Actelion Pharmaceuticals Ltd*
(a Janssen Pharmaceuticals Company of Johnson and Johnson)

Interim #7 (13 September 2017) to (14 July 2023) Non-interventional Post-authorisation Safety Study – Study Report

Post-authorisation safety study (PASS): observational cohort study of PAH patients newly treated with either Uptravi® (selexipag) or any other PAH-specific therapy, in clinical practice; and retrospective medical chart review of patients with PAH newly treated with either Uptravi® (selexipag) or any Other PAH-specific therapy

EXPOSURE (Exploratory Observational Study of Uptravi in Real-lifE) and EXTRACT (EXploratory hisToRicAl Cohort sTudy)

Protocol AC-065A401 and 67896049PAH0002

UPTRAVI® Selexipag

* Actelion Pharmaceuticals Ltd ("Actelion") is a global organisation that operates through different legal entities in various countries/territories. Therefore, the legal entity acting as the sponsor for Actelion studies may vary,such as, but not limited to Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the clinical study report to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

EU PAS Register Number: EXPOSURE – EU PAS 19085; EXTRACT – EU PAS 49227

PRINCIPAL INVESTIGATOR: Not Applicable

SPONSOR'S RESPONSIBLE MEDICAL OFFICER: Irina Konourina, MD

SPONSOR'S RESPONSIBLE PARTY: PPD

DATE STUDY INITIATED: EXPOSURE – 13 September 2017; EXTRACT – 11 February 2023 (Date the first informed consent was signed)

DATE STUDY COMPLETED: EXTRACT – 28 July 2023 (Date of last data collection as part of the database)

DATE OF DATA CUT-OFF: EXPOSURE –14 July 2023 (Date last observation was recorded as part of the database)

Status: Approved
CSR Version: 1.0 **Version Date:** 7 March 2024
Prepared by: Actelion Pharmaceuticals Ltd (a Janssen Pharmaceuticals Company of Johnson and Johnson)
EDMS number: Report Body: EDMS-RIM-1119952, 1.0

Compliance: This study was conducted in compliance with the protocol and applicable regulatory requirements.

PASS INFORMATION

Title:	**Post-authorisation safety study (PASS): observational cohort study of PAH patients newly treated with either Uptravi® (selexipag) or any other PAH-specific therapy, in clinical practice; and retrospective medical chart review of patients with PAH newly treated with either Uptravi® (selexipag) or any Other PