and unexposed cohorts, respectively) and exclusion criteria (Section 9.2.1.2 and Section 9.2.2.2 for the palovarotene-exposed and unexposed cohorts, respectively).

The FOPal registry study aims to enrol a minimum of 67 participants with FOP treated with palovarotene (exposed) and 33 participants with FOP not treated with palovarotene (unexposed) from countries/sites willing to participate. Approximately half of the participants in each cohort (exposed and unexposed) will be paediatric (8 years to less than 18 years of age for girls and 10 years to less than 18 years of age for boys).

9.2.4 Registry Study Duration

The duration of the FOPal registry study is up to 11 years, with an enrolment period of maximum 10 years from first participant, first visit, and a minimum of 1 year of data collected for participants who are enrolled within that period.

Participant enrolment will start on the date that palovarotene is commercially available in any given country for exposed participants, and once the investigational site has been activated for all participants.

The investigator must ensure that the participant receives appropriate medical follow-up and this should be properly documented in the participant's medical records and eCRFs regarding:

- AEs or their sequelae (any AE, based on the investigator's opinion, not only those assessed as related) that persist after the date of palovarotene discontinuation for exposed participants.
- Medical events of special interest (growth outcomes, including PPC, and fractures) for unexposed participants for the entire study duration.

9.2.5 Registry Study Location

Exposed participants will be recruited in countries/sites willing to participate and where palovarotene is registered/marketed. Unexposed participants to palovarotene will be recruited in the same participating sites.

9.2.6 Registry Study Schedule

The schedule of assessments that will be collected during the FOPal registry study for exposed naïve, exposed non-naïve, and unexposed participants is summarised in Table 2, Table 3 and Table 4 respectively. As this is a non-interventional, observational, prospective and retrospective registry study designed to collect and assess real-world data, these assessments are not mandated by this protocol. If some assessments are not routinely performed by the investigator, the data will not be captured in the eCRF.

Table 2 Schedule of Assessments: Exposed Naïve Participants

Assessment/Procedure	Baseline Visit	Follow-Up Visits (as per routine clinical practice[a])/ End of Study Visit
Clinic visit or telephone/video contact visit	X	X
Informed consent [b]	X	
Inclusion/exclusion criteria	X	
Baseline demographics	X	
Physical examination [c,d]	X	X
Medical or surgical history	X	
FOP history	X	
Growth status assessment (bone age, knee height and epiphyseal status) [d,e]	X	X
Tanner staging [d,e]	X	X
Linear height [f] and weight [d]	X	X
Vital signs [d,g]	X	X
Pregnancy testing [h]	X	X
Prior /concomitant medications [i]	X	X
Concomitant surgery and non-drug therapies	X	X
Prior use of palovarotene (investigational product)	X	
Palovarotene dose for chronic and flare-up treatment [j]	X	X
Spirometry and DLCO test [d,k]	X	X
CAJIS [d]	X	X
Movement mobility history (including flare-ups [l])	X	
Movement mobility changes (including flare-ups)	X	X
Spinal health assessment [m]	X	X
AEs, SAEs, Special Situations, and AESIs [n]	X	X
Participant Questionnaires:		
FOP-PFQ assessment [o]	X	X
PROMIS Global Health Scale [o]	X	X
FOP assistive devices assessment [o]	X	X

AE=Adverse Event; AESI=Adverse Event of Special Interest; CAJIS=Cumulative Analogue Joint Involvement Scale; CT= Computed Tomography; DLCO=Diffusion Capacity of the Lung for Carbon Monoxide; FEV_1=Forced Expiratory Volume in one second; FOP=Fibrodysplasia Ossificans Progressiva; FOP-PFQ=FOP-Physical Function Questionnaire; FVC=Forced Vital Capacity; HEENT= head, eyes, ears, nose and throat; PI=Prescribing Information; PROMIS=Patient-Reported Outcomes Measurement Information System; SAE=Serious Adverse Event; SS=Special Situation.

a Follow-up Visits are recommended every 6 months, or as per local label.

b If participant <18 years (or the legal age of consent in the jurisdiction in which the study is taking place), assent and parent or legally authorised representative consent will also be required.

c This includes a general assessment, dermatologic, lymph nodes, HEENT, chest, cardiac, abdomen, limb/extremities, musculoskeletal, neurologic and other.

d Not expected in the context of a telephone/video visit.

e Collected for growing children. Assessment as per local label.

f Linear height within 6 to 12 months prior to and at the Baseline Visit.

g Vital signs to be collected are respiratory rate, blood pressure and heart rate.

h Participants will be assessed for child-bearing status and pregnancy prevention measures. As per local label, pregnancy testing is carried out with a confirmation of absence of pregnancy monthly if the participant receives palovarotene and one month after stopping. These conditions also concern participants who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

i This includes a period of two months prior to the signed informed consent date.

j Not applicable for pregnant participants.

k Spirometry obtains the lung function parameters of observed and % predicted FVC and FEV_1 and the absolute and % predicted FEV_1/FVC ratio. The DLCO test obtains observed and % predicted DLCO which provides information on the efficiency of gas transfer from alveolar air into the bloodstream.

l This includes number of flare-ups over the past 12 months before the signed informed consent date.

m Spinal health assessment to be performed using radiological imaging (e.g. CT, X-ray, scintigraphy, etc).

n AE, SAE, Special Situation and AESI collection begins once the informed consent has been signed.

o Paper-based patient-reported questionnaires.

Table 3 Schedule of Assessments: Exposed Non-naïve Participants

Assessment/Procedure	**Retrospective Period** *(From first marketed palovarotene intake)*	**Baseline Visit**	**Follow-Up Visits (as per routine clinical practice[a])/ End of Study Visit**
Clinic visit or telephone/video contact visit		X	X
Informed consent [b]		X	
Inclusion/exclusion criteria		X	
Baseline demographics		X	
Physical examination [c,d]	X [p]	X	X
Medical or surgical history	X		
FOP history	X		
Growth status assessment (bone age, knee height and epiphyseal status) [d,e]	X [p]	X	X
Tanner staging	X [p]	X	X
Linear height [f] and weight [d]	X	X	X
Vital signs [d,g]	X [p]	X	X
Pregnancy testing [h]		X	X
Prior /concomitant medications [i]	X	X	X
Concomitant surgery and non-drug therapies	X	X	X
Prior use of palovarotene (investigational product)	X		
Palovarotene dose for chronic and flare-up treatment [j]	X	X	X
Spirometry and DLCO test [d,k]	X [p]	X	X
CAJIS [d]	X [p]	X	X
Movement mobility history (including flare-ups [l])	X		
Movement mobility changes (including flare-ups)		X	X
Spinal health assessment [m]	X [p]		X
Retrospective important medical events related to the disease (including vertebral fractures)	X		
AEs SAEs, Special Situations and AESIs [n]		X	X
Participant Questionnaires:			
FOP-PFQ assessment [o]		X	X
PROMIS Global Health Scale [o]		X	X
FOP assistive devices assessment [o]		X	X

AE=Adverse Event; AESI=Adverse Event of Special Interest; CAJIS=Cumulative Analogue Joint Involvement Scale; CT= Computed Tomography; DLCO=Diffusion Capacity of the Lung for Carbon Monoxide; FEV_1=Forced Expiratory Volume in one second; FOP=Fibrodysplasia Ossificans Progressiva; FOP-PFQ=FOP-Physical Function Questionnaire; FVC=Forced Vital Capacity; HEENT= head, eyes, ears, nose and throat; PI=Prescribing Information; PROMIS=Patient-Reported Outcomes Measurement Information System; SAE=Serious Adverse Event.

a Follow-up Visits are recommended every 6 months, or as per local label.

b If participant <18 years (or the legal age of consent in the jurisdiction in which the study is taking place), assent and parent or legally authorised representative consent will also be required.

c This includes a general assessment, dermatologic, lymph nodes, HEENT, chest, cardiac, abdomen, limb/extremities, musculoskeletal, neurologic and other.

d Not expected in the context of a telephone/video visit.

e Collected for growing children. Assessment as per local label.

f Linear height within 6 to 12 months prior to first marketed palovarotene intake.

g Vital signs to be collected are respiratory rate, blood pressure and heart rate.

h Participants will be assessed for child-bearing status and pregnancy prevention measures. As per local label, pregnancy testing is carried out with a confirmation of absence of pregnancy monthly if the participant receives palovarotene and one month after stopping. These conditions also concern participants who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

i This includes a period of two months prior to the first marketed palovarotene intake.

j Not applicable for pregnant participants.

k Spirometry obtains the lung function parameters of observed and % predicted FVC and FEV_1 and the absolute and % predicted FEV_1/FVC ratio. The DLCO test obtains observed and % predicted DLCO which provides information on the efficiency of gas transfer from alveolar air into the bloodstream.

l This includes number of flare-ups over the past 12 months before the first marketed palovarotene intake.

m Spinal health assessment to be performed using radiological imaging (e.g. CT, X-ray, scintigraphy, etc).

n AE, SAE, Special Situation and AESI collection begins once the informed consent has been signed.

o Paper-based patient-reported questionnaires.

p Retrospective data collected only at the first marketed palovarotene intake.

Table 4 Schedule of Assessments: Unexposed Participants

Assessment/Procedure	**Retrospective Period *** *(12 Months before baseline)*	**Baseline Visit**	**Follow-Up Visits (as per routine clinical practice[a])/ End of Study Visit [j]**
Clinic visit or telephone/video contact visit		X	X
Informed consent [b]		X	
Inclusion/exclusion criteria		X	
Baseline demographics		X	
Physical examination [c,d]	X [i]	X	X
FOP history	X		
Growth status assessment (bone age, knee height and epiphyseal status) [d,e]	X [i]	X	X
Tanner staging	X [i]	X	X
Linear height and weight [d]	X	X	X
Vital signs [d,f]	X [i]	X	X
medications	X	X	X
Concomitant surgery and non-drug therapies	X	X	X
Spirometry and DLCO test [d,g]	X [i]	X	X
CAJIS [d]	X [i]	X	X
Movement mobility history (including flare-ups)	X		
Movement mobility changes (including flare-ups)		X	X
Medical events of special interest	X	X	X
Participant Questionnaires:			
FOP-PFQ assessment [h]		X	X
PROMIS Global Health Scale [h]		X	X
FOP assistive devices assessment [h]		X	X

CAJIS=Cumulative Analogue Joint Involvement Scale; DLCO=Diffusion Capacity of the Lung for Carbon Monoxide; FEV_1=Forced Expiratory Volume in one second; FOP=Fibrodysplasia Ossificans Progressiva; FOP-PFQ=FOP-Physical Function Questionnaire; FVC=Forced Vital Capacity; HEENT= head, eyes, ears, nose and throat; PROMIS=Patient-Reported Outcomes Measurement Information System;.

* Retrospective period starts 12 months preceding the signed informed consent but only from the time the child has reached the age of 8 years for girls and 10 years for boys.

a Follow-up Visits are recommended every 6 months.

b If participant <18 years (or the legal age of consent in the jurisdiction in which the study is taking place), assent and parent or legally authorised representative consent will also be required.

c This includes a general assessment, dermatologic, lymph nodes, HEENT, chest, cardiac, abdomen, limb/extremities, musculoskeletal, neurologic and other.

d Not expected in the context of a telephone/video visit.

e Collected for growing children.

f Vital signs to be collected are respiratory rate, blood pressure and heart rate.

g Spirometry obtains the lung function parameters of observed and % predicted FVC and FEV_1 and the absolute and % predicted FEV_1/FVC ratio. The DLCO test obtains observed and % predicted DLCO which provides information on the efficiency of gas transfer from alveolar air into the bloodstream.

h Paper-based patient-reported questionnaires.

i Closest available value to 12 months preceding signed informed consent.

j Previously unexposed participants starting palovarotene and remaining in FOPal should follow the exposed naïve participants schedule from the first marketed palovarotene intake (See Table 2 and Section 9.2.8).

9.2.7 Registry Study Visit(s)

Visits will be in accordance with routine clinical practice (Follow-up Visits are recommended every 6 months).

The FOPal registry study will collect data at the Baseline Visit, Follow-up Visits / End of Study Visit.

The Baseline Visit can be performed by either telephone/video contact or clinic visit (preferred) as per the investigator's judgement.

9.2.7.1 Baseline Visit for Exposed Participants

Investigators at participating FOPal registry sites will identify participants who fulfil the inclusion and exclusion criteria. Signed informed consent should be obtained prior to enrolment according to local regulations and once inclusion and exclusion criteria have been satisfied. If the participant is <18 years old (or the legal age of consent in the jurisdiction in which the study is taking place), assent and parent or legally authorised representative consent will also be required.

The participants will attend a clinic (preferred) or telephone/video visit and assessments will be performed according to routine clinical care. The following variables will be captured from Baseline Visit records as available:

For exposed naïve participants (Table 2)

- Baseline demographics;
- Physical examination including a general assessment as well as dermatologic, lymph nodes, head, eyes, ears, nose and throat (HEENT), chest, cardiac, abdomen, limb/extremities, musculoskeletal, neurologic and other assessments (as per routine clinical care);
- Medical or surgical history (12 months before the Baseline Visit);
- FOP history (date of symptom onset, date of diagnosis by a physician, method of diagnosis, date of genetic test if performed and type of FOP genetic variant);
- Growth status assessment for growing children (bone age, knee height and epiphyseal status assessment);
- Tanner staging for growing children;
- Linear height and weight (linear height within 6 to 12 months prior to the Baseline Visit will also be collected);
- Vital signs (respiratory rate, blood pressure and heart rate);
- Pregnancy test (as per local label, participants are assessed for child-bearing status and pregnancy prevention measures. These conditions also concern participants who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy);
- Prior (two months before the Baseline Visit) and concomitant medications;
- Concomitant surgery and non-drug therapies;
- Prior use of palovarotene (investigational product);
- Marketed palovarotene dose for chronic and flare-up treatment;
- Spirometry and DLCO test;
- CAJIS for FOP;

- Movement mobility history including flare-ups (over the past 12 months prior to the Baseline Visit);
- Movement mobility history including flare-ups (from Baseline Visit);
- Spinal health assessment using radiological imaging (e.g. Computed tomography (CT), X-ray, scintigraphy, etc);
- AEs, SAEs, Special Situations and Adverse Events of Special Interest (AESIs) (following provision of the signed informed consent);
- FOP-PFQ (the adult form should be used for participants 15 years and older and for participants under 15 years old, there is a self-completed paediatric form (developed for participants 8 to 14 years old) and a proxy completed paediatric form (developed for participants 5 to 14 years old));
- PROMIS Global Health Scale (the adult form should be used for participants 15 years and older and for participants under 15 years old, there is a self-completed paediatric form (developed for participants 8 to 14 years old) and a proxy completed paediatric form (developed for participants <15 years old));
- FOP assistive devices assessment.

For exposed non-naïve participants (Table 3):

- Baseline demographics;
- Physical examination including a general assessment as well as dermatologic, lymph nodes, HEENT, chest, cardiac, abdomen, limb/extremities, musculoskeletal, neurologic and other assessments (as per routine clinical care);
- Medical or surgical history (12 months before the first marketed palovarotene intake);
- FOP history (date of symptom onset, date of diagnosis by a physician, method of diagnosis, date of genetic test if performed and type of FOP genetic variant);
- Growth status assessment for growing children (bone age, knee height and epiphyseal status assessment) at the first marketed palovarotene intake and at the Baseline Visit;
- Tanner staging for growing children at the first marketed palovarotene intake and at the Baseline Visit;
- Linear height and weight from the first marketed palovarotene intake and at the Baseline Visit (linear height within 6 to 12 months prior to the first marketed palovarotene intake will also be collected);
- Vital signs (respiratory rate, blood pressure and heart rate);
- Pregnancy test (as per local label, participants are assessed for child-bearing status and pregnancy prevention measures. These conditions also concern participants who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy);
- Prior (two months prior to the first marketed palovarotene intake and until the Baseline Visit) and concomitant medications;
- Concomitant surgery and non-drug therapies;
- Prior use of palovarotene (investigational product);
- Marketed palovarotene dose for chronic and flare-up treatment;
- Spirometry and DLCO test at the first marketed palovarotene intake and at the Baseline Visit;

- CAJIS for FOP at the first marketed palovarotene intake and at the Baseline Visit;
- Movement mobility history, including flare-ups (over the past 12 months prior to the first marketed palovarotene intake and until Baseline Visit);
- Movement mobility changes, including flare-ups (from Baseline Visit);
- Spinal health assessment using radiological imaging (e.g. CT, X-ray, scintigraphy, etc) at the first marketed palovarotene intake and at the Baseline Visit;
- Retrospective important medical events related to the disease (including vertebral fractures) at the first marketed palovarotene intake and until the Baseline Visit;
- AEs, SAEs, Special Situations and AESIs (following provision of the signed informed consent);
- FOP-PFQ (the adult form should be used for participants 15 years and older and for participants under 15 years old, there is a self-completed paediatric form (developed for participants 8 to 14 years old) and a proxy completed paediatric form (developed for participants 5 to 14 years old)) at the first marketed palovarotene intake and at the Baseline Visit;
- PROMIS Global Health Scale (the adult form should be used for participants 15 years and older and for participants under 15 years old, there is a self-completed paediatric form (developed for participants 8 to 14 years old) and a proxy completed paediatric form (developed for participants <15 years old)) at the first marketed palovarotene intake and at the Baseline Visit;
- FOP assistive devices assessment at the first marketed palovarotene intake and at the Baseline Visit.

9.2.7.2 Baseline Visit for Unexposed Participants

Investigators at participating FOPal registry sites will identify participants who fulfil the inclusion and exclusion criteria. Signed informed consent should be obtained prior to enrolment according to local regulations and once inclusion and exclusion criteria have been satisfied. If the participant is <18 years old (or the legal age of consent in the jurisdiction in which the study is taking place), assent and parent or legally authorised representative consent will also be required.

The participants will attend a clinic (preferred) or telephone/video visit and assessments will be performed according to routine clinical care. The following variables will be captured from Baseline Visit records as available (Table 4):

- Baseline demographics;
- Physical examination including a general assessment as well as dermatologic, lymph nodes, HEENT, chest, cardiac, abdomen, limb/extremities, musculoskeletal, neurologic and other assessments (as per routine clinical care);
- FOP history (date of symptom onset, date of diagnosis by a physician, method of diagnosis, date of genetic test if performed and type of FOP genetic variant);
- Growth status assessment for growing children (bone age, knee height and epiphyseal status assessment);
- Tanner staging for growing children;
- Linear height and weight;
- Vital signs (respiratory rate, blood pressure and heart rate);

- Concomitant medications;
- Concomitant surgery and non-drug therapies;
- Spirometry and DLCO test;
- CAJIS for FOP;
- Movement mobility history including flare-ups (over the past 12 months prior to the Baseline Visit);
- Movement mobility changes including flare-ups (from Baseline Visit);
- Medical events of special interest (over the past 12 months prior to the Baseline Visit);
- FOP-PFQ (the adult form should be used for participants 15 years and older and for participants under 15 years old, there is a self-completed paediatric form (developed for participants 8 to 14 years old) and a proxy completed paediatric form (developed for participants 5 to 14 years old));
- PROMIS Global Health Scale (the adult form should be used for participants 15 years and older and for participants under 15 years old, there is a self-completed paediatric form (developed for participants 8 to 14 years old) and a proxy completed paediatric form (developed for participants <15 years old));
- FOP assistive devices assessment.

9.2.7.3 Follow-up Visits/End of Study Visit for Exposed Participants

The participants will attend a clinic or telephone/video visit and assessments will be performed according to routine clinical care. For the FOPal registry study, the following variables will be captured from medical records as available:

- Physical examination;
- Growth status assessment for growing children (bone age, knee height and epiphyseal status, assessment as per local label);
- Tanner staging for growing children;
- Linear height and weight;
- Vital signs (respiratory rate, blood pressure and heart rate);
- Pregnancy test (as per local label, pregnancy tests should be performed monthly while treatment with palovarotene is ongoing and one month after treatment is stopped) and change in fertility status;
- Concomitant medications;
- Concomitant surgery and non-drug therapies;
- Marketed palovarotene dose for chronic and flare-up treatment;
- Spirometry and DLCO test;
- CAJIS for FOP;
- Number of flare-ups since Last Visit;
- Movement mobility changes;
- Spinal health assessment using radiological imaging (e.g. CT, X-ray, scintigraphy, etc);
- AEs, SAEs, Special Situations, and AESIs;
- FOP-PFQ;
- PROMIS Global Health Scale;
- FOP assistive devices assessment.

9.2.7.4 Follow-up Visits/End of Study Visit for Unexposed Participants

The participants will attend a clinic or telephone/video visit and assessments will be performed according to routine clinical care. For the FOPal registry study, the following variables will be captured from medical records as available:

- Physical examination;
- Growth status assessment for growing children (bone age, knee height and epiphyseal status, assessment as per local label);
- Tanner staging for growing children;
- Linear height and weight;
- Vital signs (respiratory rate, blood pressure and heart rate);
- Concomitant medications;
- Concomitant surgery and non-drug therapies;
- Spirometry and DLCO test;
- CAJIS for FOP;
- Number of flare-ups since Last Visit;
- Movement mobility changes;
- Medical events of special interest;
- FOP-PFQ;
- PROMIS Global Health Scale;
- FOP assistive devices assessment.

9.2.8 Registry Study Discontinuation/Withdrawal

The participant can withdraw (or be withdrawn if the subject is a child upon legal representative's decision) from the FOPal registry study at any time. The date and primary reason for withdrawal should be recorded in the eCRF as well as whether the participant stopped or not palovarotene for exposed participants.

Should the participant withdraw from the study, no further data will be collected, nevertheless, data collected up to the time of the withdrawal will be kept for analysis, safety and integrity of study results.

The participant will be withdrawn from the FOPal registry study if:

- The participant enrols in any interventional clinical trial for FOP, or,
- For exposed participants: the participant is no longer receiving palovarotene (except if palovarotene is discontinued due to a safety concern or pregnancy, in such cases the participant will be monitored for safety, see Section 11.4 for follow-up of AEs and Section 11.1.3.1 for follow-up of pregnancies).
- For unexposed participants: the participant becomes pregnant or starts a treatment for FOP other than palovarotene. In case the participant starts palovarotene, they should have the option to remain in the registry. Previously unexposed participants starting palovarotene and remaining in the registry will follow the exposed naïve participants schedule (Table 2) from the first marketed palovarotene intake.

Investigators, participants or/and parents may decide to stop the participation in the FOPal registry study at any time without consequences on the normal participant clinical care.

9.2.9 Treatment Discontinuation (Palovarotene)

Palovarotene treatment may be discontinued in the event of any AEs (see Section 11.1.1 for definition), SAEs (see Section 11.1.2 for definition), Special Situations (see Section 11.1.3 for definition), or AESIs (see Section 11.1.4 for definition) deemed by the investigator to warrant treatment discontinuation. In the event of pregnancy, palovarotene treatment must be discontinued (see Section 11.1.3.1).

Discontinuation of treatment due to AEs should be distinguished from discontinuation/withdrawal from the registry study due to participant/parent decision or end of follow-up.

If AEs or their sequelae (any AE, based on the investigator's opinion, not only those assessed as related) persist after the date of palovarotene discontinuation, the investigator must ensure that the participant receives appropriate medical follow-up and this should be properly documented in the participant's medical records.

All participants discontinuing palovarotene treatment will be followed up to 30 days after last palovarotene intake (unless consent is withdrawn).

9.2.10 Early Registry Study Termination

The sponsor can decide at any time to discontinue the FOPal registry study for any reason. Investigators will be informed of the decision. Ethics committees and Competent Authorities (CAs) will also be informed if required by local regulations.

9.3 Endpoints and Variables

9.3.1 Endpoints

9.3.1.1 Primary Endpoints

- Incidence and description of all TEAEs, whether or not they are considered as related to palovarotene;
- Incidence and description of all serious TEAEs, whether or not they are considered as related to palovarotene;
- Incidence and description of all nonserious TEAEs whether or not they are considered as related to palovarotene;
- Incidence and description of all serious and nonserious treatment-related TEAEs.

9.3.1.2 Secondary Endpoints

For participants with FOP exposed and unexposed to palovarotene:

- Raw values and change from Baseline in CAJIS total score at each Follow-up Visit;
- Raw values and shift from Baseline in use of assistive devices and adaptations for daily living at each Follow-up Visit;
- Raw values and change from Baseline in % of worst score for total score, upper extremities subscore and mobility subscore using age-appropriate forms of the FOP-PFQ at each Follow-up Visit;
- Raw values and change from Baseline in observed and % predicted FVC at each Follow-up Visit;
- Raw values and change from Baseline in observed and % predicted FEV_1 at each Follow-up Visit;
- Raw values and change from Baseline in absolute and % predicted FEV_1/FVC ratio at each Follow-up Visit;

- Raw values and change from Baseline in observed and % predicted DLCO at each Follow-up Visit;
- Raw values and change from Baseline in physical and mental function (mean global physical and mental health score converted into T-scores) for participants ≥15 years old and overall QoL (mean total score converted into T-scores) for participants <15 years old using age-appropriate forms of PROMIS Global Health Scale at each Follow-up Visit;
- Annualised frequency of flare-ups, categorised by overall occurrence;
- Number of locations impacted by movement mobility change per participant annually and change from Baseline;
- Any movement mobility change (better movement/the same movement/slightly worse movement/moderately worse movement/severely worse movement) by body location and annually;
- Evolution of locations impacted by movement mobility change (how many times a location is impacted) per body location, annually and change from baseline;
- Movement mobility outcomes (change in extra bone growth and change in movement), causes, associated symptoms if preceded by a flare-up event by body location;
- Frequency, severity, outcome and descriptive characteristics of any fractures, overall and at each Follow-up Visit, categorised by location;
- Annualised frequency and descriptive characteristics of bone fractures, categorised by overall occurrence and location;
- Incidence of pregnancy.

For participants with FOP exposed to palovarotene who become pregnant while enrolled in FOPal:

- Pregnancy characteristics and outcomes;
- Pregnancy-related AEs through the first year postpartum;
- Birth and developmental outcomes through the infant(s)' first year of life.

For growing children with FOP exposed and unexposed to palovarotene:

- Raw values and change from Baseline in linear height and knee height velocity at each Follow-up Visit until skeletal maturity or final adult height is reached;
- Baseline linear height z-scores and change from Baseline at each Follow-up Visit until skeletal maturity or final adult height is reached;
- Mean difference between chronological age and bone age at each Follow-up Visit;
- Frequency, severity and descriptive details of PPC overall and at each Follow-up Visit.

For participants with FOP exposed to palovarotene:

- Mean dose/year for chronic treatment;
- Mean dose/cycle for flare-up treatment.

9.3.2 Variables

Only the data collected as part of routine medical care will be captured using the eCRF by the investigator (patient-reported questionnaires will be completed directly by the participant on paper and returned to the site for data entry into the eCRF). If some assessments are not routinely performed by the investigator, they will not complete the corresponding sections in the eCRF.

The FOPal registry captures individual participants' data as follows:

9.3.2.1 Demographic and Baseline Characteristics

The FOPal registry study will collect the following data at the Baseline Visit if available:

- Baseline demographics including date of birth, gender and race, where permitted;
- Reason for absence of treatment for unexposed participants, when available;
- Physical examination (only if clinic visit) including a general assessment as well as dermatologic, lymph nodes, HEENT, chest, cardiac, abdomen, limb/extremities, musculoskeletal, neurologic and other assessments (as per routine clinical care) for all participants at the Baseline Visit, at the first marketed palovarotene intake for exposed non-naïve participants and at the Follow-up/End of Study Visits;
- Medical or surgical history, excluding FOP-related history, within the 12 months before the signed informed consent date for exposed naïve or unexposed participants and within the past 12 months prior to the first marketed palovarotene intake for exposed non-naïve participants;
- FOP history including the date of symptom onset, date of diagnosis by a physician, method of diagnosis, date of genetic test if performed and type of FOP genetic variant;
- Number of flare-ups over the past 12 months prior to the first marketed palovarotene intake and until the signed informed consent date for exposed non-naïve participants or 12 months preceding the signed informed consent date for exposed naïve or unexposed participants;
- Movement mobility history within the 12 months before the signed informed consent date for exposed naïve or unexposed participants and over the past 12 months prior to the first marketed palovarotene intake and until the signed informed consent date for exposed non-naïve patients. The latter includes locations, mobility impact start date, change in movement, change in extra bone growth, symptoms if preceded by a flare-up event and causes.

9.3.2.2 Prior and Concomitant Medication

The FOPal registry study will collect the use of prior and concomitant medication including dose, frequency, start/end dates and reason for prescription at the Baseline Visit and at the Follow-up/End of Study Visits if available.

9.3.2.3 Concomitant Surgery

The FOPal registry study will collect the following data on concomitant surgery at the Baseline Visit and at the Follow-up/End of Study Visits if available:

- Surgical procedure name;
- Indication;
- Reason for concomitant surgery;
- Date of surgery.

9.3.2.4 Linear Height and Weight

The FOPal registry study will collect linear height and weight for all participants at the Baseline Visit, at the first marketed palovarotene intake (for exposed non-naïve participants) and at the Follow-up/End of Study Visits (only if clinic visit) if available. Linear height within the past 6 to 12 months prior to the first palovarotene intake will also be collected if available.

9.3.2.5 Adverse Events, Special Situations, and Adverse Events of Special Interest for Exposed Participants

Adverse Events and Special Situations

The FOPal registry study will collect the following AE data from the signing of the informed consent form (ICF) until last palovarotene intake + 30 days, and will include retrospective AEs from the first dose of marketed palovarotene intake for non-naïve participants:

- All AEs, TEAEs, irrespective of causality, including serious TEAEs, start/end date, time to onset, nature, severity, seriousness, causality assessment, any treatment administered for the AE, action taken and outcome (definitions, management and reporting of AEs are described in Section 11);
- Deaths, irrespective of causality, including date and cause of death;
- Special Situations (defined in Section 11.1.3), irrespective of causality, including start/end date, category, description, whether the Special Situation led to an AE and outcome.

Retrospective AE from the first marketed palovarotene intake and until the signed informed consent date will be collected as "Retrospective important medical events related to the disease (including vertebral fractures") as specified in Table 3.

If AEs or their sequelae (any AE, based on the investigator's opinion, not only those assessed as related) persist after the date of palovarotene discontinuation, the investigator must ensure that the participant receives appropriate medical follow up and this should be properly documented in the participant's medical records.

All participants discontinuing palovarotene treatment will be followed up in the registry up to 30 days after last palovarotene intake (unless consent is withdrawn).

Adverse Events of Special Interest

The FOPal registry study will collect the following AESIs:

- PPC;
- Fractures;
- Psychiatric AEs;
- Hepatic AEs;
- Convulsions AEs.

These events must be collected on the AE form of the eCRF according to the completion guideline and using the specific AESI reporting option.

If they meet the seriousness criteria, they should also be reported as SAEs.

9.3.2.6 Medical Events of Special Interest for Unexposed Participants

The FOPal registry will collect medical events within12 months preceding the signed informed consent, at Baseline Visit and at the Follow-up/End of Study Visits if available.

Medical events of special interest include, but are not limited to:

- Growth outcomes, including PPC;
- Fractures.

9.3.2.7 Safety Variables

Vital Signs

The FOPal registry study will collect respiratory rate, blood pressure and heart rate at the Baseline Visit, at the first marketed palovarotene intake (for exposed non-naïve participants) and at the Follow-up/End of Study Visits (only if clinic visit) if available.

Growth Status

The FOPal registry study will collect bone age, knee height and epiphyseal status ("open/partially closed/closed/not assessable") for growing children at the Baseline Visit, at the first marketed palovarotene intake (for exposed non-naïve participants) and at the Follow-up/End of Study Visits if available.

Growing children are those in whom the growth plates have not fused. Whether the participant is a growing child is based on the investigator's assessment.

Tanner Staging

The FOPal registry study will collect Tanner stage (rating of development of secondary sex characteristics; pubic hair, testicular volume, breast development, where Stage 1 corresponds to the pre-pubertal form and Stage 5, the final adult form [35]) for growing children at the Baseline Visit, at the first marketed palovarotene intake (for exposed non-naïve participants) and at the Follow-up/End of Study Visits if available.

Pregnancy Testing for Exposed Participants

Participants will be assessed for child-bearing status and pregnancy prevention measures prior to receiving palovarotene. As per local label, pregnancy testing will be carried out with a confirmation of absence of pregnancy for as long as the participant receives palovarotene and for one month after stopping. These conditions also apply to participants who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Pregnancy is contraindicated during treatment with palovarotene, therefore if a participant is pregnant or has a positive pregnancy test at any time during the registry study, this will result in immediate discontinuation of palovarotene. A pregnant participant will be followed throughout her pregnancy and through the first year postpartum to monitor pregnancy-related AEs and the birth and developmental outcomes of the infant(s)' through the first year of life (see Section 11.1.3.1).

Spinal Health Assessment for Exposed Participants

The FOPal registry study will collect the outcome/results of radiological imaging and the type of imaging used to assess the participants' spinal health status in clinical practice, as recommended by the product label. The type of radiological imaging techniques for which outcomes/results will be collected include, but are not limited to, CT, X-ray and scintigraphy.

Fractures (including vertebral fractures)

The FOPal registry study will collect the severity and descriptive details of any fractures (including vertebral fractures) in the SAE eCRF page from the signed informed consent date. For exposed non-naïve participants, any fractures that occurred between the first marketed palovarotene intake and the signed informed consent date will be recorded at the Baseline Visit using a different form. For unexposed participants, any fractures occurring within 12 months preceding the signed informed consent date and during the study will be recorded using the medical events of special interest eCRF pages.

9.3.2.8 Effectiveness Variables

Cumulative Analogue Joint Involvement Scale

The CAJIS for FOP will be collected at the Baseline Visit and at the Follow-up/End of Study Visits (only if a clinic visit) if available.

The CAJIS is an objective measure of joint movement completed by the investigator to document total joint involvement [36]. This scale, which was developed by the investigators from the Center for Research in FOP and Related Disorders, assesses functional disability by categorising ROM across 12 joints (both right and left shoulder, elbow, wrist, hip, knee and ankle joints) and three body regions (cervical spine, thoracic/lumbar spine and jaw), with each joint/region assessed as: 0=normal (<10% deficit); 1=partially impaired (10% to 90% deficit); 2=functionally ankylosed (>90% deficit). The CAJIS total score is calculated as the sum of the scores of all joints/regions and ranges from 0 (no involvement) to 30 (maximally involved).

The examiner must also note and record (yes/no) if the participant:

- Can walk;
- Uses a wheelchair;
- Needs some help with activities of daily living;
- Needs complete help with activities of daily living.

Use of Assistive Devices and Adaptations for Daily Living

The use of assistive devices and adaptations for daily living will be collected at the Baseline Visit and at the Follow-up/End of Study Visits if available.

The questionnaire will be filled in by the participant or the proxy as per below table:

Questionnaire	If participant is an Adult (≥15 years)	If participant is a Child (<15 years)	
	Filled by	Filled by	
	Participant	Participant	Proxy
FOP assistive devices assessment (Version 1.0)	X*		X

* If participants are unable to answer on their own, an individual can be involved and reports only the participant's response on their behalf.

FOP=Fibrodysplasia Ossificans Progressiva.

In case of PRO completion by an individual (if participants are unable to answer on their own), the recommendations for such administration are detailed below:

- The individual should be different from a healthcare professional and should be the same across multiple assessments.
- The individual must only report the participant's response without any amendments or interpretation.

Assistive devices and adaptations for daily living (including healthcare utilisation) include:

- Mobility aids;
- Eating tools;
- Personal care tools;
- Bathroom aids and devices;
- Bedroom aids and devices;
- Home adaptations;

- Work environment adaptations;
- Technology adaptations;
- Sports and recreation adaptations;
- School adaptations;
- Medical therapies for daily living;
- Healthcare utilisation.

Physical and Mental Function

Physical function as assessed by the age-appropriate forms of the FOP-PFQ and physical and mental function (overall QoL for participants <15 years old) as assessed by the age-appropriate forms of the PROMIS Global Health Scale will be collected at the Baseline Visit and at the Follow-up/End of Study Visits if available.

Questionnaires will be filled in by the participant or the proxy as per below table:

Questionnaires	If participant is an Adult (≥15 years)	If participant is a Child (<15 years)	
	Filled by	Filled by	
	Participant	Participant	Proxy
FOP-PFQ assessment – (8-14) years – proxy questionnaire (Version 1.0)			X
FOP-PFQ assessment – (8-14) years – self questionnaire (Version 1.0)		X*	
FOP-PFQ assessment – adult questionnaire (Version 1.0)	X*		
PROMIS Global Health Scale – (8- 14) years – proxy questionnaire (Version 1.0)			X
PROMIS Global Health Scale – (8- 14) years – self questionnaire (Version 1.0)		X*	
PROMIS Global Health Scale – adult questionnaire (Version 1.2)	X*		

* If participants are unable to answer on their own, an individual can be involved and reports only the participant's response on their behalf.

FOP-PFQ=FOP-Physical Function Questionnaire; PROMIS=Patient-Reported Outcomes Measurement Information System.

In case of PRO completion by an individual (if participants are unable to answer on their own), the recommendations for such administration are detailed below:

- The individual should be different from a healthcare professional and should be the same across multiple assessments.
- The individual must only report the participant's response without any amendments or interpretation.

The FOP-PFQ is a disease-specific patient-reported outcome measure of physical impairment which includes questions related to activities of daily living and physical performance. There are adult and paediatric versions of the FOP-PFQ; the adult form should be used for participants 15 years and older and for participants under 15 years old, there is a self-completed paediatric

form (developed for participants 8 to 14 years old) and a proxy-completed paediatric form (developed for participants 5 to 14 years old).

The FOP-PFQ consists of 28 questions in the adult version and 26 questions in the paediatric version which are scored on a scale of 1 to 5, with lower scores indicating that the participant has more difficulty completing those tasks. Score calculations are described in Section 9.7.3.3.

PROMIS Global Health Scale is a patient-reported outcome measure of physical and mental function in participants ≥15 years old and overall QoL for participants <15 years old. There are adult and paediatric versions of the PROMIS Global Health Scale; the adult form should be used for participants 15 years and older and for participants under 15 years old, there is a self-completed paediatric form (developed for participants 8 to 14 years old) and a proxy completed paediatric form (developed for participants <15 years old).

The PROMIS Global Health Scale consists of 10 questions in the adult version and 9 questions in the paediatric version. For the adult form, two scores are calculated: the global physical health score and the global mental health score, both ranging from 4 (worse health) to 20 (better health). For the paediatric form, only a total score is calculated, ranging from 7 (worse health) to 35 (better health). All scores are converted to T-scores, with a higher T-score value indicating better health. Score calculations and conversion to T-scores are described in Section 9.7.3.3.

Lung Function Parameters

Lung function parameters will be collected at the Baseline Visit and at the Follow-up/End of Study Visits (only if clinic visit) if available.

The lung function parameters of observed FVC (litres) and % predicted FVC, observed FEV_1 (litres) and % predicted FEV_1 and the absolute and % predicted FEV_1/FVC ratio are obtained by spirometry.

The parameters of observed (traditional unit of mL/min/mmHg or SI unit of mmol/min/kPa) [37] and % predicted DLCO is obtained by the DLCO test. This provides information on the efficiency of gas transfer from alveolar air into the bloodstream. Carbon monoxide (CO) has a high affinity for haemoglobin and it follows the same pathway as that of oxygen to finally bind with haemoglobin. Inhaled CO is used for this test due to its high affinity for haemoglobin which is 200-250 times that of oxygen [38].

Flare-ups

At Baseline, the investigator will ask the participant how many flare-ups they experienced over the past 12 months. At each Follow-up Visit, the investigator will ask the participant how many flare-ups they experienced since the last visit.

Movement Mobility Change

For each movement mobility change, the impacted location, start date, causes, the outcome (change in extra bone growth, change in movement and associated flare-up event, if any) at the Baseline Visit and Follow-up/End of Study associated Visits if available. Movement mobility history over the past 12 months prior to the Baseline Visit will also be collected at the Baseline Visit.

Symptoms associated with flare-ups include, but are not limited to, pain, swelling, stiffness, redness, warmth, fever, lethargy, loss of appetite, decreased range of motion and change in mood or behaviour.

At each visit, the investigator will ask the participant if they experienced any movement mobility change since their last visit.

9.3.2.9 Treatment Variables for Exposed Participants

The registry study will collect the following data on chronic and flare-up palovarotene treatment at the Baseline Visit and at the Follow-up/End of Study Visits if available:

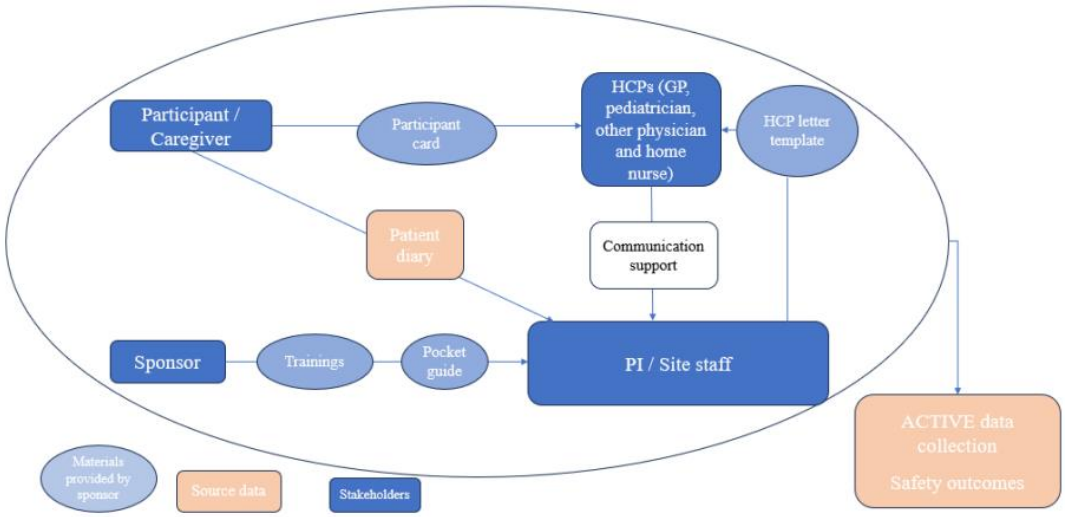
- Dose and frequency of palovarotene for chronic and flare-up treatment;
- Dose modifications, interruptions, start date and end date.

9.4 Data Sources

Source data includes any data collected as part of routine medical care which will be captured in an eCRF by the investigator and transmitted to the sponsor for analysis. The patient-reported questionnaires (FOP-PFQ, PROMIS Global Health Scale and FOP assistive devices assessment) will be completed directly by the participant or proxy on paper (see Section 9.3.2.8).

In observational studies like FOPal, data collection relies on several stakeholders: 1) investigators and site staff; 2) Healthcare professionals (HCPs) including general practitioners (GP), paediatrician, other physicians and home nurses; and 3) patients. Sponsor consultation with physicians who are expert in managing FOP confirms that in the real-world setting, while formal in-person visits may be scheduled annually, patients are also in contact with these experts throughout the year on an ad hoc basis for many aspects of FOP care. Active data collection is only managed via the sites and the sponsor has multiple strategies to ensure the sites regularly provide structured data collection. This active data collection process is summarised in Figure 3.

Figure 3 Active data collection process flow



Abbreviations: GP= General practitioner, HCP= Healthcare professional, PI= Principal Investigator.

9.5 Registry Study Size

The FOPal registry study aims to enrol a minimum of 67 participants with FOP treated with palovarotene and 33 participants with FOP not treated with palovarotene. Approximately half of the participants in each cohort (exposed and unexposed) will be paediatric (8 years to less than 18 years of age for girls and 10 years to less than 18 years of age for boys).

9.6 Data Management

Data management for FOPal will be conducted by a Service Provider (SP) directed by the sponsor's Global Medical Affairs Biometry Department. All data management procedures will be completed in accordance with the Standard Operating Procedures (SOPs) of Ipsen and the contracted SP.

9.6.1 Data Collection

The specific data to be collected at each visit, if available, are summarised in the Schedule of Assessments (Table 2,Table 3 and Table 4).

All relevant data collected as part of routine medical care will be captured using the eCRF by the investigator (patient-reported questionnaires will be completed directly by the participant or proxy on paper and returned to the site for data entry into the eCRF) and transmitted to the sponsor. If some assessments are not routinely performed by the investigator, they will not complete the corresponding sections in the eCRF.

Data will be collected in an eCRF via the internet utilising a secured website. The sponsor and the SP will ensure that the eCRF developed is appropriate to capture the data required by the protocol. The sponsor will ensure that the entrusted SP uses adequate technology to ensure data security transfer and backup.

Each site is required to have a computer and internet connection available for site entry of clinical data. Data entry in the eCRF will be performed by the investigator or by the designated person from their team and to ensure confidentiality and security of the data, all entries into the eCRF will be made under the electronic signature (e-signature) of the person performing the action (username and password). Only sponsor-authorised users will be given access to the eCRF as appropriate for their study responsibilities. All users must have successfully undergone software application training prior to entering data into the eCRF.

Once written informed consent (and assent, if applicable) has been obtained, the eCRF will provide a numeric participant identifier to pseudonymise the data from each participant. Data for each participant must be entered into the eCRF within 5 days of the participant's enrolment, each Follow-Up Visit and the End of Study Visit. Data transmitted will be pseudonymised and will be identified only by the participant number. Only investigating sites will be able to link the numeric identifier to each participant's identity.

In compliance with Good Pharmacoepidemiology Practices (GPP), the participant's medical records should be clearly marked and permit easy identification of their participation in this study.

Medical and surgical history, non-drug therapies, concomitant surgeries, Special Situations and AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and prior/concomitant medication will be coded using the World Health Organization Drug Dictionary (WHODD) by the contracted SP and reviewed by the sponsor.

Queries will be edited in English and addressed to the investigational site using the eCRF and will be answered by investigators or authorised registry study staff members directly into the eCRF.

The eCRF will be signed electronically by the investigator to certify that all the data recorded in it are consistent with the source documents and reflect the status of the participant during the corresponding part of the registry study.

9.6.2 Data Archiving and Retention

During the site initiation visits, the monitor must ensure that the archiving facilities are adequate and archiving/retention responsibilities of the investigator have been discussed.

The FOPal registry study documents should be retained for at least 15 years after registry study completion. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by agreement with the sponsor. The investigator should take measures to prevent accidental or premature destruction of these documents. The final archiving arrangements will be confirmed by the monitor when closing-out the site. The sponsor will inform the investigator, in writing, as to when these documents no longer need to be retained.

If the investigator relocates or retires, or otherwise withdraws their responsibility for maintenance and retention of registry study documents, the sponsor must be notified (preferably in writing) so that adequate provision can be made for their future maintenance and retention.

9.7 Data Analysis

9.7.1 Analyses Population Definitions

For the purposes of analyses, the following populations are defined:

- Enrolled Population including all participants who signed the ICF.
- Safety Exposed Population including all enrolled participants who have taken at least one dose of marketed palovarotene at any time before the signed ICF or during the study;

  A distinction will be made depending on time of start of marketed palovarotene:
  - Palovarotene prevalent users: participants who received palovarotene before or at the time of ICF signed;
  - Palovarotene incident users: participants who started receiving palovarotene after enrolment in the registry. Two time periods will be defined: Period 1 is from enrolment to last day before the first dose of marketed palovarotene; Period 2 is after the first dose of marketed palovarotene.
- Safety Exposed Paediatric Population including all paediatric participants (8 years to less than 18 years of age for girls and 10 years to less than 18 years of age for boys) from the Safety Exposed Population.
- Safety Unexposed Population including all enrolled participants who never received at least one dose of marketed palovarotene before or during their participation in the registry;
- Safety Unexposed Paediatric Population including all paediatric participants (8 years to less than 18 years of age for girls and 10 years to less than 18 years of age for boys) from the Safety Unexposed Population.

9.7.2 Sample Size Determination

The FOPal registry study aims to enrol a minimum of 67 participants with FOP treated with palovarotene and 33 participants with FOP not treated with palovarotene. Approximately half of the participants in each cohort (exposed and unexposed) will be paediatric (8 years to less than 18 years of age for girls and 10 years to less than 18 years of age for boys).

9.7.3 Statistical and Analytical Methods

This section is a summary of the planned statistical analysis of the primary and secondary endpoints for the FOPal registry study. A Statistical Analysis Plan (SAP) with a more technical

and detailed description of the statistical analysis, with a table, a figure and listing templates, will be developed as a separate document.

9.7.3.1 Statistical Analyses – General Considerations

The statistical analyses will be performed by an external SP, managed by the sponsor's Medical Affairs Biometry Department.

Statistical evaluation will be performed using Statistical Analysis System (SAS)® (Version 9.2 or higher).

No formal statistical testing will be performed and all the analyses will be primarily descriptive in nature. When appropriate and unless otherwise specified, 2-sided 95% CI will be displayed and if p-values are presented, they will be for exploratory purposes only.

Descriptive summary statistics will include the number of documented data, number of missing data and the following:

- Mean, standard deviation, 95% CI of the mean/median when appropriate, median, minimum and maximum for continuous variables;
- Frequency count and percentages for categorical nominal variables.

Missing data will not be replaced but will be summarised in all relevant tables.

Percentages will be based on the number of non-missing observations.

9.7.3.2 Analysis of Primary Endpoints – Safety Evaluation

Adverse Events, Special Situations and Adverse Events of Special Interest

All AEs, Special Situations and AESIs will be included in the participant data listings using the Safety Exposed Population. Analyses and summary tables will be presented in the Safety Exposed Population.

Adverse events will be coded according to MedDRA and will be classified by PT and SOC. Adverse events listings will be presented by participant, SOC and PT.

The incidence of all reported TEAEs, serious and nonserious treatment-related TEAEs, all serious TEAEs, all nonserious TEAEs, AEs leading to death, AEs leading to treatment discontinuation, Special Situations and AESIs will be tabulated separately. In addition, summary tables for TEAEs will be presented by maximum intensity and drug relationship (investigator-reported causality assessment).

A TEAE is defined as any AE that occurs from the first dose of marketed palovarotene intake until the last palovarotene intake + 30 days if:

- It was not present prior to receiving the first dose of palovarotene; or
- It was present prior to receiving the first dose of palovarotene but the event worsened during treatment with palovarotene.

All TEAEs will be flagged in the AE listings.

9.7.3.3 Analysis of Secondary Endpoints – Effectiveness Evaluation

Effectiveness data will be included in the participant data listings using the Safety Exposed and the Safety Unexposed Populations. Analyses and summary tables will be presented in the Safety Exposed and the Safety Unexposed Populations.

Data will be tabulated descriptively, i.e. the number and percentage of participants for each category for categorical parameters and the number, mean, standard deviation, 95% CIs of the mean/median when appropriate, median, minimum and maximum for continuous parameters will be tabulated.

Cumulative Analogue Joint Involvement Scale

Actual values as well as the change from the Baseline Visit in CAJIS total score will be presented for each visit.

Actual values as well as the shift from the Baseline Visit in ambulation and use of assistive devices/adaptations for daily living will also be presented for each visit.

Use of Assistive Devices and Adaptations for Daily Living

Actual values as well as the shift from the Baseline Visit in the use of assistive devices and adaptations for daily living will be presented for each visit.

Fibrodysplasia Ossificans Progressiva-Physical Function Questionnaire

The FOP-PFQ consists of 28 questions in the adult version and 26 questions in the paediatric version which are scored on a scale of 1 to 5.

The total score will be calculated as follows:

- Adult version: the sum of the scores from each question which will range from 28 × 1 = 28 to 28 × 5 = 140;
- Paediatric version: the sum of the scores from each question which will range from 26 × 1 = 26 to 26 × 5 = 130.

The upper extremities subscore will be calculated as follows:

- Adult version: the sum of the scores from 15 questions (Questions 1-12, 14, 25 and 26) which will range from 15 × 1 = 15 to 15 × 5 = 75;
- Paediatric version: the sum of the scores from 18 questions (Questions 1, 2, 6-11, 16-19 and 21-26) which will range from 18 × 1 = 18 to 18 × 5 = 90.

The mobility subscore will be calculated as follows:

- Adult version: the sum of the scores from 13 questions (Questions 13, 15-24, 27 and 28) which will range from 13 × 1 = 13 to 13 × 5 = 65;
- Paediatric version: the sum of the scores from 8 questions (Questions 3, 4, 5, 12-15 and 20) which will range from 8 × 1 = 8 to 8 × 5 = 40.

Missing scores for individual questions will not be imputed, but they will be taken into account according to the rules described below:

(1) If more than 20% of the questions contributing to the total score are missing, the total score will not be calculated. It will be considered as missing;

(2) If less than 20% of the questions contributing to the total score are missing, the total score will be calculated by summing all observed question scores, divided by the number of questions that were answered and by multiplying this average score by the total number of questions that were meant to be answered (i.e. × 28 for the adult version and × 26 for the paediatric form).

The two rules described above also apply to the upper extremities subscore and the mobility subscore.

As the analysis for FOP-PFQ will be performed across all participants (paediatric and adult) and the number of contributing questions differs, the scores will be transformed to reflect a percentage of worst score. The percentage of worst score ranges from 0% to 100% with 0% indicating the best possible function and 100% indicating the worst possible function.

The % of worst scores (for total score, upper extremities subscore and mobility subscore) as well as the change from the Baseline Visit will be presented for each visit overall and by age group.

Patient-Reported Outcomes Measurement Information System Global Health Scale

For the adult version, the global physical health and global mental health scores will be calculated as follows:

- Global physical health scores will be calculated as the sum of scores from Questions 3, 6, 7 and 8 and will range from 4 (worse health) to 20 (better health);
- Global mental health scores will be calculated as the sum of scores from Questions 2, 4, 5 and 10 and will range from 4 (worse health) to 20 (better health).

In the calculation of the above scores, the Question 7, 8 and 10 will be rescaled as shown in Table 5.

If a participant is missing any of the contributing raw scores, the corresponding score (global physical health or global mental health score) will not be calculated for that participant.

Table 5 Rescaled Global Physical and Mental Health Scores for the Adult Version of PROMIS

Questions	Raw Score	Rescaled Score
7	0	5
	1-3	4
	4-6	3
	7-9	2
	10	1
8 and 10	1	5
	2	4
	3	3
	4	2
	5	1

PROMIS=Patient-Reported Outcomes Measurement Information System

For the paediatric version, the total score will be calculated as the sum of scores from the first 7 questions and will range from 7 (worse health) to 35 (better health).

If more than 3 questions contributing to the total score are missing, the total score will not be calculated. It will be considered as missing.

If not more than 3 questions contributing to the total score are missing, the total score will be calculated by summing all observed question scores, divided by the number of questions that were answered and by multiplying this average score by the total number of questions that were meant to be answered (i.e. × 7).

The global physical health score, the global mental health score and the total score will also be converted into T-scores. T-score distributions are standardised such that a value of 50 represents the average (mean) for the general population and increments of ±10 points represent ±1 standard deviation away from the norm. Higher T-scores indicate better physical/mental health. A T-score <50 indicates worse health than the general population, while a T-score >50 indicates better health.

For example, a participant who has a T-score of 60 is 1 standard deviation better (healthier) than the general population. Conversion tables are provided in Appendix 2.

Actual values as well as the change from the Baseline Visit in mean global physical and mental health score converted into T-scores (for participants ≥15 years old) and mean total score converted into T-scores (for participants <15 years) will be presented for each visit overall and by age group.

Lung Function Parameters

Actual values as well as the change from the Baseline Visit in observed and % predicted FVC, observed and % predicted FEV_1, absolute and % predicted FEV_1/FVC ratio and observed and % predicted DLCO will be presented for each visit.

The DLCO value is reported in either traditional units (mL/min/mmHg) or SI units (mmol/min/kPa). Values in SI units can be multiplied by 2.987 to obtain values in traditional units [37].

Mobility change

Any movement mobility change (better/the same/slightly worse/moderately worse/severely worse movement) will be summarised by body locations and annually.

Actual values as well as the change from the Baseline Visit in number of impacted locations per patient will be presented annually.

The evolution of impacted location will be presented annually by summarising for each location (some grouping might be done) the number of times the location is impacted.

Movement mobility outcomes (change in extra bone growth, change in movement), causes, associated symptoms if preceded by a flare-up will be summarised by location.

9.7.3.4 Analysis of Secondary Endpoints – Key Safety Outcomes Evaluation

All key safety outcomes will be included in the participant data listings using the appropriate Safety Populations. Analyses and summary tables will be presented using the appropriate Safety Populations.

Flare-ups

The number of flare-ups over the past 12 months prior to baseline and since the last visit will be presented for each visit.

Growth Status

Height, bone age, skeletal maturity and epiphyseal status will be analysed for growing children (paediatric).

Linear height velocity, linear height z-scores, knee height velocity, and chronological age will be derived for growing children. Annualised height velocity will be derived once two consecutive measurements are spaced by a minimum of 6 months and a maximum of 12 months.

Actual values and changes from the Baseline Visit in linear height and knee height velocity and the difference between chronological age and bone age will be presented at each visit. Linear height z-scores and change from Baseline until final adult height (defined clinically as last height velocity <1cm/year or radiologically as closed epiphysis of hand-wrist or knee) is achieved will be presented at each visit. The frequency, severity and descriptive details of PPC in growing children will also be presented overall.

Fractures (including vertebral fractures)

Fractures will be coded according to MedDRA and will be classified by PT and SOC. Fracture listings will be presented by participant, SOC and PT.

The incidence of all reported fractures will be tabulated separately. In addition, summary tables will be presented by maximum intensity and drug relationship (investigator-reported causality assessment).

Pregnancy

Confirmation of an absence of pregnancy will be included in the participant data listings using the Safety Exposed Population only.

Incidence of all pregnancies will be summarised for those exposed and unexposed to palovarotene in the Safety Exposed Population. For these analyses, the pregnancy will be considered as exposed to palovarotene if it occurs whilst the participant is using the medicinal product or within 2 days after stopping the product (based on the estimated date of conception).

For participants who become pregnant while enrolled in FOPal, whether exposed or not to palovarotene, pregnancy characteristics and outcomes, pregnancy-related AEs through the first year postpartum, and birth and developmental outcomes through the infant(s)' first year of life will be descriptively summarised by palovarotene exposure status (exposed and unexposed).

Comparison of key safety outcomes between the Safety Exposed and the Safety Unexposed Populations

The key secondary endpoints that will be descriptively compared between exposed and unexposed participants with FOP in the FOPal registry, include: 1) Annualised frequency of flare-ups categorised by overall occurrence; 2) Annualised linear height velocity and height z-scores until skeletal maturity or final adult height is reached; knee height may also be evaluated depending on data availability, and 3) Annualised frequency and descriptive characteristics of bone fractures, categorised by overall occurrence and location.

The index date (Day 1) corresponds to the initial administration of marketed palovarotene for the exposed participants (naïve and non-naïve), and to the ICF signed date for unexposed participants.

Participants in the Safety Unexposed Population will be followed from their index date until data extraction at the end of FOPal registry, or until start date of palovarotene, or any investigational or commercialised FOP first treatment intake, whichever comes first.

Matching of Exposed Participants to Unexposed Participants

The Safety Exposed Population will be matched with the Safety Unexposed Population. To minimise potential selection bias resulting from differences between these two populations, the PS method will be employed with the Inverse Probability of Treatment Weighting (IPTW) method, ensuring that both populations are balanced concerning crucial baseline variables.

For constructing the PS model, logistic regression will be used. This model will encompass essential baseline covariates (at index date), including age, gender, time since the last flare-up, and the total CAJIS score. Additional covariates may be included if deemed necessary. Balance diagnostics before and after applying weights will be reviewed to assess if there is any important residual imbalance. Standardised mean differences (SMDs) will be used to compare baseline covariates and estimated propensity scores between exposed and unexposed populations. SMDs greater than 0.1 for individual covariates on the weighted sample signify residual imbalance that may lead to biased results. A density plot of the estimated propensity scores by population will be generated to visually inspect the amount of overlap between the populations. A box plot of the propensity score weights for the unexposed population will also be generated to visually inspect for highly influential observations.

Other methods will be detailed in the SAP if needed.

The number and proportion of missing data for each baseline covariate to be included in the propensity score model will be reported for exposed and unexposed populations. The analysis

methods will proceed as a complete case analysis if, and only if, the proportion of participants in the unexposed participants with at least one missing value among variables required for the model is less than 5%. Otherwise, in addition to the complete case analysis, multiple imputation will be used as a sensitivity analysis to handle missing data. The methods to evaluate the effect of missingness and to handle missing data will be detailed in the SAP.

For participants who start palovarotene (or any investigational or commercialised FOP treatment) after being in the unexposed population, only their data until palovarotene intake with a minimum of 6 months of data collected will be included in the analysis.

The final report for key safety outcomes comparison between the exposed and unexposed populations will state the estimates and 95% CI and no hypothesis testing is intended to be performed.

9.7.3.5 Other Analyses

Demographic and Baseline Characteristics

Demographic and Baseline data will be included in the participant data listings using the Safety Exposed and the Safety Unexposed Populations.

Descriptive statistics of demographic and Baseline data will be presented for the Safety Exposed and the Safety Unexposed Populations.

Medical and surgical history will be coded using MedDRA and summarised.

Prior and Concomitant Medication

Prior and concomitant medication will be included in the participant data listings using the Safety Exposed and the Safety Unexposed Populations.

Descriptive statistics of prior and concomitant medication will be presented for the Safety Exposed and the Safety Unexposed Populations.

Prior and concomitant medication will be coded using the WHODD and summarised by drug categories.

Concomitant Surgery and non-drug Therapies

Concomitant surgery and non-drug therapies data will be included in the participant data listings using the Safety Exposed and the Safety Unexposed Populations.

Descriptive statistics of concomitant surgery and non-drug therapies will be presented for the Safety Exposed and the Safety Unexposed Populations.

Participant Disposition and Withdrawals

The numbers and percentages of participants included in the analysis populations will be tabulated overall and by country and site. The reasons for participant exclusions from each of the populations will also be tabulated.

In addition, the number of participants who discontinued treatment or withdrew from the registry study will be presented with the primary reasons for discontinuation/withdrawal.

Linear Height and Weight

Linear height and weight will be included in the participant data listings using the Safety Exposed and the Safety Unexposed Populations.

Actual values and mean changes from the Baseline Visit in linear height and weight will be presented at each visit for the Safety Exposed and the Safety Unexposed Populations.

Abnormal findings considered clinically significant by the investigator will be reported as an AE.

Vital Signs

Vital signs (respiratory rate, blood pressure and heart rate) will be included in the participant data listings using the Safety Exposed and the Safety Unexposed Populations.

Actual values and mean changes from the Baseline Visit in respiratory rate, blood pressure and heart rate will be presented at each visit for the Safety Exposed and the Safety Unexposed Populations.

Abnormal findings considered clinically significant by the investigator will be reported as an AE.

Tanner Staging

Tanner stage will be included in the participant data listings for growing children using the Safety Exposed and the Safety Unexposed Paediatric Populations.

Actual values as well as the shift from the Baseline Visit in Tanner stage will be presented at each visit.

Spinal Health Assessment

Spinal health status, assessed by radiological imaging, will be included in the participant data listings using the Safety Exposed Population.

Treatment Evaluation

The treatment duration as well as the dose of palovarotene at each visit will be described using the Safety Exposed Population. The mean dose per year will be calculated for chronic treatment (excluding flare-up treatment) and the mean dose per cycle will be calculated for flare-up treatment.

Dose modifications, interruptions, start date and end date will be summarised.

9.7.4 Subgroup Analysis

Subgroup analyses will be performed by age group and gender. Additional subgroup analysis may be conducted as required.

9.7.5 Interim Analyses

The sponsor will review safety data on an ongoing basis as per Ipsen Medical Safety Governance.

Interim effectiveness and safety descriptive analyses are planned to be delivered for publication purposes as required. The interim reports will present estimates and their associated 95% CI, without conducting hypothesis testing.

Depending on the recruitment rate, an interim analysis may be performed if the required number of palovarotene-exposed and unexposed paediatric and adult participants have been enrolled and followed-up for at least 2 years.

9.8 Quality Control

9.8.1 Routine Monitoring and Monitoring Procedures

The monitoring procedures of the FOPal registry study may be conducted by an external SP directed by the sponsor's Global Medical Affairs, Clinical Operations Department. All monitoring activities will be completed in accordance with Ipsen and the SP's SOPs and as per the monitoring plan. The monitoring of the FOPal registry study should ensure that the rights

and wellbeing of the participants are protected, the data are accurate (complete and verifiable to source data) and the registry study is conducted in compliance with the protocol, GPP [39] and regulatory requirements.

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 and the results of any other assessments. In addition, the source documents may come from local HCP/GPs. All information in the eCRF must be traceable to these source documents in the participant's file. Data not requiring a separate written record will be defined before study start and will be recorded directly in the eCRF. The investigator must also keep the original ICF signed by the participant (or assent, if applicable) or their parent/legally authorised representative and a signed copy is given to them.

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry.

Ipsen monitoring standards require full verification for the presence of informed consent/assent, 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.

The frequency of the monitoring may be adapted according to participant recruitment rate or any other suitable reason. The investigator will allow direct access to all relevant files (for all participants) for the purpose of verifying entries made in the eCRF and assist with the monitor's activities, if requested. Adequate time and space for monitoring visits should be made available by the investigator.

The site investigator or authorised FOPal registry study staff members must complete the eCRF in a timely manner and on an ongoing basis to allow regular review by the registry study monitor.

Whenever a participant's name is revealed on a document required by the sponsor (e.g. laboratory print-outs), the name must be blacked out permanently by the site personnel and annotated with the participant number as identification.

Before study initiation, at a site initiation visit or remote site initiation visit, an Ipsen/delegated SP representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Ipsen (or designee) employs several methods of ensuring protocol, GPP and Good Pharmacovigilance Practices (GVP) 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 GPP and GVP and the progress of enrolment. 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 a centralised Ipsen/delegated SP. In addition to on-site monitoring visits, the sites will receive regular monitoring phone calls from monitors, in order to:

- Allow for early identification and direct solving of any issue with the site;
- Follow the enrolment of the participants listed in the patient screening log and in particular, to remind the sites to propose the registry study to all eligible participants presenting for a consultation and to identify any issue related to recruitment (e.g. to identify a site with specific difficulties in collecting informed consents, etc);
- Follow the included participants and avoid/limit the drop out of participants;

Answer any questions related to the completion of the eCRF.

9.8.2 Inspections and Auditing Procedures

Authorised personnel from external CA and sponsor-authorised Quality Assurance personnel may carry out inspections and audits. The purpose of an audit is to ensure that ethical, regulatory and quality requirements are fulfilled in all studies performed by the sponsor.

Auditors and inspectors must have direct access to registry study documents and site facilities and to any other locations used for the purpose of the registry study in question (e.g. laboratories).

In the event of the site being notified directly of a regulatory inspection, the investigator must notify the sponsor representative as soon as possible, to assist with preparations for the inspection.

9.8.3 Source Data Verification

According to the FOPal registry study monitoring plan, during monitoring visits, the monitor will verify, by direct reference to the source documents, that the data required by the protocol are accurately reported in the eCRF. However, this verification will only address key data of the eCRF and only be based on available investigator's participant notes.

The source documents must, as a minimum, contain the following: a statement that the participant is included in a registry study, the date on which the informed consent (and assent, if applicable) was obtained prior to participation in the registry study, the identity of the registry study, diagnosis and eligibility criteria, visit dates and any AEs and associated concomitant medication.

Definitions for source data and source documents are given below:

- **Source data:** all original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the registry study. Source data are contained in source documents (original records or certified copies);
- **Source documents:** original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, participant files and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the registry study).

The participant (if adult) or their parent/legally authorised representative (if participant is not an adult) must have consented to their medical records being viewed by sponsor-authorised personnel, and by local, and possibly foreign, CA. This information is included in the ICF.

9.8.4 Data Quality

The investigator is responsible for the validity of all data collected in the FOPal registry and must provide an e-signature, consisting of an individual and confidential username and password combination, to each eCRF to attest to the accuracy and completeness of all the data. This e-signature is declared to be the legally binding equivalent of the handwritten signature.

The eCRF is a validated system with restricted access to study staff only with a personal username and password. The eCRF data transferred from the investigational site to the assigned Data Management group will be reviewed for completeness, consistency, and protocol compliance. Inadequate data can be queried for clarification and any queries generated during the data management process will be tracked by the contracted data management SP according

to the Data Handling Manual. Of note, due to the nature of the FOPal registry study, missing data are expected.

Data consistency and accuracy will be ensured by running real-time checks at the time of data entry in the eCRF. All corrections to the eCRF data are recorded in the system audit trail which automatically tracks the data changes, the user, the time, and the reason. The audit trail function will also allow the changes and clarifications made to be viewed.

9.9 Limitations of the Research Methods

FOPal is an observational, prospective and retrospective registry study designed to collect and assess real-world data on participants with FOP exposed and unexposed to palovarotene. Participants with FOP will be treated in accordance with usual medical practice during their participation in the FOPal registry study. Only relevant data collected as part of routine medical care will be captured using an eCRF by the investigator (patient-reported questionnaires will be completed directly by the participant on paper). If some assessments are not routinely performed by the investigator, they will not complete the corresponding sections in the eCRF. Therefore, some key data may be missing, and the assessments performed and the data provided from different study sites may vary depending on local medical practice. This, however, is an inherent limitation to the observational design of this study, crucial in gathering real-world data on participants with FOP exposed and unexposed to palovarotene.

No formal statistical testing will be performed, and all the analyses will be primarily descriptive in nature.

9.10 Other Aspects

None.

9.11 Regulatory and Ethics Approval

The SP will ensure that all legal and regulatory aspects are covered, including submitting the protocol to the national CA in accordance with local regulatory requirements and obtaining any necessary approvals from the appropriate regulatory authorities prior to registry study initiation.

Before initiating the FOPal registry study, the investigator/institution should have written and dated approval/favourable opinion from the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) for the registry study protocol/amendment(s), inform consent form, any ICF updates, participant recruitment procedures (e.g. advertisements), any written information to be provided to participants such as the Participant Information Sheet and a statement from the IEC/IRB that they comply with local requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

Any changes to the protocol after IEC/IRB approval will require a formal protocol amendment. Changes that do not affect participant safety or data integrity are classified as administrative changes and generally do not require ethics approval. If ethically relevant aspects are concerned, the IEC/IRB must be informed and, if necessary, approval sought prior to implementation. Ethics approval of administrative changes will be obtained if required by local/site IEC/IRB.

Any protocol amendments will be submitted to CA and IEC/IRBs according to local regulatory requirements.

9.12 Compliance with Good Pharmacoepidemiology Practice and Ethical Considerations

The FOPal registry study will be conducted in accordance with the principles of the World Medical Association Declaration of Helsinki (Helsinki, 1964, and all subsequent amendments)

[40], International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) – Good Clinical Practice (GCP) guidelines and the International Ethical Guidelines for Epidemiological Studies, Council for International Organizations of Medical Sciences (CIOMs) [41].

The FOPal registry study is non-interventional and falls outside the scope of European Commission European Union (EU) Directive 2001/20/EC [42] and EU Directive 2005/28/EC [43].

The FOPal registry study complies with Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data [44].

The FOPal registry study will also follow the recommendations of the International Epidemiological Association Guidelines for the Proper Conduct in Epidemiologic Research (GEP) [45], the International Society for Pharmacoepidemiology (ISPE) Guidelines for GPP [39], the European Medicines Agency (EMA) Guideline on GVP [46, 47] (unless safety data collection and reporting is dictated by relevant local legislation in which case that must be followed instead) and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology [48]. The completed ENCePP Checklist for Study Protocols is provided in Appendix 1.

The FOPal registry study will also be conducted in compliance with the ENCePP Code of Conduct for Scientific Independence and Transparency in the Conduct of Pharmacoepidemiological and Pharmacovigilance Studies [49], Ipsen's Code of Ethical Conduct and any other applicable local regulations.

9.13 Informed Consent

Prior to the FOPal registry study entry, the investigator (or a person designated by the investigator) will explain the nature, purpose, benefits, and risks of participation in the registry study to each participant, the participant's parents, or the participant's legally authorised representative. Participants (if adult) or parents/legally authorised representatives (if not an adult) will be provided with a Participant Information Sheet containing information in readily understood language on the benefits and risks associated with participating in the registry study and will be given sufficient time to discuss any concerns and to consider their decision to participate. Signed written informed consent (and assent, if applicable) must be obtained prior to the participant entering the registry study and maintained during the registry study. The sponsor will provide a template of the ICF. The ICF and any participant recruitment materials will follow ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent process may be performed remotely (e.g. to reduce unnecessary burden to patients to come to the clinic) instead of face-to-face (in person and in clinic) with the agreement of the participant, participant's Legally Acceptable Representative (LAR) and/or the impartial witness, and when authorised locally. If authorised locally, the remote informed consent process will follow the same requirements as in person consenting (i.e. ethical standards, local regulatory requirements, and legal requirements, including applicable privacy laws).

The participant, the participant's LAR and/or the impartial witness will be provided with a copy of the ICF by post prior to the remote consent meeting.

The communication channel used for the remote informed consent meeting should protect the confidential information that will be discussed. The participant, participant's LAR and/or the

impartial witness will be informed of the private nature of the discussion that will take place in a remote manner and, if needed, will be encouraged to relocate to a more private setting.

As for in person consenting, participants must have the opportunity to ensure the investigator's identity. Similarly, the investigator should make every effort to check the identity of the participant. Participants will be given the opportunity to ask questions about the study before signing the ICF.

After the consent discussion, the participant, participant's LAR and/or the impartial witness sign (wet ink signature) and date the ICF and send it back by post to the site. The signed ICF should include all pages, including the information sheet, not just the signature page. The investigator (or a person designated by the investigator) will sign (wet ink signature) the form and will send a copy to the participant and/or LAR.

For participants already enrolled in the study, the same process may be applicable in case of any amended ICF. The final versions of the forms must be approved by the sponsor and the IEC/IRB and must contain all the elements included in the template form, in language readily understood by the participant. Each participant's original ICF, personally signed and dated by the participant, the participant's parents or by the participant's legally authorised representative, and by the person who conducted the informed consent discussion, will be retained by the investigator. The investigator will supply all enrolled participants with a copy of their signed ICF.

The ICF may need to be revised during the course of the FOPal registry study if new information becomes available that may be relevant to the safety of the participant or as a result of protocol amendments. In this instance, approval should always be given by the IEC/IRB. It is the investigator's responsibility to ensure that all participants subsequently entered the FOPal registry study, as well as those currently in the registry study, sign the amended form. This is documented as previously described. Parents of participants (or participants' legally authorised representatives) and participants having completed the registry study should be informed of any new information that may impact on their welfare/wellbeing.

The investigator should, with the consent/assent of the participant, the consent of the participant's parents or the participant's legally authorised representative, inform the participant's primary GP about their participation in the FOPal registry study.

For participants already enrolled in the FOPal registry study, eligibility must be reconfirmed, and a new written informed consent must be obtained as per local regulations for any substantial protocol amendments before implementing them.

Participants already enrolled in the FOPal registry study that reach the legal age of consent as per the jurisdiction in which the study is taking place must provide a new written informed consent to remain in the study.

10 PROTECTION OF HUMAN PARTICIPANTS

10.1 Data Collection, Privacy and Confidentiality

After recruitment, each site will be assigned a unique identification number. At enrolment, each participant will be assigned a unique identification number by the sponsor.

Data will be collected in an eCRF via the internet utilising a secured website. Data entry in the eCRF will be performed by the investigator or by the designated person from their team to ensure confidentiality and security of the data.

Any data transmitted will be pseudonymised and will be identified only by the participant number. Only investigating sites will be able to link the numeric identifier to each participant's identity.

The participant must be informed that their personal FOPal registry study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent/assent for their data to be used as described in the informed consent.

The participant must be informed that their medical records may be examined by the sponsor's auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

In case of public data presentation or publication, personal identifiers of participants will not be used.

10.2 Data Protection

As the data controller (study sponsor) is located in France, this study will be conducted in compliance with EU data protection requirements and in particular the EU General Data Protection Regulation 2016/679 [44].

In addition, the sponsor will ensure that all applicable local regulatory requirements for data protection are met.

10.3 Insurance

Insurance may be contracted according to local regulatory requirements.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, SPECIAL SITUATIONS AND ADVERSE EVENTS OF SPECIAL INTEREST FOR EXPOSED PARTICIPANTS

11.1 Definitions

11.1.1 Adverse Event

AE Definition
An AE is any untoward medical occurrence in a patient/participant, administered a medicinal product (palovarotene) and which does not necessarily have a causal relationship with this treatment. NOTE: An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product, whether or not related to the medicinal product.

Events Meeting the AE Definition
Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. electrocardiograms, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e. not related to progression of underlying disease). Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. New condition detected or diagnosed after study treatment administration even though it may have been present before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. For studies involving marketed products in established indications: The signs, symptoms and/or clinical sequelae resulting from lack of effectiveness will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. The disease/disorder being studied or expected progression (e.g. flare-up), signs, or symptoms of the disease/disorder being studied, unless judged by the investigator to be more severe than expected for the participant's condition. Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the AE.

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

11.1.2 Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g. hospitalisation for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalisation or prolongation of existing hospitalisation In general, hospitalisation signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.
Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other important medical event Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Any radiological or clinical fracture, or PPC, must be reported as serious (seriousness criteria should be "important medical event" if no other seriousness criteria are present (e.g. hospitalisation)).
Is a suspected transmission of any infectious agent via an authorised medicinal product

11.1.3 Special Situations

A Special Situation is any incidence of drug exposure during pregnancy (i.e. drug exposure to a foetus in utero (whether the foetus is exposed via the mother taking the product)) or breastfeeding, overdose, underdose, off-label use, misuse, abuse, occupational exposure, medication errors/Intercepted medication error/Potential medication error, counterfeit/falsified medicinal product, unexpected therapeutic benefit, suspected transmission of an infectious agent via a medicinal product, drug interaction, drug dependence or lack of therapeutic effectiveness whilst using the medicinal product. A "Special Situation" should be collected by the investigator and reported to Ipsen whether or not these "Special Situations" are associated with an AE.

11.1.3.1 Pregnancy or Breastfeeding

Pregnancy

Palovarotene is highly teratogenic and must not be used by participants who are or may become pregnant.

In accordance with the label, if pregnancy occurs in a participant exposed to palovarotene, treatment must be stopped immediately, and the participant should be referred to a physician for evaluation and advice. Participants of child-bearing potential must use at least one highly effective method of contraception (e.g. intrauterine device (IUD)) or two effective methods (e.g. combined hormonal contraception in combination with another method of contraception such as a barrier method) during the course of the study.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the product has interfered with a contraceptive method. If pregnancy occurs while enrolled in FOPal, the outcome of the pregnancy will then need to be collected. This applies irrespective of whether the pregnancy is considered to be related to interference with a contraceptive method by the product.

The following maternal, neonatal, and infant outcomes will be assessed:

- Maternal outcomes:
  - Foetal loss: miscarriage, spontaneous abortion, stillbirth, elective or therapeutic abortion, foetal loss – type not specified.
- Neonatal outcomes (from birth to one month):
  - Neonatal death with or without congenital abnormalities (major or minor);
  - Live birth with congenital abnormalities (major* and minor);
  - Live birth without congenital abnormalities;
  - Preterm birth;
  - Small for gestational age.

  ** Major birth defects are defined as major structural or genetic birth defects as conditions that 1) result from a malformation, deformation, or disruption in one or more parts of the body, a chromosomal abnormality, or a known clinical syndrome; 2) are present at birth; and 3) have a serious, adverse effect on health, development, or functional ability.*

- Infant outcomes (from one month to one year, end of follow-up period):
  - Infant death;
  - Postnatal growth deficiency;
  - Infant developmental delay;
  - Infant hospitalisation due to serious illness.

Details of all pregnancies in participants will be collected from the signing of the ICF and the participant will be followed through the first year postpartum to monitor pregnancy-related AEs, and the birth and developmental outcomes through the infant(s)' first year of life. The following monitoring schedule is recommended for data collection:

- Baseline;
- Mid-pregnancy;
- Estimated Due Date (EDD);
- EDD + 6 months;
- EDD + 12 months.

For live-born infants, data should be assessed at 3 timepoints during the data collection: at EDD; EDD + 6 months; and EDD + 12 months.

Information regarding any pregnancies must be collected on the electronic data collection tool or the "Adverse Event and Other Safety Events Report Form for Company-Sponsored Non-Interventional Studies" (134232-FOR) if the electronic data collection tool is unavailable. Pregnancy information, including birth and developmental status of the infant will also be collected in the Drug Exposure During Pregnancy Form for Company-Sponsored Clinical Studies (458088-FOR) and should be provided for all pregnancies, regardless of the outcome.

Abnormal pregnancy outcomes (such as spontaneous abortion, foetal death, stillbirth, livebirth with congenital abnormalities (major and minor), ectopic pregnancy, termination of pregnancy, preterm birth, small for gestational age or foetal growth restriction, neonatal or infant death, and any other foetal or infant abnormalities that may be medically important) are considered SAEs.

Reports of pregnancy must be reported to Ipsen within 24 hours of the investigator's knowledge.

Breastfeeding

Breastfeeding is contraindicated to palovarotene use. No data are available on the presence of palovarotene in human milk, or the effects of palovarotene on the breastfed child, or on milk production. Because of the potential for serious adverse reactions from palovarotene in a breastfed child, lactating women should not breastfeed during treatment with palovarotene.

Any use of an Ipsen product during lactation/ breastfeeding must be collected on the electronic data collection tool or the "Adverse Event and Other Safety Events Report Form for Company-Sponsored Non-Interventional Studies" (134232-FOR) if the electronic data collection tool is unavailable.

11.1.3.2 Overdose, Off-label Use, Misuse, Abuse, Occupational Exposure, Medication Error, Lack of Effectiveness, and other Special Situations

Overdose

Any dose higher than the maximum recommended dose in local label/SmPC. For products which require gradual titration, any dose (initial or maintenance) which is higher than the recommended regime or labelling text will be assessed as 'overdose'. Overdose should be reported in the Special Situations eCRF page whether or not it was associated with an AE. If the Special Situation is associated with an AE, the AE should be reported in the AE eCRF page and AE number should be mentioned in the Special Situations eCRF page. All overdoses should be reported to Ipsen within 7 calendar days using the electronic data collection tool or the "Adverse Event and Other Safety Events Report Form for Company-Sponsored Non-Interventional Studies" (134232-FOR) if the electronic data collection tool is unavailable.

Underdose

Underdose refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is less than the minimum recommended dose according to the authorised product information. Clinical judgement should always be applied.

Underdose use should be reported in the Special Situations eCRF page whether or not it was associated with an AE. If the Special Situation is associated with an AE, the AE should be reported in the AE eCRF page and AE number should be mentioned in the Special Situations eCRF page. All underdose should be reported to Ipsen within 7 calendar days using the electronic data collection tool or the "Adverse Event and Other Safety Events Report Form for Company-Sponsored Non-Interventional Studies" (134232-FOR) if the electronic data collection tool is unavailable.

Off-label Use

Off-label use relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorisation.

Off-label use should be reported in the Special Situations eCRF page whether or not it was associated with an AE. If the Special Situation is associated with an AE, the AE should be reported in the AE eCRF page and AE number should be mentioned in the Special Situations eCRF page. All off-label use should be reported to Ipsen within 7 calendar days using the electronic data collection tool or the "Adverse Event and Other Safety Events Report Form for Company-Sponsored Non-Interventional Studies" (134232-FOR) if the electronic data collection tool is unavailable.

Misuse

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the Marketing Authorisation.

Misuse should be reported in the Special Situations eCRF page whether or not it was associated with an AE. If the Special Situation is associated with an AE, the AE should be reported in the AE eCRF page and AE number should be mentioned in the Special Situations eCRF page. All misuse should be reported to Ipsen within 7 calendar days using the electronic data collection tool or the "Adverse Event and Other Safety Events Report Form for Company-Sponsored Non-Interventional Studies" (134232-FOR) if the electronic data collection tool is unavailable.

Abuse

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Abuse should be reported in the Special Situations eCRF page whether or not it was associated with an AE. If the Special Situation is associated with an AE, the AE should be reported in the AE eCRF page and AE number should be mentioned in the Special Situations eCRF page. All abuse should be reported to Ipsen within 7 calendar days using the electronic data collection tool or the "Adverse Event and Other Safety Events Report Form for Company-Sponsored Non-Interventional Studies" (134232-FOR) if the electronic data collection tool is unavailable.

Occupational Exposure

Occupational exposure refers to the exposure to a medicinal product, as a result of one's professional or non-professional occupation. It does not include the exposure to one of the ingredients during the manufacturing process before the release as finished product.

Occupational exposure should be reported in the Special Situations eCRF. All occupational exposure should be reported to Ipsen within 7 calendar days using the electronic data collection tool or the "Adverse Event and Other Safety Events Report Form for Company-Sponsored Non-Interventional Studies" (134232-FOR) if the electronic data collection tool is unavailable.

Medication Error, Intercepted Medication Error, Potential Medication Error

Medication error is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the participant.

An intercepted medication error indicates that an intervention caused a break in the chain of events in the treatment process before reaching the patient which would have resulted in a "potential" AE. The intervention has prevented actual harm being caused to the patient.

Potential medication error refers to all possible mistakes in the prescribing, storing, dispensing, preparation for administration or administration of a medicinal product by all persons who are involved in the medication process and may lead to a medication error with or without harm.

These situations should be reported in the Special Situations eCRF whether or not it was associated with an AE. If the Special Situation is associated with an AE, the AE should be reported in the AE eCRF page and AE number should be mentioned in the Special Situations eCRF page. It should be reported to Ipsen within 7 calendar days using the electronic data collection tool or the "Adverse Event and Other Safety Events Report Form for Company-Sponsored Non-Interventional Studies" (134232-FOR) if the electronic data collection tool is unavailable.

Drug Interactions

Drug interactions involve the effects of one drug being altered by the presence of another drug, food, device or substance. Drug interactions may make the drug less effective, cause unexpected side effects, or increase the action of a particular drug.

Drug interaction should be reported in the Special Situations eCRF whether or not it was associated with an AE. If the Special Situation is associated with an AE, the AE should be reported in the AE eCRF page and AE number should be mentioned in the Special Situations eCRF page. All drug interactions should be reported to Ipsen within 7 calendar days using the electronic data collection tool or the "Adverse Event and Other Safety Events Report Form for Company-Sponsored Non-Interventional Studies" (134232-FOR) if the electronic data collection tool is unavailable.

Drug Dependence

This refers to an overwhelming desire by a patient or consumer to take a drug together with inability to control or stop its use despite harmful consequences.

Drug dependence should be reported in the Special Situations eCRF whether or not it was associated with an AE. If the Special Situation is associated with an AE, the AE should be

reported in the AE eCRF page and AE number should be mentioned in the Special Situations eCRF page. All drug dependence should be reported to Ipsen within 7 calendar days using the electronic data collection tool or the "Adverse Event and Other Safety Events Report Form for Company-Sponsored Non-Interventional Studies" (134232-FOR) if the electronic data collection tool is unavailable.

Lack of Effectiveness

Lack of effectiveness can be defined as the extent to which a drug does not achieve its intended effect in the usual clinical setting.

Lack of therapeutic effectiveness should be reported in the Special Situations eCRF page whether or not it was associated with an AE. If the Special Situation is associated with an AE, the AE should be reported in the AE eCRF page and AE number should be mentioned in the Special Situations eCRF page. All lack of therapeutic effectiveness should be reported to Ipsen within 7 calendar days using the electronic data collection tool or the "Adverse Event and Other Safety Event Report Form for Company-Sponsored Non-Interventional Studies" (134232-FOR) if the electronic data collection tool is unavailable.

Unexpected Therapeutic Benefit

Unanticipated desirable and beneficial effects resulting from a medical treatment.

Unexpected therapeutic benefit should be reported in the Special Situations eCRF page whether or not it was associated with an AE. If the Special Situation is associated with an AE, the AE should be reported in the AE eCRF page and AE number should be mentioned in the Special Situations eCRF page. All unexpected therapeutic benefit should be reported to Ipsen within 7 calendar days using the electronic data collection tool or the "Adverse Event and Other Safety Event Report Form for Company-Sponsored Non-Interventional Studies" (134232-FOR) if the electronic data collection tool is unavailable.

Suspected transmission of an infectious agent via a medicinal product

Any suspected transmission of an infectious agent via a medicinal product should be considered as a serious adverse reaction.

Any organism, virus or infectious particle (e.g. prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

Suspected transmission of an infectious agent via a medicinal product should be reported in the Special Situations eCRF page whether or not it was associated with an AE. If the Special Situation is associated with an AE, the AE should be reported in the AE eCRF page and AE number should be mentioned in the Special Situations eCRF page. They should be reported to Ipsen within 7 calendar days using the electronic data collection tool or the "Adverse Event and Other Safety Event Report Form for Company-Sponsored Non-Interventional Studies" (134232-FOR) if the electronic data collection tool is unavailable.

Counterfeit/Falsified Medicinal Product (only if the product has been administered)

Counterfeit medicine is one which is deliberately and fraudulently mislabelled with respect to identity and/or source, infringing Ipsen intellectual property rights. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient ingredients or with fake packaging.

Falsified medicinal product is any medicinal product with a false representation of:

(a) its identity, including its packaging and labelling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients;

(b) its source, including its manufacturer, its country of manufacturing, its country of origin or its MAH; or

(c) its history, including the records and documents relating to the distribution channels used.

These Special Situations should be reported in the Special Situations eCRF page whether or not it was associated with an AE. If the Special Situation is associated with an AE, the AE should be reported in the AE eCRF page and AE number should be mentioned in the Special Situations eCRF page. All situations of Counterfeit/Falsified medicinal product administration should be reported to Ipsen within 7 calendar days using the electronic data collection tool or the "Adverse Event and Other Safety Event Report Form for Company-Sponsored Non-Interventional Studies" (134232-FOR) if the electronic data collection tool is unavailable.

11.1.4 Adverse Events of Special Interest

Adverse events of special interest are AEs that may not be serious but are of special importance to a particular drug or class of drugs.

Adverse events of special interest for this study include:

- PPC;
- Fractures;
- Psychiatric AEs;
- Hepatic AEs.
- Convulsions AEs

These events must be collected on the AE form of the eCRF according to the completion guideline and using the specific AESI reporting option.

If they meet the seriousness criteria, they should also be reported as SAEs (Section 11.1.2).

11.2 Time Period and Frequency for Collecting and Reporting of AEs, SAEs, Special Situations and AESIs Information

11.2.1 Collection of AEs/SAEs/Special Situations/AESIs in the eCRF

The collection and reporting of AEs/SAEs/Special Situations/AESIs will follow regulations related to non-interventional studies (NIS).

All AEs/SAEs/AESIs, whether they are serious/nonserious or related/unrelated, and all Special Situations should be collected in the eCRF during the course of the FOPal registry study. Adverse events will be assessed according to incidence, intensity, causality, outcome, action taken and seriousness.

All AEs/SAEs/Special Situations/AESIs will be collected in the eCRF from the signing of the ICF until the last palovarotene intake + 30 days, and will include retrospective AEs (i.e. retrospective important medical events) from the first dose of marketed palovarotene intake for exposed non-naïve participants until signed informed consent.

11.2.2 Reporting of SAEs, AESIs, Nonserious Adverse Drug Reactions and Special Situations to Sponsor Pharmacovigilance

Investigators must report to Ipsen Pharmacovigilance all the following events using the electronic data collection tool or the “Adverse Event and Other Safety Events Report Form for Company-Sponsored Non-Interventional Clinical Studies” (134232-FOR) if the electronic data collection tool is unavailable:

- All SAEs: related and non-related;
- All AESIs: related and non-related;
- All related nonserious AEs (adverse drug reactions);
- Any Special Situations (see definitions in Section 11.1.3).

Retrospective SAEs, AESIs, related nonserious AEs and Special Situations (i.e. retrospective important medical events) should not be reported to the sponsor **except if** they have never been reported as spontaneous cases.

Primary Data Collection NIS		
Safety Event	**Collected on the eCRF**	**Reported on the « AE and Other Safety Events for Company-Sponsored NIS Form » (134232-FOR) to Ipsen Global Pharmacovigilance (if the electronic data collection tool is unavailable)**
Nonserious AE	All AEs related or not	Only the related AEs — within 7 calendar days of awareness
SAE	All SAEs related or not	All — within 24 hours of awareness
AESI	All AESIs related or not	All – within 24 hours of awareness
Pregnancy	All pregnancies	All — within 24 hours of awareness*
Special Situations	All Special Situations related or not (regardless of whether associated with an AE)	All (regardless of whether associated with an AE) — within 7 calendar days of awareness

* Drug Exposure During Pregnancy Form for Company-Sponsored Clinical Studies (458088-FOR) should also be completed.

AE=Adverse Event; AESI=Adverse Event of Special Interest; eCRF= electronic Case Report Form; NIS=Non-Interventional Study; SAE=Serious Adverse Event.

All SAEs, AESIs and pregnancies will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours (once known), as indicated below. The investigator will submit any updated SAE, AESI, and pregnancy data to the sponsor within 24 hours of it being available.

All nonserious related AEs and Special Situations (except pregnancy) will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 7 calendar days (once known), as indicated below.

AE (related), SAE, Special Situation and AESI Reporting to the sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an AE (related), SAE, Special Situation or AESI to the sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper NIS AE form (134232-FOR) to report the AESI, SAE and pregnancy within 24 hours of awareness of the event and to report nonserious related AE and Special Situation (excluding pregnancy and Special Situations associated with an SAE or AESI) within 7 calendar days. The site will enter the AE (related), SAE, Special Situation and AESI data into the electronic system as soon as it becomes available again.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new AE (related), SAE, Special Situation or AESI from a study participant or receives updated data on a previously reported AE (related), SAE Special Situation or AESI after the electronic data collection tool has been taken off-line, then the site can report this information on a paper NIS AE form (134232-FOR) (see next section).
- Contacts for AE (related), SAE, Special Situation, or AESI reporting can be found on the NIS AE form (134232-FOR).

AE (related), SAE, Special Situation or AESI Reporting to sponsor via paper NIS AE form
• The site will email the NIS AE form (134232-FOR) to the sponsor if the electronic data collection tool is unavailable (**Email:** PPD). It must be retrospectively recorded as soon as the electronic data collection tool becomes available. • Contacts for AE (related), SAE, Special Situation or AESI reporting can be found on the NIS AE form (134232-FOR).

All AEs will be processed by Ipsen according to their relevant SOPs. This includes the follow up of AE reports with the investigator, as required.

If an AE occurs with a "non-Ipsen product", the investigator should consider informing the CA in the Member State where the event occurred or to the Marketing Authorisation Holder (MAH) of the suspected medicinal product, but not to both (to avoid duplicate reporting).

Mandatory Information for reporting an Adverse Event

The following information is the minimum that must be provided to Ipsen's Pharmacovigilance contact within 24 hours for an SAE, AESI and pregnancy and within 7 days for a nonserious related AE of awareness for each AE:

- Participant identifier;
- Product name;
- AE description including assessment of causal relationship and seriousness;
- Investigator name and contact details.

The additional information included in the AE report form must be provided to Ipsen as soon as it is available.

The investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The investigator should also try to separate a primary AE considered as the foremost untoward medical occurrence from secondary AEs which occurred as complications. The investigator should also provide the batch number and expiry date of the concerned product wherever possible.

11.3 Method of Detecting AEs, SAEs and AESIs

The method of recording, evaluating, and assessing causality of AEs, SAEs and AESIs and the procedures for completing and transmitting related AE/SAE/AESI reports are provided below.

Care will be taken not to introduce bias when detecting AEs, SAEs and/or AESIs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

AE/SAE/AESI Recording

- When an AE/SAE/AESI occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/AESI information in the eCRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to sponsor pharmacovigilance in lieu of completion of the AE/SAE/AESI eCRF page.
- There may be instances when copies of medical records for certain cases are requested by sponsor pharmacovigilance. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor pharmacovigilance.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE/AESI.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE, SAE and AESI reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Other measures to evaluate AEs, SAEs and AESIs may be utilised (e.g. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE)).

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE/AESI.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.

- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in their assessment.
- For each AE/SAE/AESI, the investigator must document in the medical notes that they has reviewed the AE/SAE/AESI and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to sponsor pharmacovigilance. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor pharmacovigilance.
- The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

11.4 Follow-up of AEs, SAEs, Special Situations and AESIs

After the initial AE/SAE/Special Situation/AESI report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs including, SAEs (defined in Section 11.1.2), Special Situations (defined in Section 11.1.3), and AESIs (defined in Section 11.1.4) will be followed until resolution, the event is otherwise explained, the participant is lost to follow-up or up to 30 days after last palovarotene intake. Further information on follow-up procedures is provided below.

Follow-up of AEs, SAEs, Special Situations and AESIs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the registry study or during a recognised follow-up period, the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE and AESI data to the sponsor within 24 hours of receipt of the information.

11.5 Regulatory Reporting Requirements for SAEs and Related AEs

- Prompt notification by the investigator to the sponsor of a SAE/related AE is essential so that legal obligations and ethical responsibilities towards the safety of participants are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of any medicinal product. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs and investigators.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will review and then file it and will notify the IRB/IEC, if appropriate according to local requirements.

11.6 Expectedness of Events

The reference document for assessing expectedness of AEs/events in this study will be the current approved United States Prescribing Information (USPI) for palovarotene.

12 PLANS FOR DISSEMINATING AND COMMUNICATING REGISTRY STUDY RESULTS

12.1 Registry Study Reports

A final registry study report will be prepared once the registry study is complete.

Interim effectiveness and safety descriptive analyses are planned to be delivered for publication purposes as required.

12.2 Publication Policy

12.2.1 Ethical Obligation to Publish

Ipsen is committed to disclosing information about the studies it sponsors. Results may be communicated at scientific meetings and all reasonable efforts must be made to seek publication of key data in a peer-reviewed scientific journal.

As a minimum, a summary of the final data should be posted in an associated publicly available database.

12.2.2 Publications Steering Committee

There will be a Publications Steering Committee composed of external experts (clinicians and scientists) as well as patients and representatives of patient associations with the main objective of driving publications. The committee will meet annually. A charter has been developed to describe the roles and responsibilities of the committee.

The Steering Committee should discuss and agree the publication plan and appropriate authors to be invited for planned publications in advance. Where possible, all contributing investigators should be acknowledged, together with any others who may have contributed, but not sufficiently to qualify for authorship.

The Steering Committee will also involve the Global Medical Publications and Communications (GMPC) Manager and other Ipsen personnel (e.g. Medical Director, Biometry lead), to plan publications and review data sharing requests.

12.2.3 Company-sponsored Publications

Specific publication concepts, including data to be covered, target congress/journal and proposed authors, should be discussed with the appropriate GMPC Manager, reviewed by the Publications Strategy Group, and incorporated in the relevant publication plan before initiation.

All company-sponsored publications arising from the FOPal registry study will be reviewed by relevant functions at Ipsen, coordinated by GMPC as per the applicable SOP. Requests and suggestions for changes will be discussed with all authors (and medical writer, if applicable). Resolution of scientific differences in the presentation or interpretation of the registry study findings will be conducted along principles of honest scientific debate and mediated by the lead author. Review comments must be answered before a final version for submission can be approved by the authors. All company-sponsored manuscripts should be published as immediate open access.

12.2.4 Non-company-sponsored Publications

For publications not sponsored by Ipsen, the sponsor requires that reasonable opportunity be given to review the content and conclusions of any abstract, presentation, or manuscript before the material is submitted for publication or communicated. This condition also applies to any amendments that are subsequently requested by referees or journal editors. Ipsen will undertake to comment on the draft documents within the period agreed in the contractual arrangements (different time periods are allowed according to the types of publication), including registry

study agreements, governing the relationship between Ipsen and authors (or the author's institution). Requested amendments should be carefully considered by the author(s), provided they do not alter the scientific value of the material. Where possible, non-company-sponsored manuscripts should be published as immediate open access.

12.2.5 Authorship

Selection of authors for scientific publications will follow the International Committee of Medical Journal Editors guidelines (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html). Those named as authors, whether employed by Ipsen or an Ipsen affiliate, or external investigators, 'should have participated sufficiently in the work to take public responsibility for the content'. Time spent on authorship activities should not be reimbursed.

Authorship should be based on:

- Substantial contributions to the conception and design, or acquisition of data, or analysis and interpretation of data;
- Drafting the article or revising it critically for important intellectual content;
- Final approval of the version to be published;
- Agreement to be accountable for all aspects for the work, thereby ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

All authors of a publication should meet all four criteria. Every author must agree to their inclusion in the list of authors. Professional medical writing support may be used.

12.2.6 Intellectual Property

If patentability would be adversely affected by data publication, publication will be delayed until (i) a patent application has been filed for the content of the publication in accordance with applicable provisions of the registry study agreement concerned, (ii) Ipsen consents to the publication, or (iii) after such a time as may be agreed in the contractual arrangements, including registry study agreements, governing the relationship between Ipsen and authors (or authors' institution) after receipt of the proposed publication by Ipsen, whichever of these provisos (i), (ii) or (iii) is satisfied first.

The author(s) undertake(s) to reasonably consider Ipsen's request for delay to the proposed publication should the sponsor reasonably deem it premature to publish the results obtained at the stage of the registry study concerned.

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LIST OF APPENDICES

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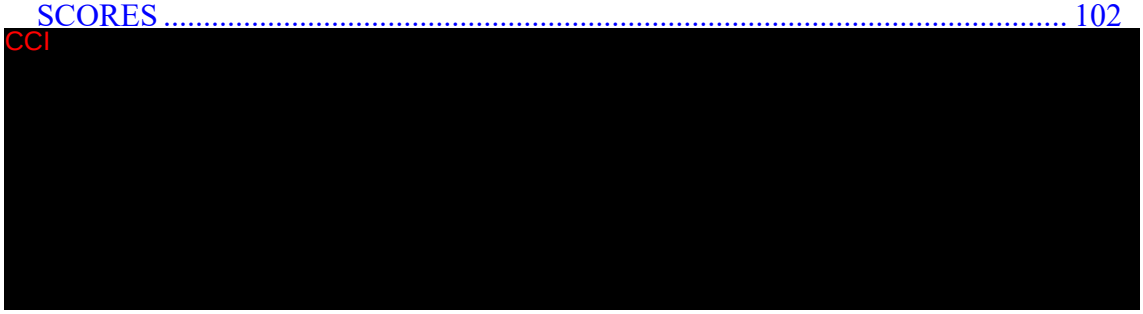

Appendix 1 EUROPEAN NETWORK OF CENTRES FOR PHARMACOEPIDEMIOLOGY AND PHARMACOVIGILANCE (ENCEPP) CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer "N/A" (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: An International Observational Registry Study to Further Describe Long-term Safety and Effectiveness of Palovarotene in Patients with Fibrodysplasia Ossificans Progressiva (FOP)

Study reference number: CLIN-60120-453

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	N/A
1.1.4 Interim report(s)	☐	☒	☐	6
1.1.5 Registration in the EU PAS Register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6
Comments:				

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.4, 8.1
2.1.2 The objective(s) of the study?	☒	☐	☐	8.2
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.3
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	N/A
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	N/A
Comments: Analyses in this study are primarily descriptive in nature, no formal statistical testing will be performed, therefore hypotheses are not applicable.				

1 Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
2 Date from which the analytical dataset is completely available.

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g. rate, risk, prevalence)	☐	☐	☒	N/A
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	N/A
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11
Comments: Analyses in this study are primarily descriptive in nature, no formal statistical testing will be performed.				

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	9.2.3
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2.4
4.2.2 Age and sex	☒	☐	☐	9.2.1, 9.2.3
4.2.3 Country of origin	☐	☒	☐	9.2.1, 9.2.3
4.2.4 Disease/indication	☒	☐	☐	9.2.3
4.2.5 Duration of follow-up	☒	☐	☐	9.2.4
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1, 9.2.2
Comments: The registry study will be implemented in participating countries where palovarotene is marketed.				

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.2.7
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	N/A
5.3 Is exposure classified according to time windows?	☐	☐	☒	N/A
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.2.7
5.5 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	N/A
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	N/A
Comments: This study will report the use of palovarotene in a real-world setting and is primarily descriptive in nature.				

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3, 9.7
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	N/A
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☒	☐	☐	9.3
Comments:				

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	N/A
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	N/A
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	N/A
Comments:				

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7.4
Comments:				

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4, 9.8.3
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4, 9.8.3
9.1.3 Covariates and other characteristics?	☐	☐	☒	N/A
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.2, 9.8.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2, 9.8.3
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle, etc.)	☐	☐	☒	N/A
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.7.3.3

Section 9: Data sources	Yes	No	N/A	Section Number
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.7.3.7.1
9.3.3 Covariates and other characteristics?	☐	☐	☒	N/A
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.6.1
Comments:				

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7.3
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.3
10.4 Are stratified analyses included?	☐	☐	☒	N/A
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.4
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	N/A
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.3.1
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	N/A
Comments:				

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	N/A
Comments:				

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				

Section 12: Limitations	Yes	No	N/A	Section Number
12.1.1 Selection bias?	☐	☐	☒	N/A
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	N/A
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.2.4, 9.5,
Comments:				

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.11
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	N/A
13.3 Have data protection requirements been described?	☒	☐	☐	10.1, 10.2
Comments:				

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5
Comments:				

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12
Comments:				

Name of the main author of the protocol:
Date: / /
Signature: _____

Appendix 2 CONVERSION TABLES OF PROMIS RAW SCORE INTO T-SCORES

Table 6 PROMIS T-Score Conversions for Adult Global Physical and Mental Health

Adult Global Physical Health			Adult Global Mental Health		
Raw Score	**T-Score**	**Standard Error**	**Raw Score**	**T-Score**	**Standard Error**
4	16.2	4.8	4	21.2	4.6
5	19.9	4.7	5	25.1	4.1
6	23.5	4.5	6	28.4	3.9
7	26.7	4.3	7	31.3	3.7
8	29.6	4.2	8	33.8	3.7
9	32.4	4.2	9	36.3	3.7
10	34.9	4.1	10	38.8	3.6
11	37.4	4.1	11	41.1	3.6
12	39.8	4.1	12	43.5	3.6
13	42.3	4.2	13	45.8	3.6
14	44.9	4.3	14	48.3	3.7
15	47.7	4.4	15	50.8	3.7
16	50.8	4.6	16	53.3	3.7
17	54.1	4.7	17	56	3.8
18	57.7	4.9	18	59	3.9
19	61.9	5.2	19	62.5	4.2
20	67.7	5.9	20	67.6	5.3

PROMIS=Patient-Reported Outcomes Measurement Information System

Table 7 PROMIS T-Score Conversions for Paediatric Global Health

Paediatric Self-Completed Total			Paediatric Proxy-Completed Total		
Raw Score	**T-Score**	**Standard Error**	**Raw Score**	**T-Score**	**Standard Error**
7	16	3.4	7	14.7	2.9
8	17.1	3.6	8	15.3	3.1
9	18.3	3.7	9	16	3.2
10	19.7	3.8	10	16.9	3.4
11	21.2	3.8	11	18.1	3.6
12	22.8	3.7	12	19.4	3.7
13	24.4	3.6	13	21	3.8
14	26.1	3.6	14	22.7	3.8
15	27.6	3.5	15	24.4	3.7
16	29.2	3.5	16	26.1	3.7
17	30.8	3.5	17	27.7	3.7
18	32.4	3.6	18	29.4	3.8
19	34	3.6	19	31.2	3.8
20	35.6	3.6	20	32.9	3.8
21	37.2	3.6	21	34.6	3.8
22	38.8	3.6	22	36.2	3.8
23	40.4	3.6	23	37.9	3.9
24	42.1	3.7	24	39.7	4
25	43.9	3.7	25	41.7	4
26	45.7	3.6	26	43.6	3.9
27	47.5	3.6	27	45.4	3.8
28	49.2	3.6	28	47.3	3.9
29	51.1	3.7	29	49.3	4.1
30	53.3	3.9	30	51.8	4.4
31	55.7	4.2	31	54.5	4.7
32	58.3	4.5	32	57.3	5
33	61.1	4.9	33	60.2	5.4
34	64.2	5.4	34	63.2	6
35	67.5	6.1	35	66.1	6.5

PROMIS=Patient-Reported Outcomes Measurement Information System

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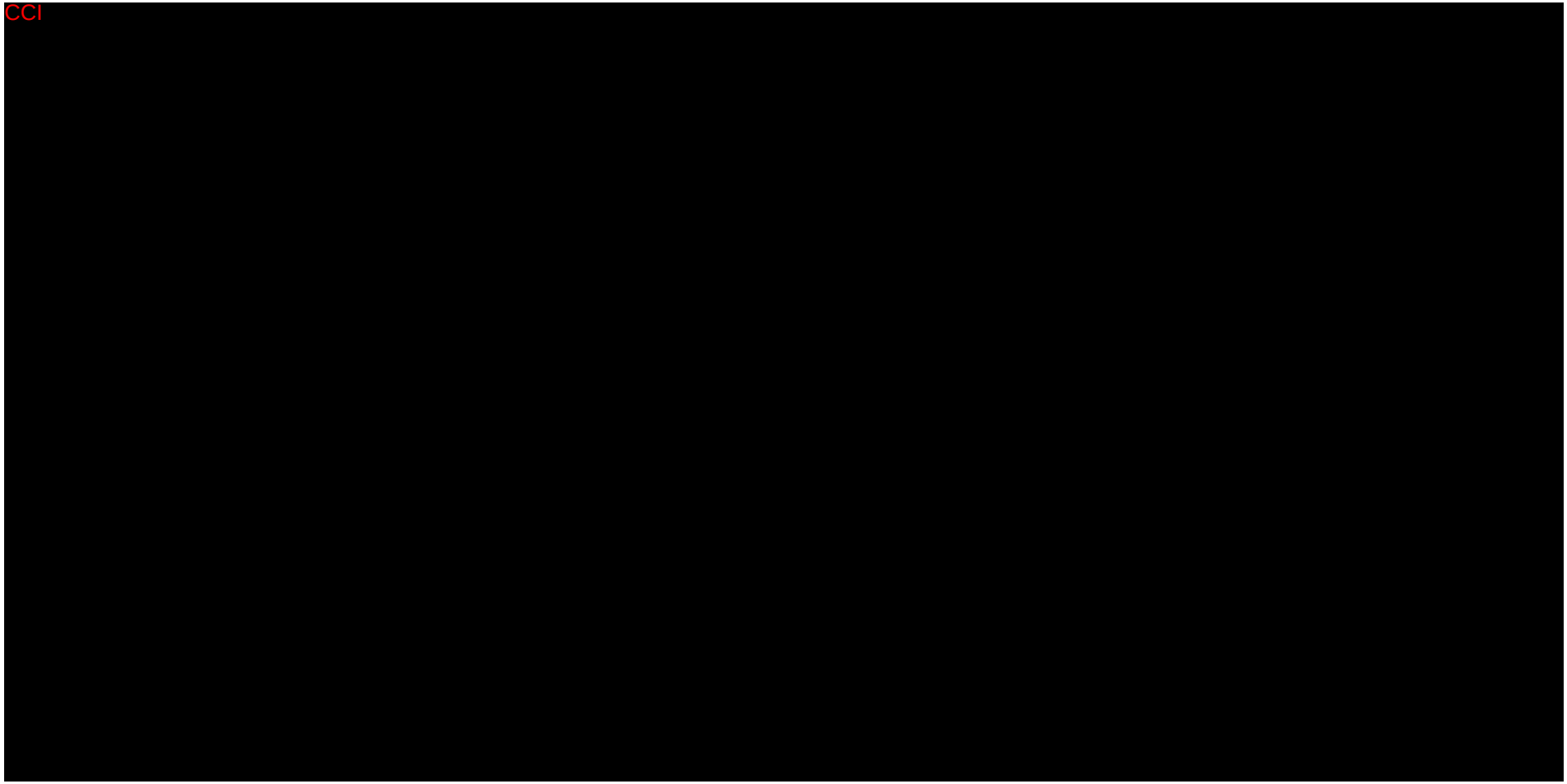
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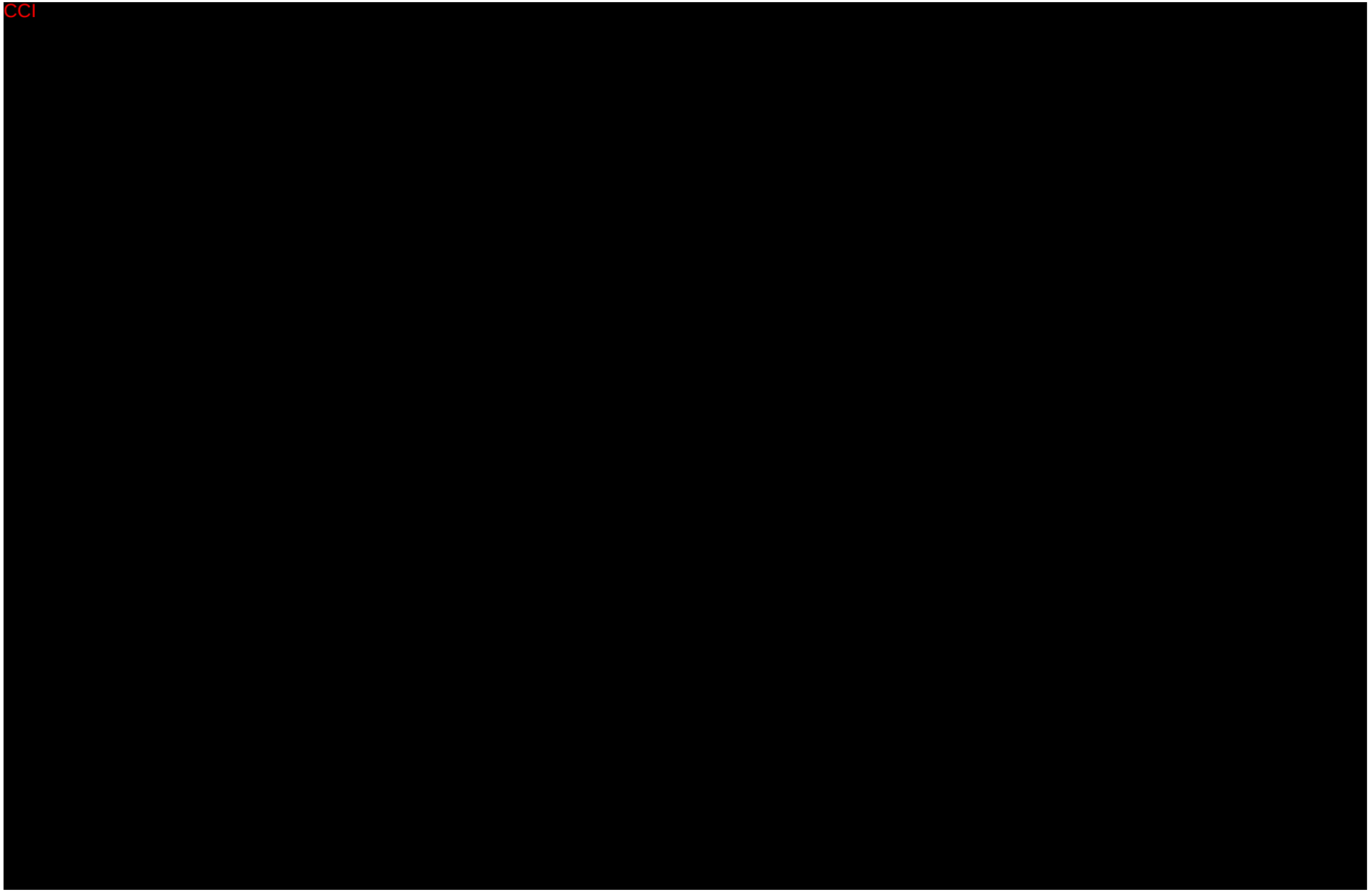

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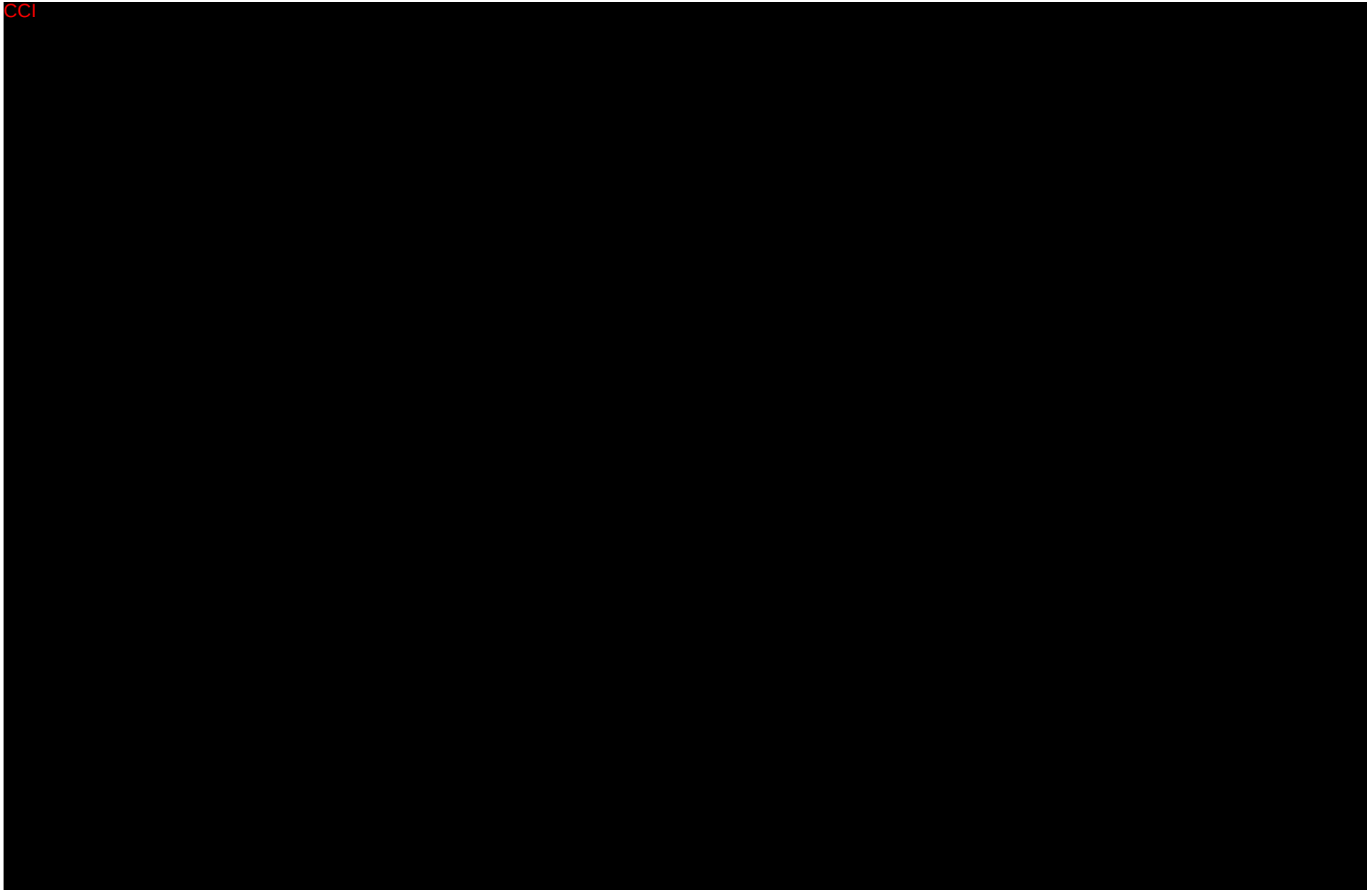

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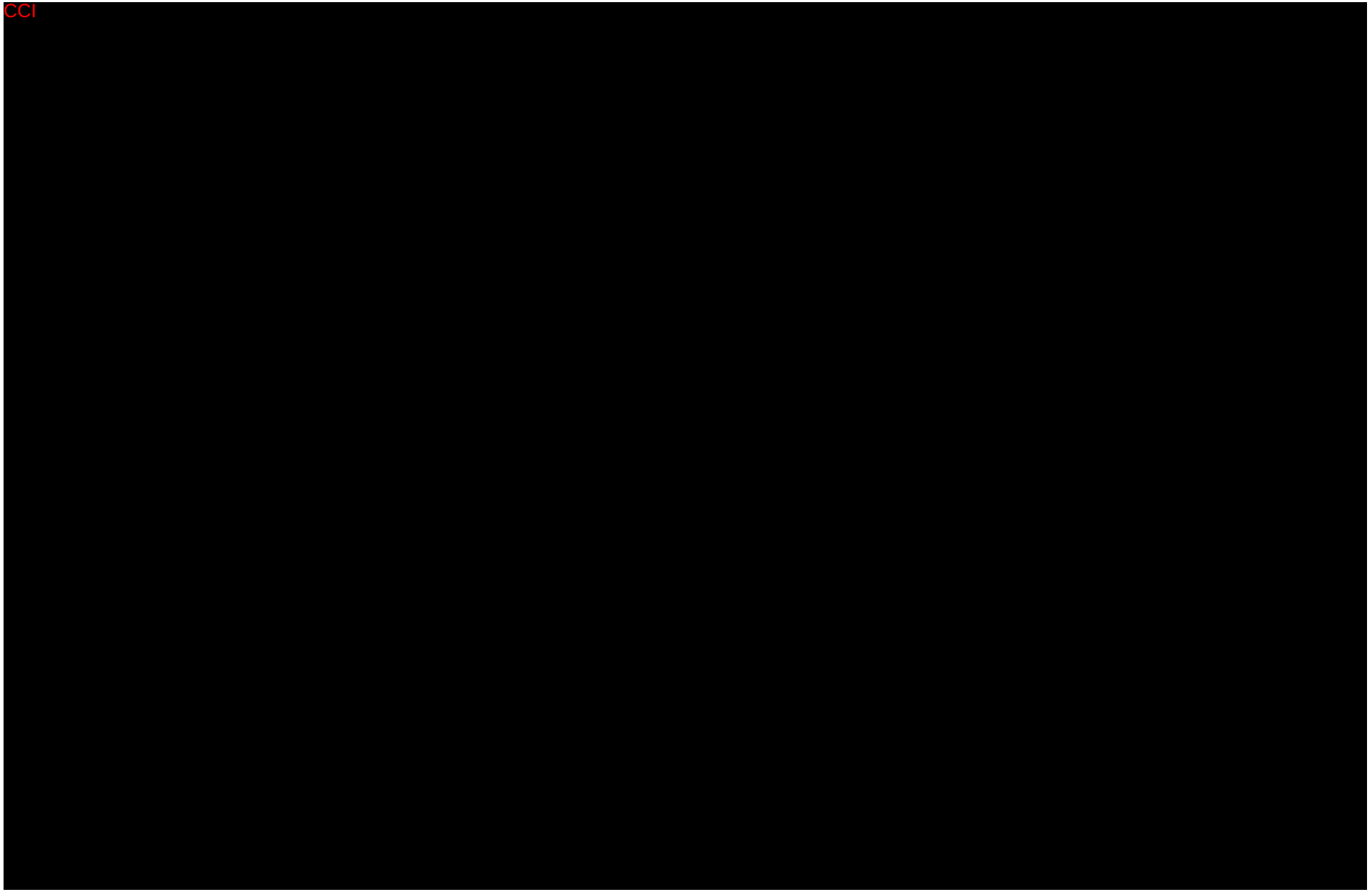

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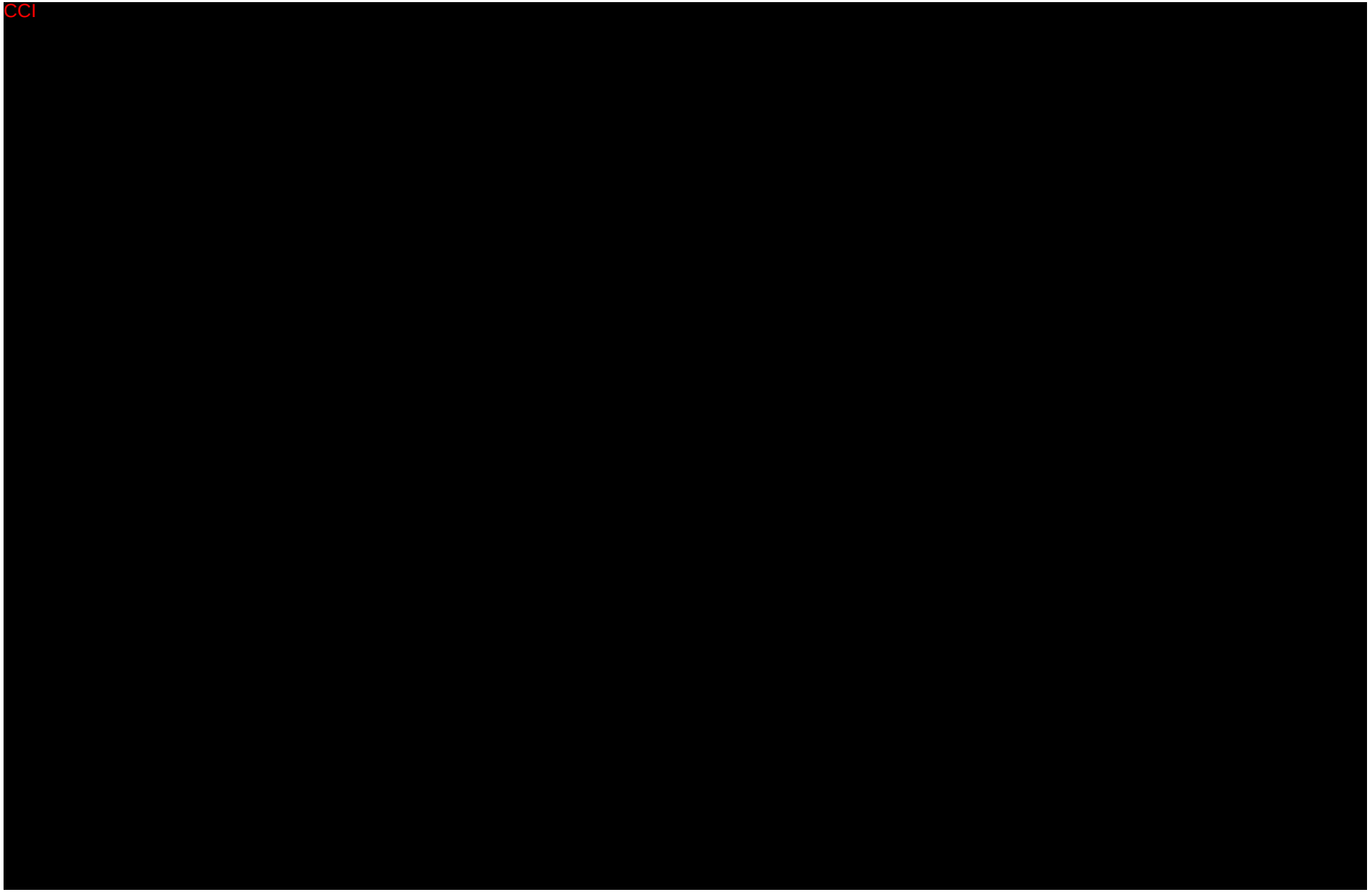

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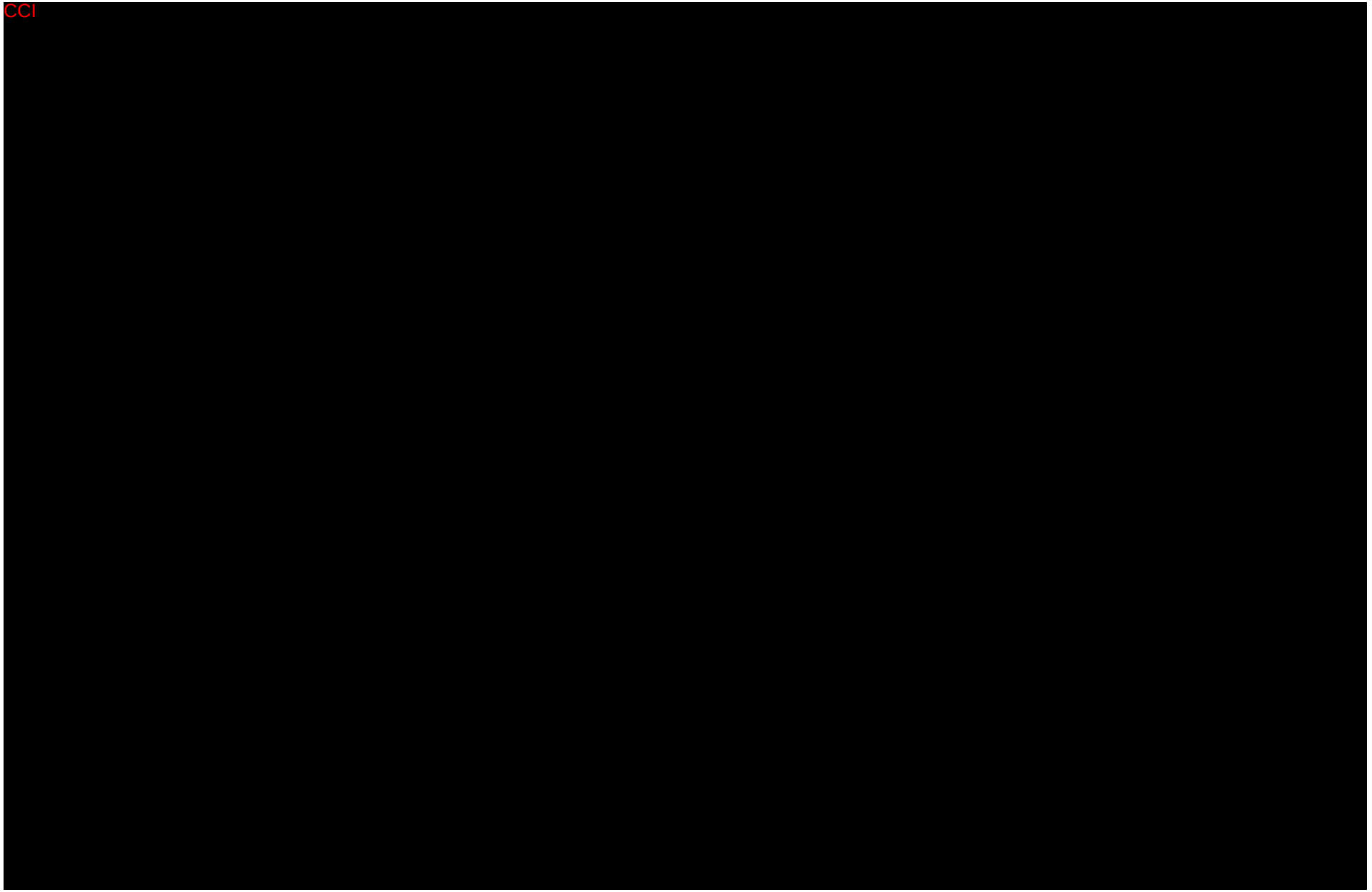

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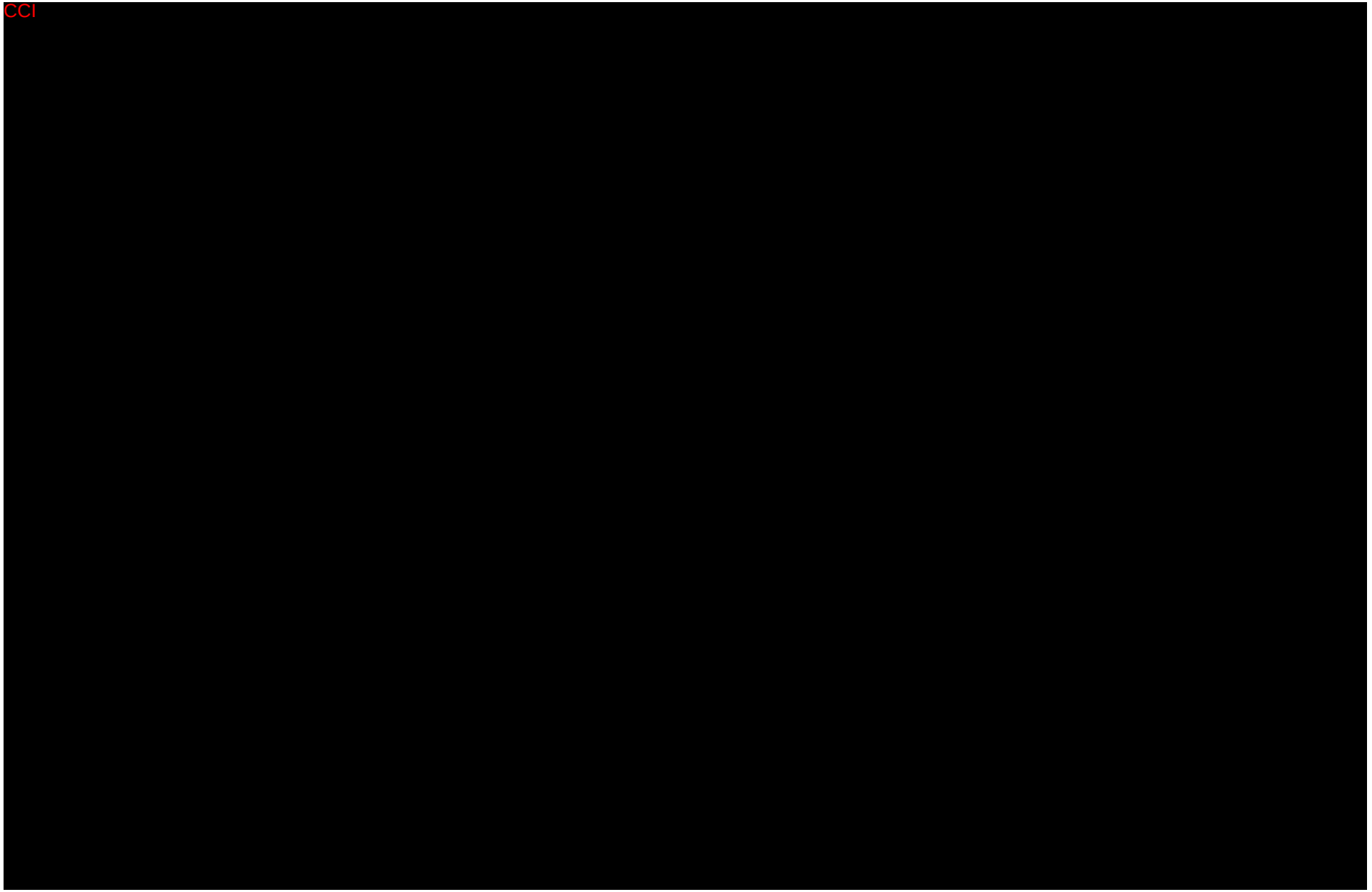

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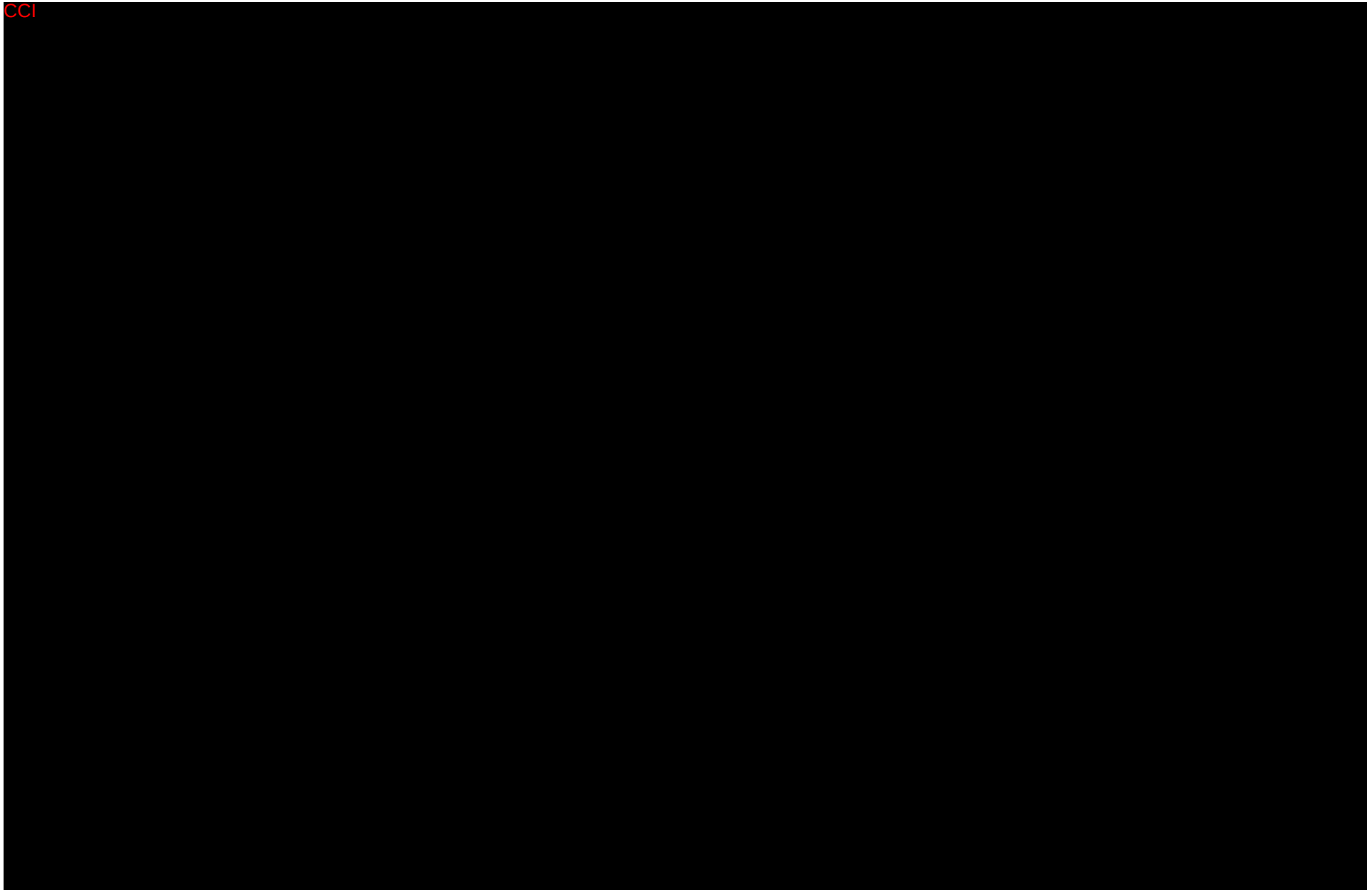

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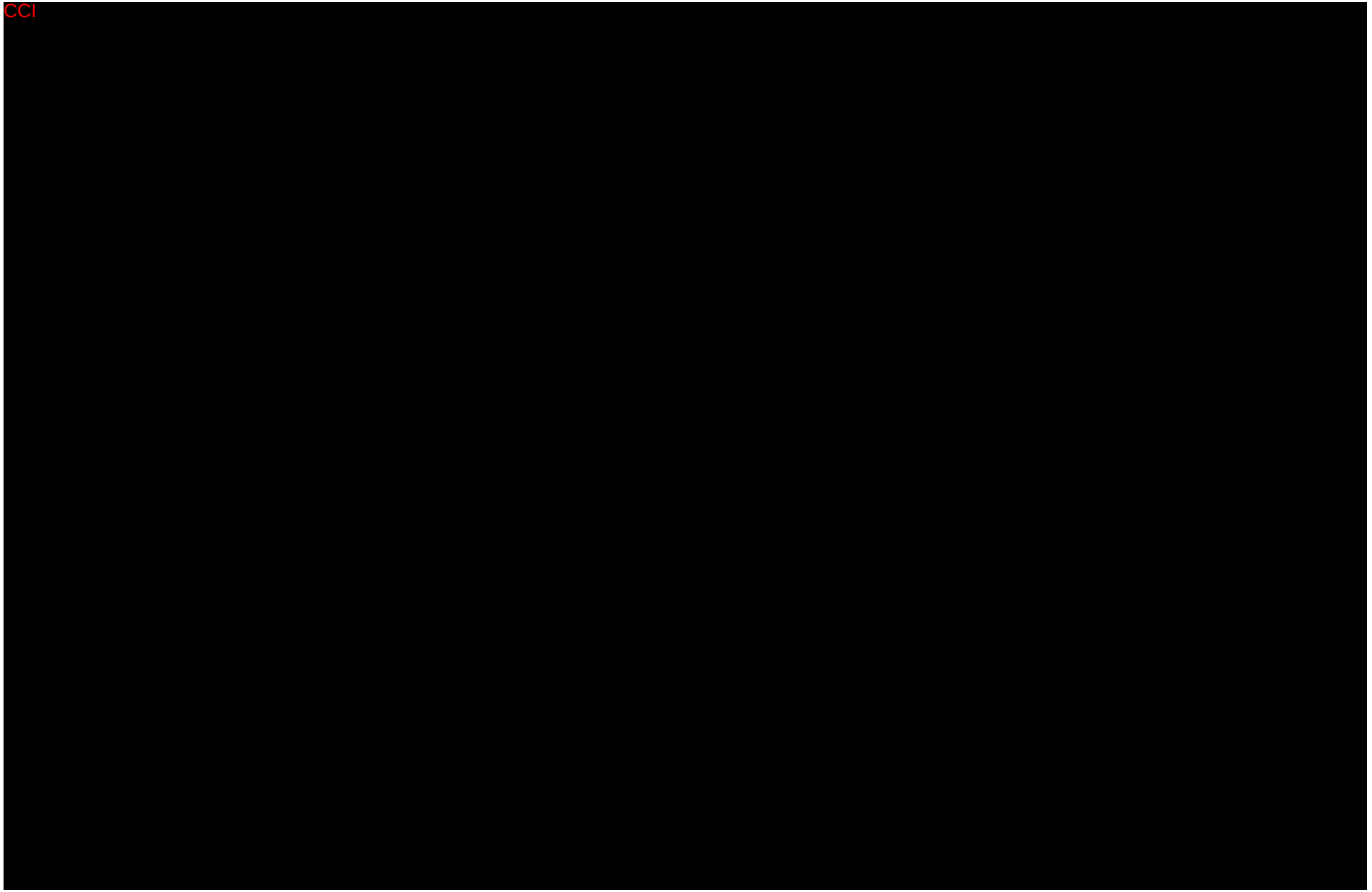

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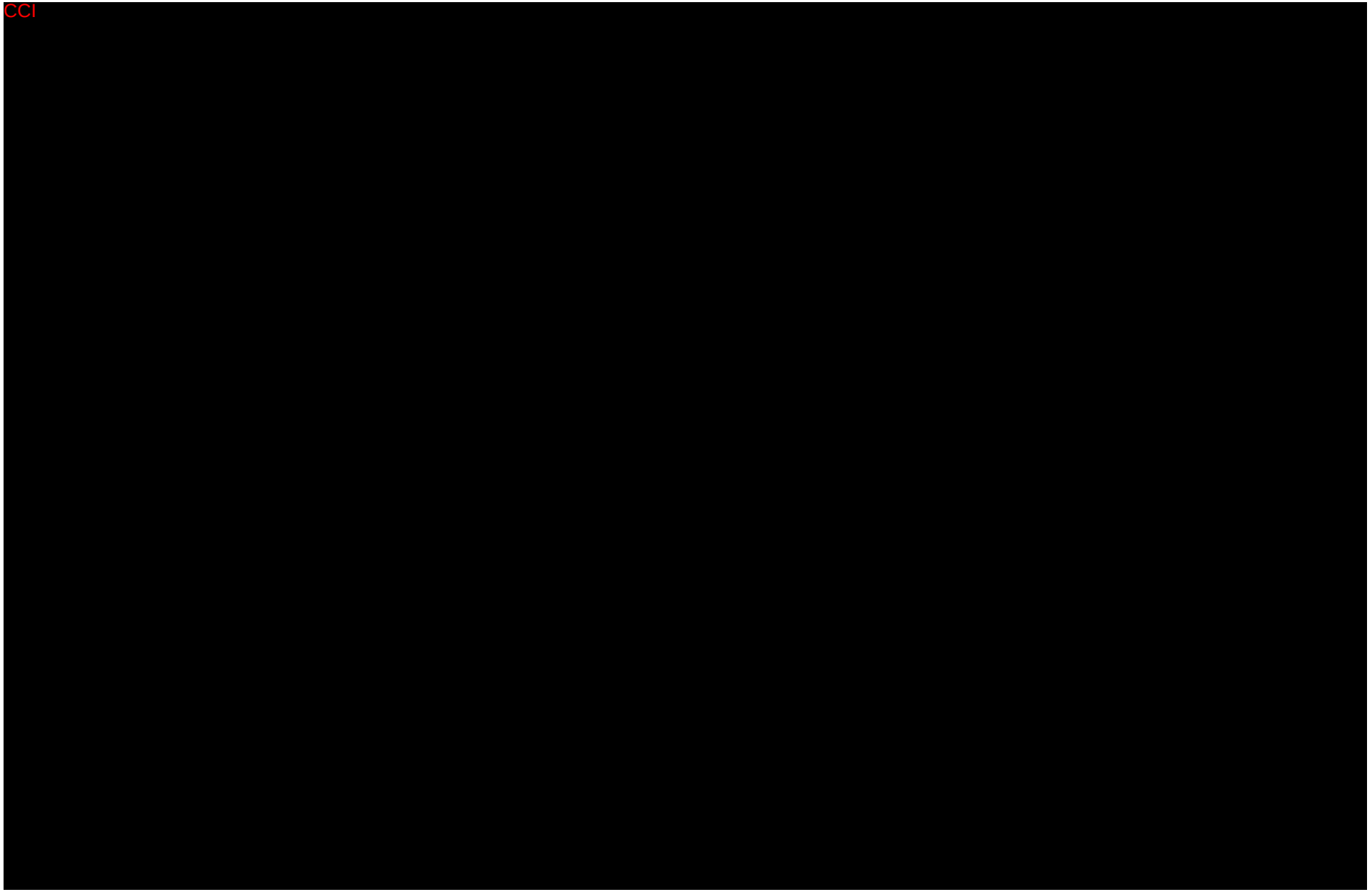

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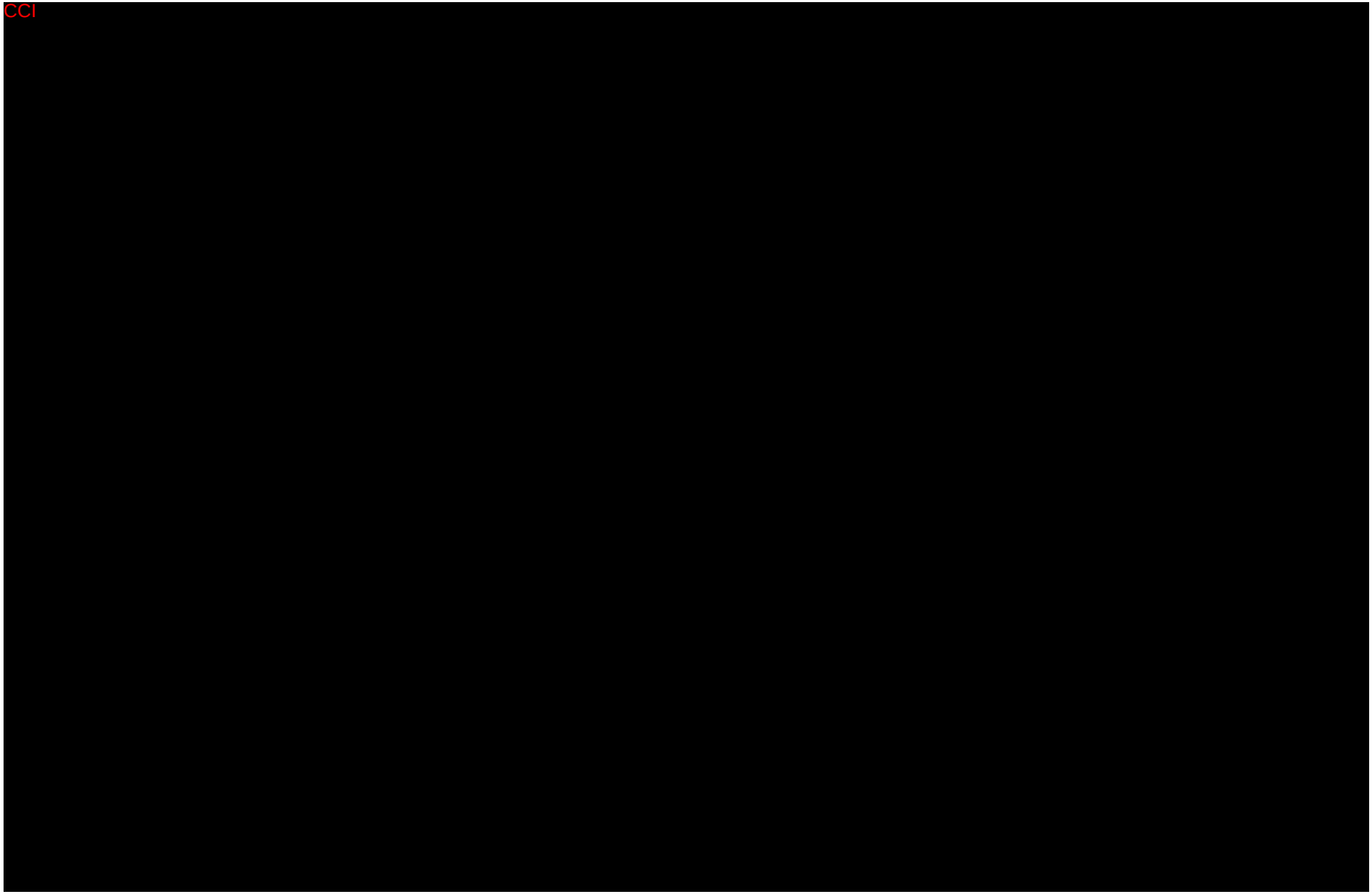

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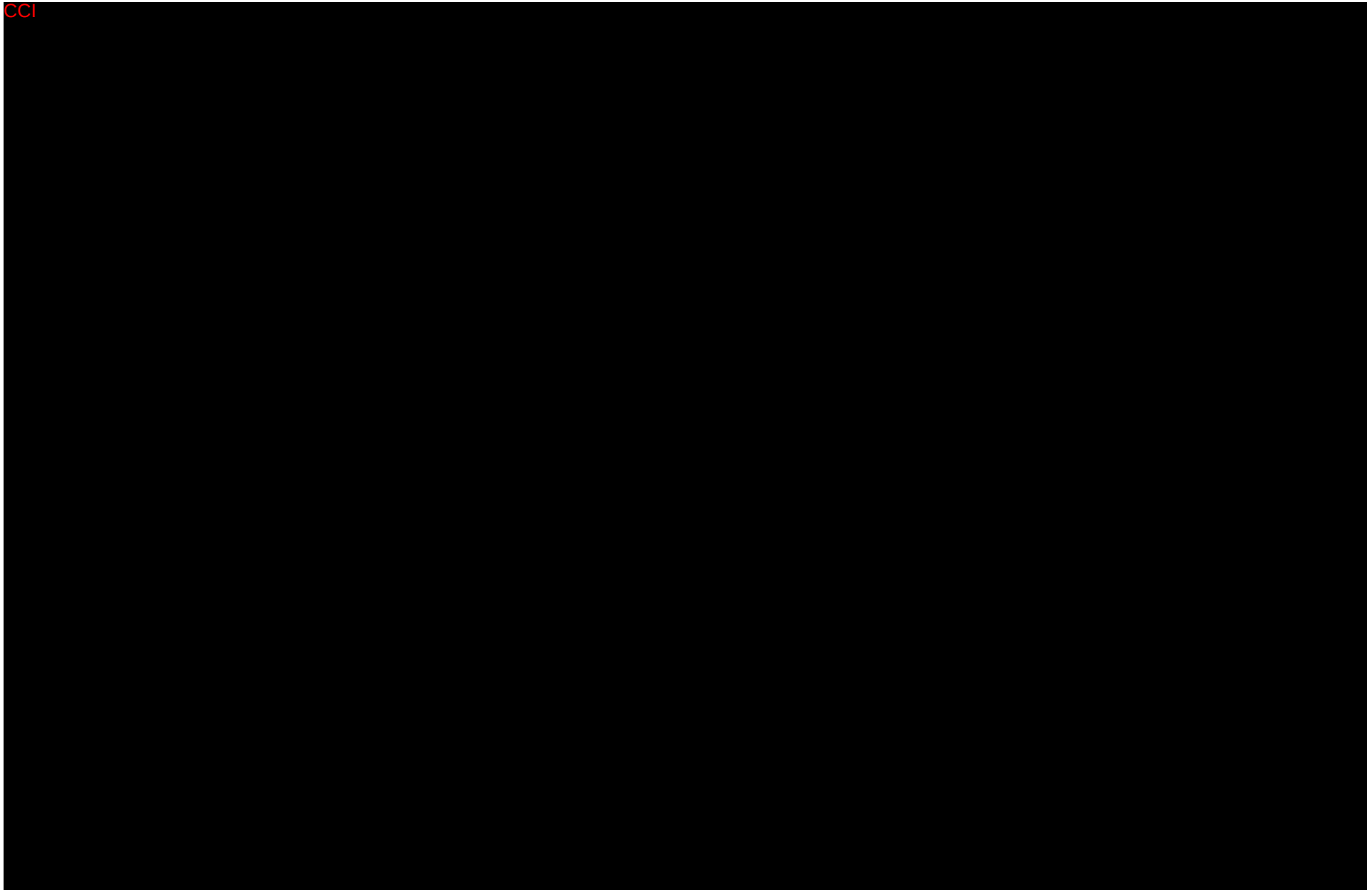

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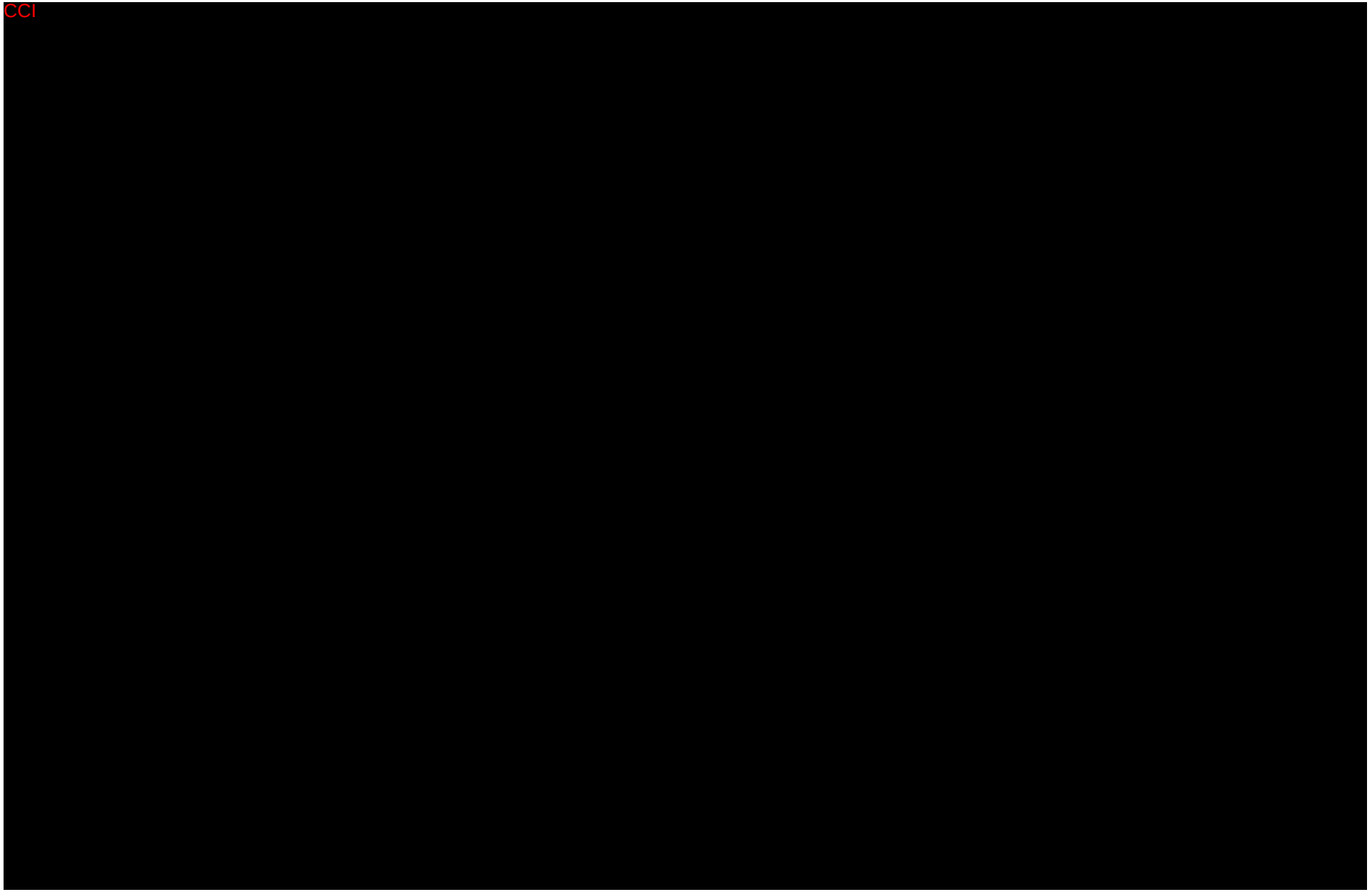

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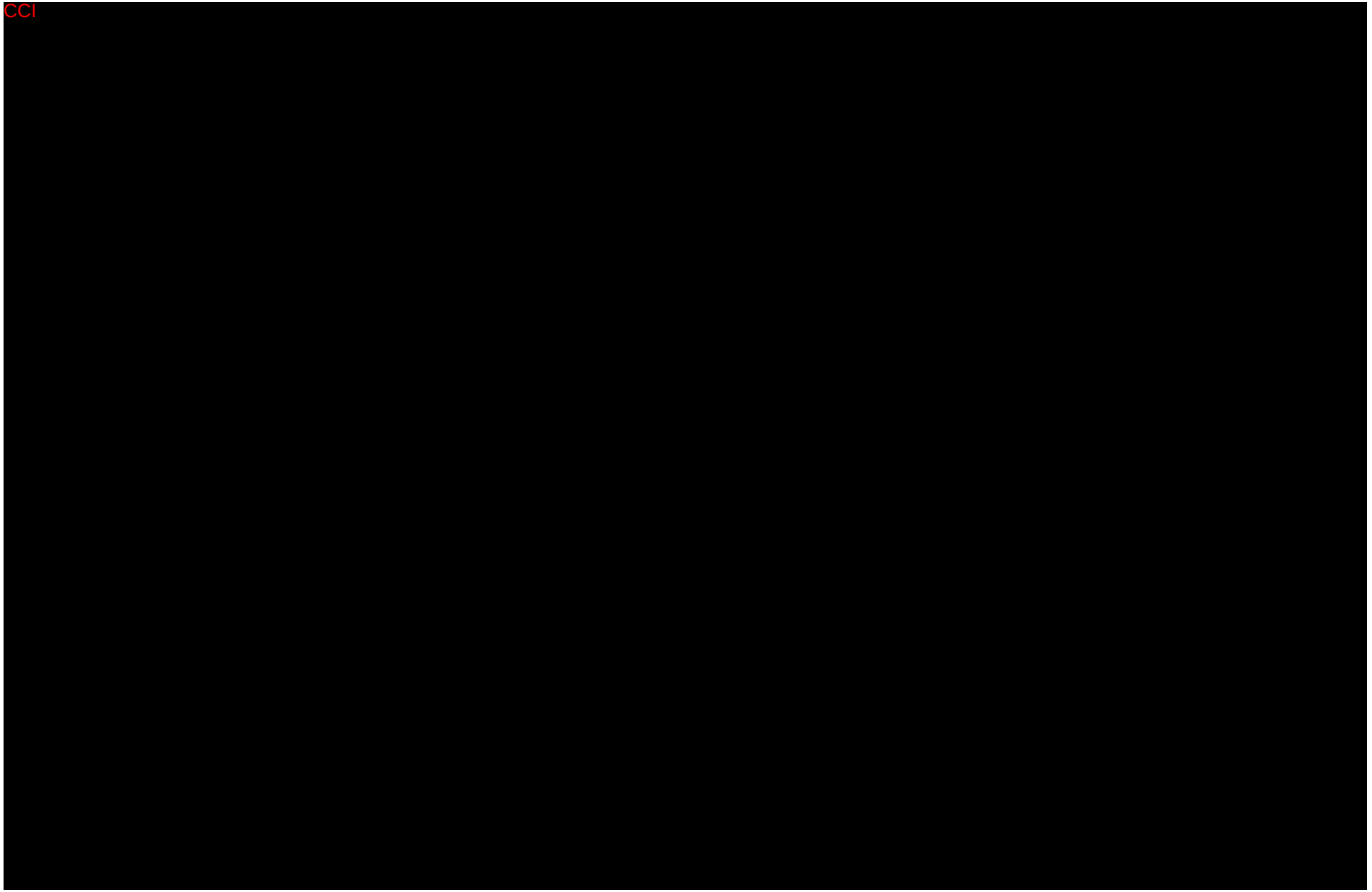

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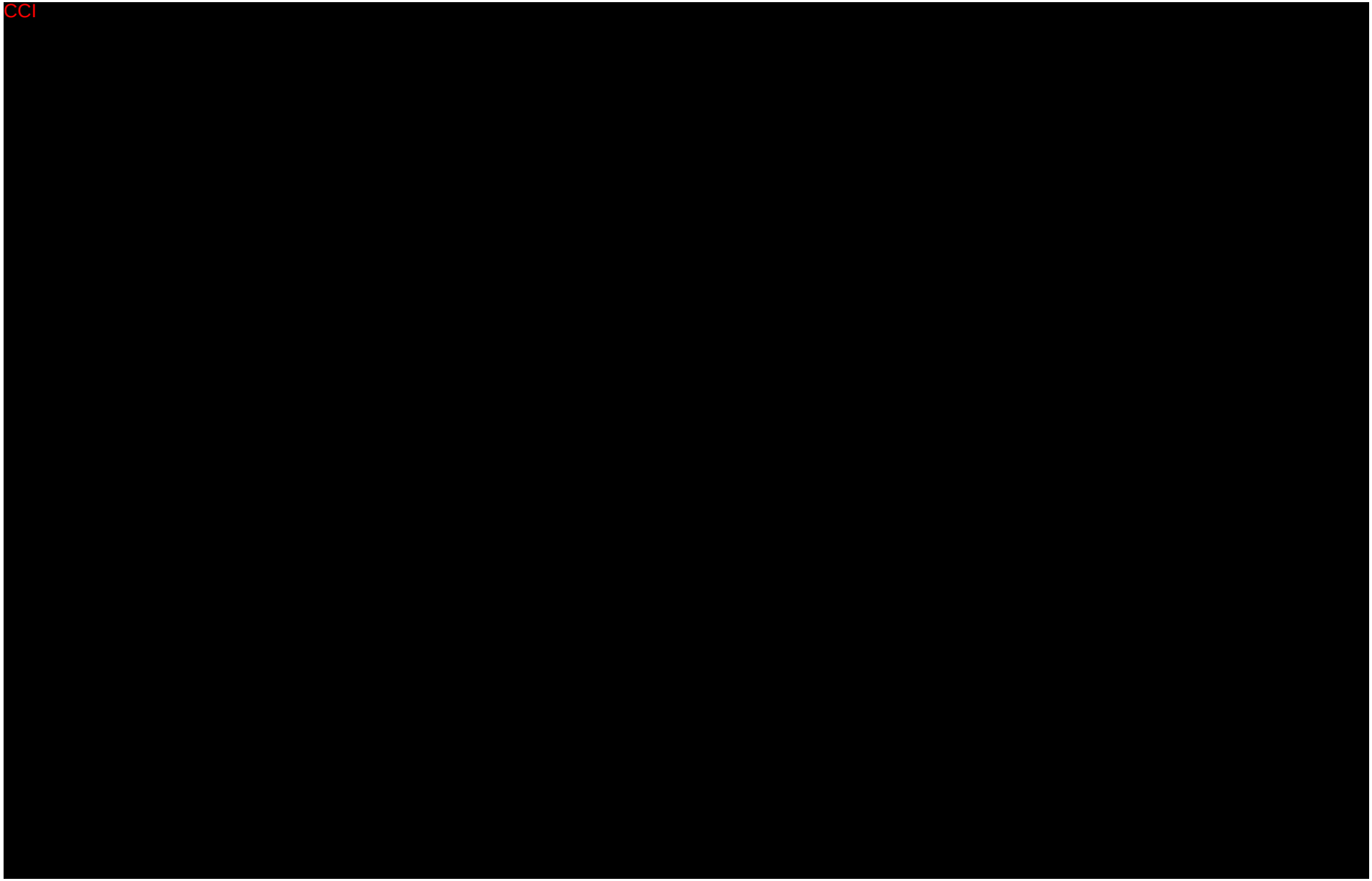

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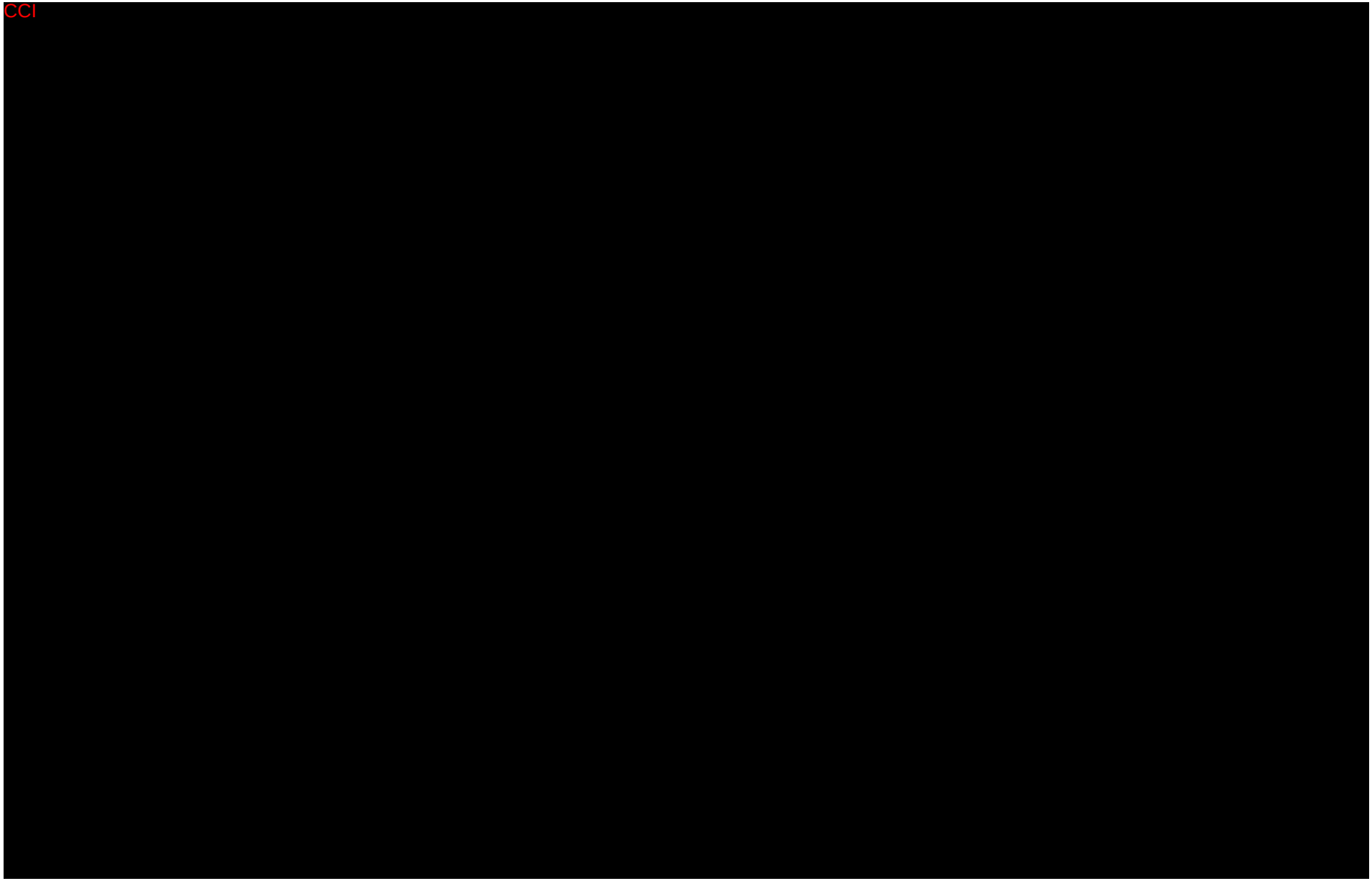

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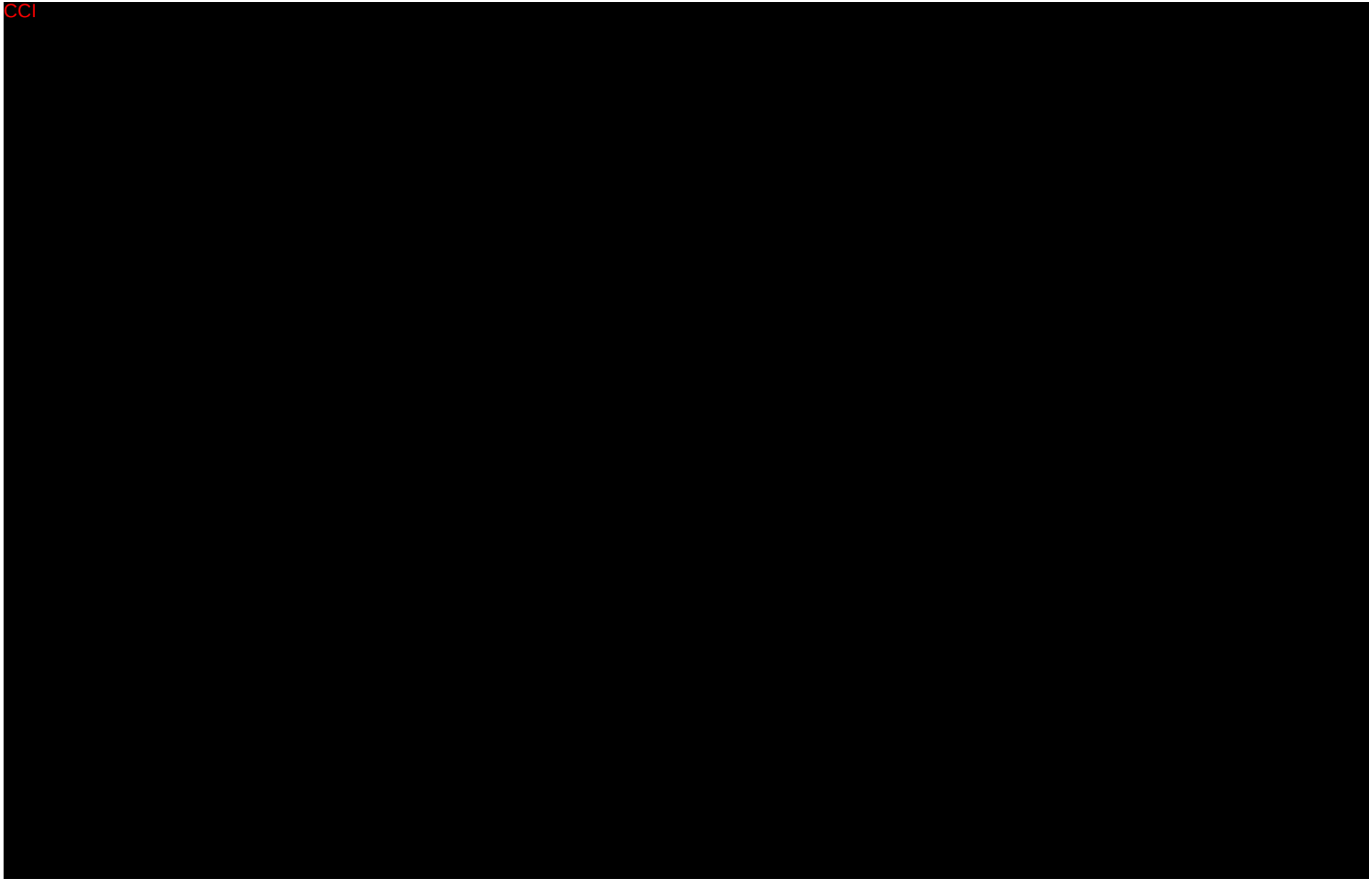

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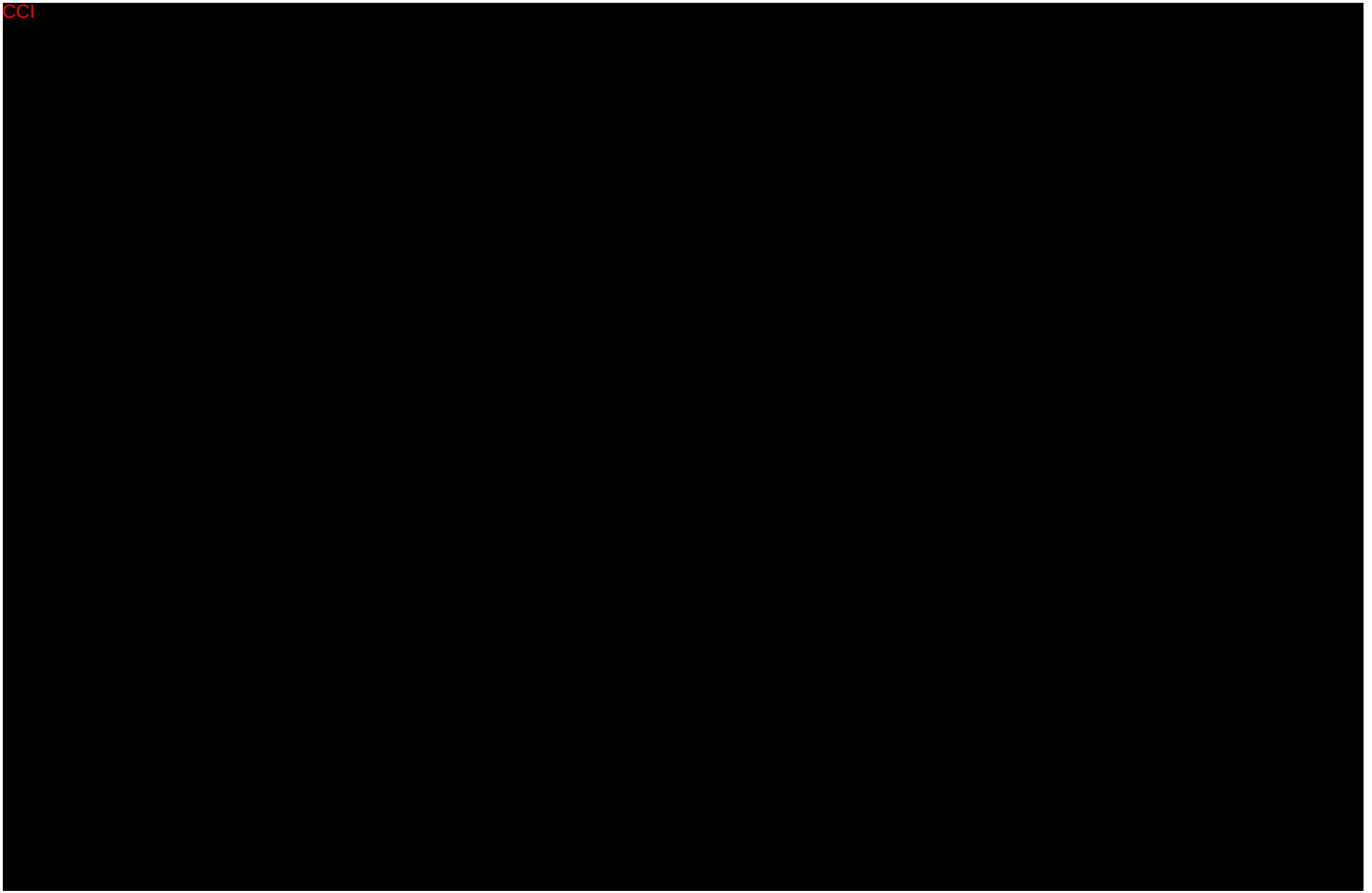

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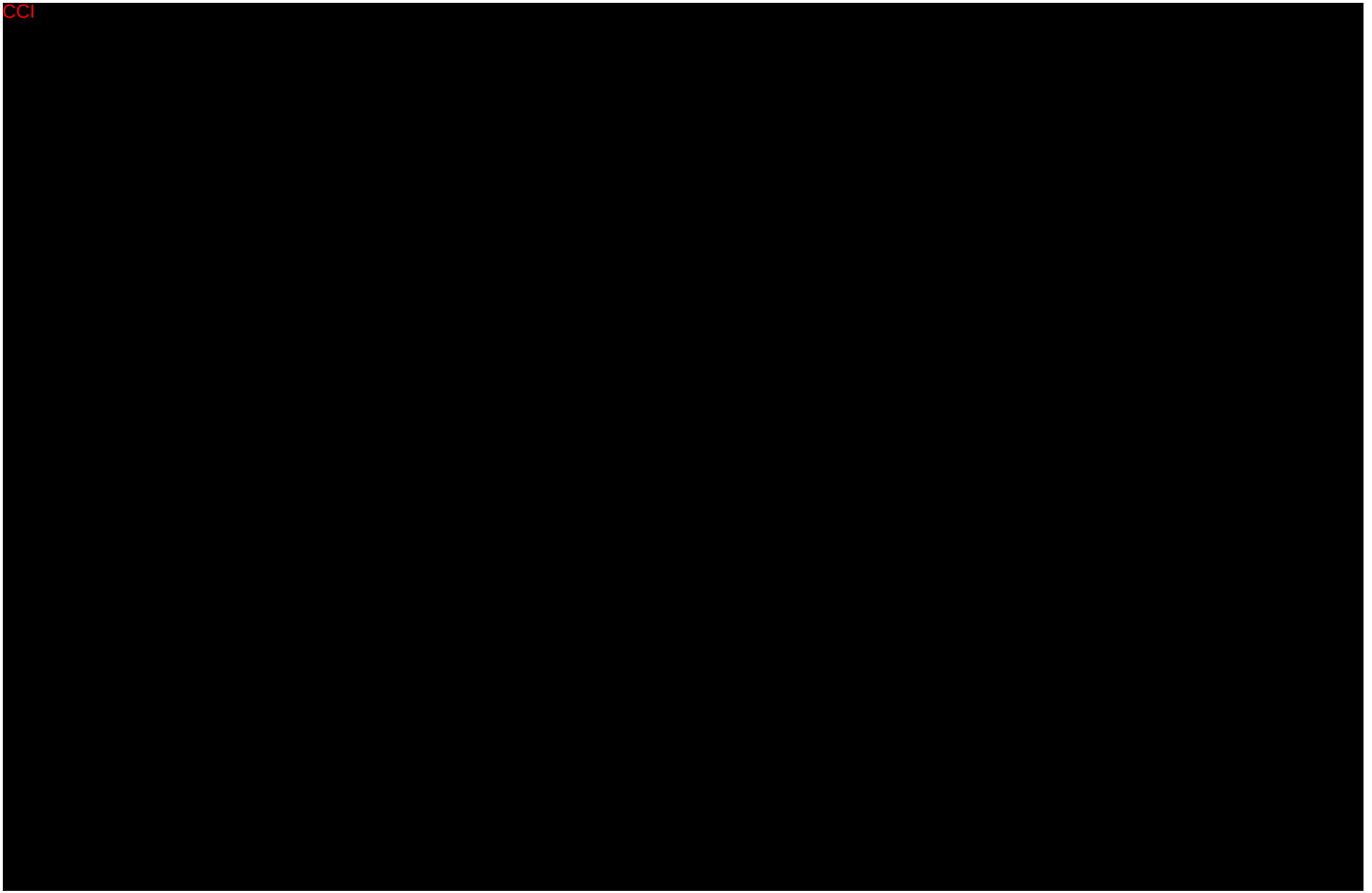

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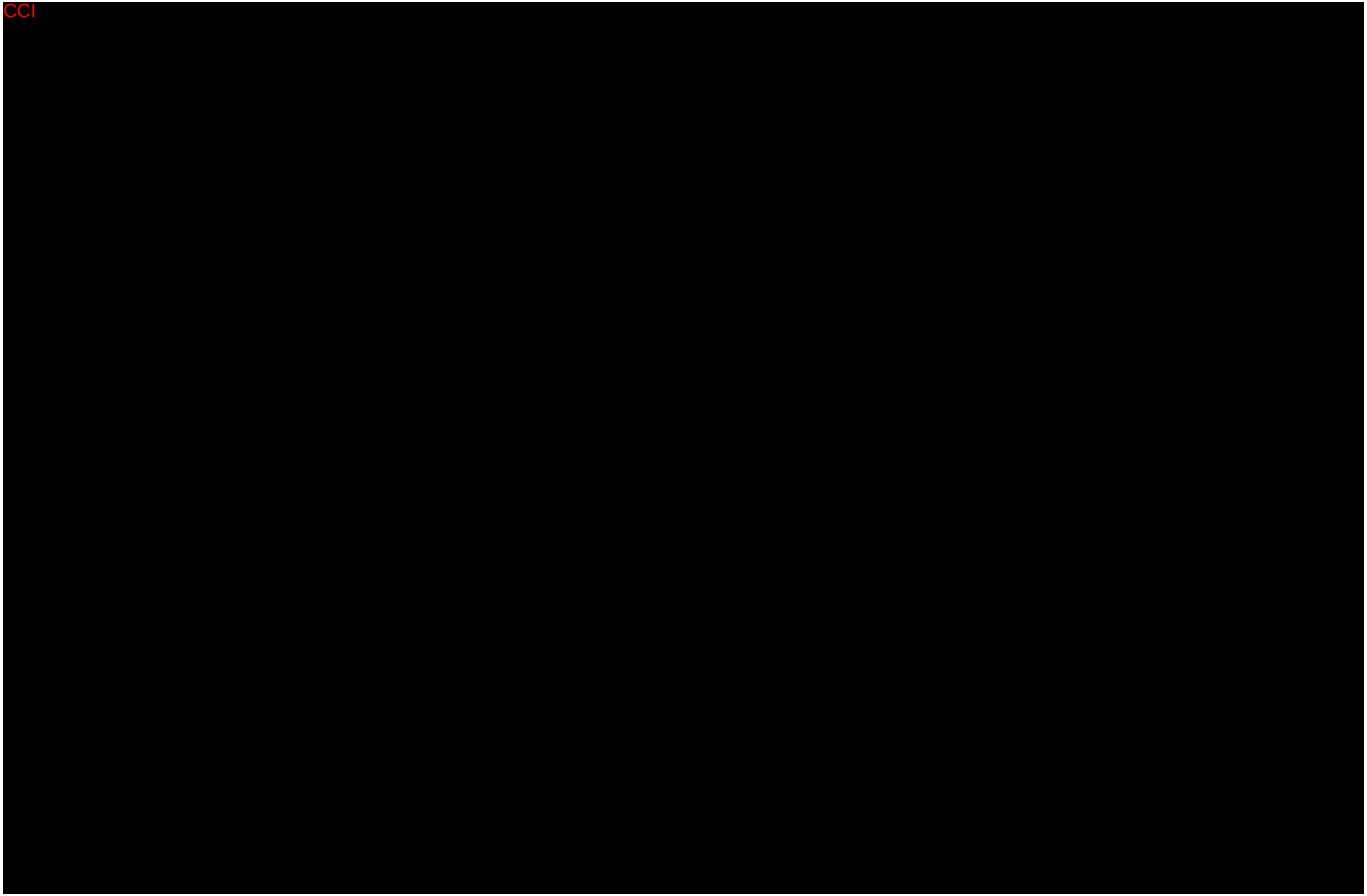

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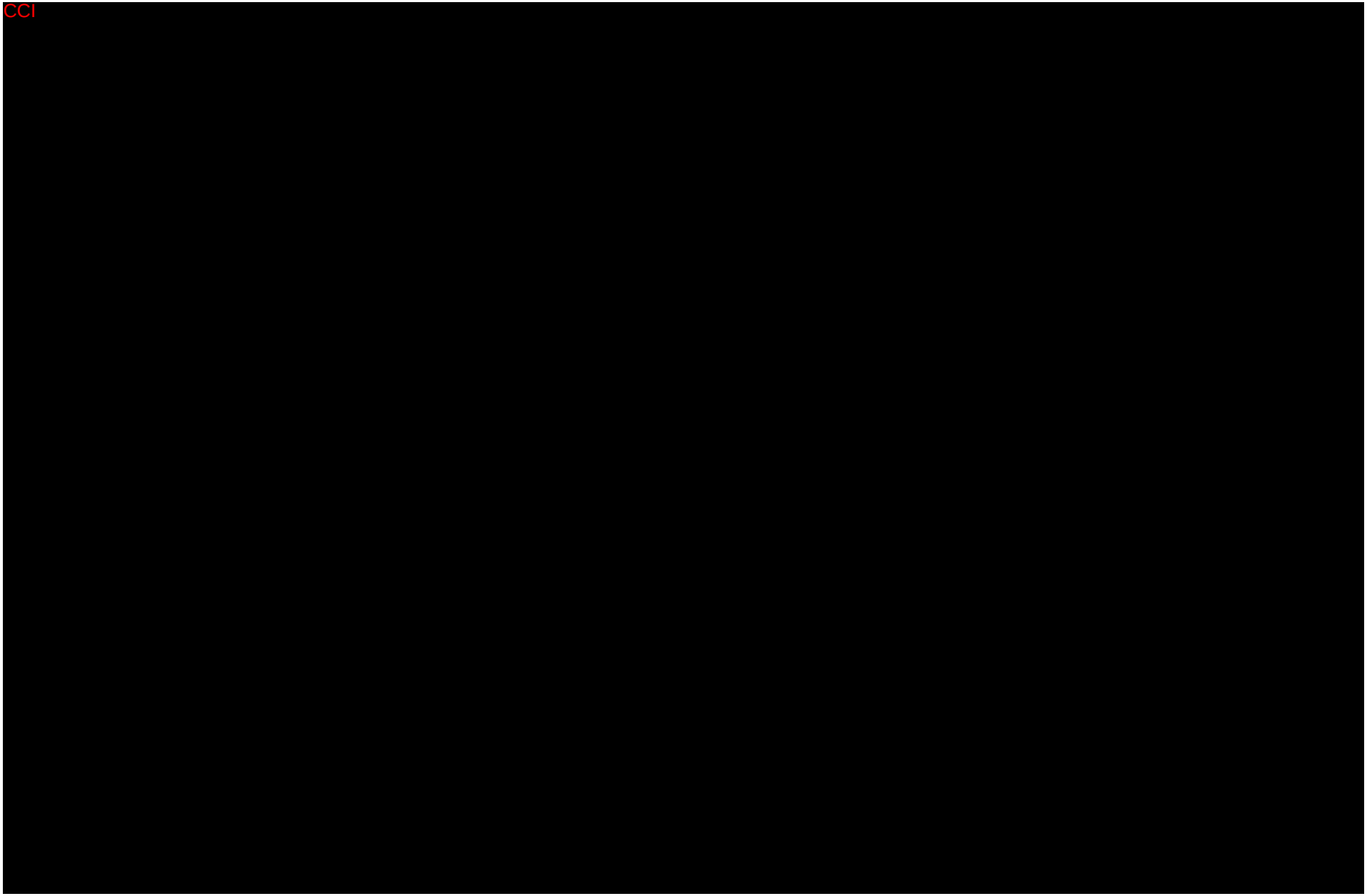

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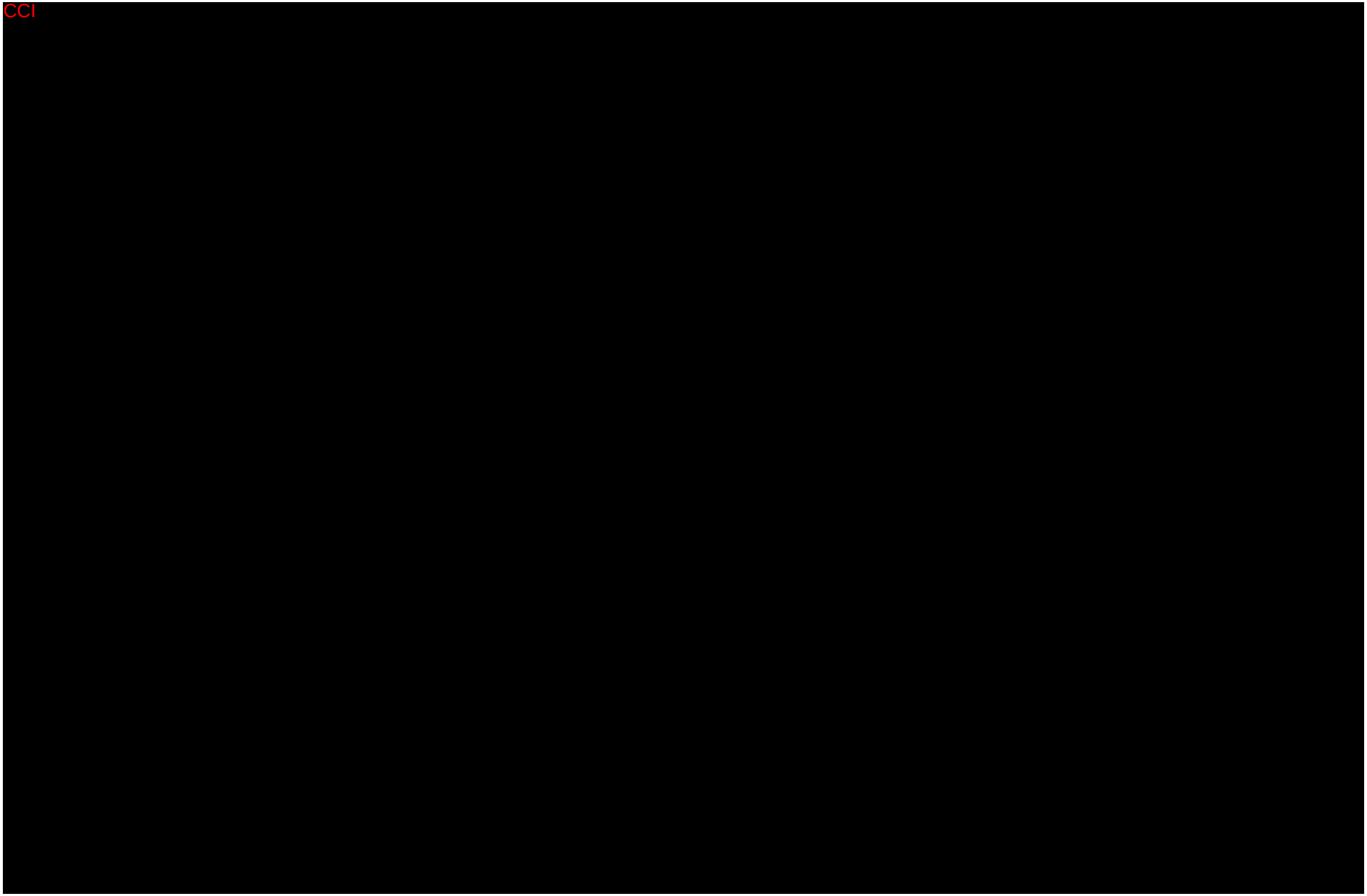

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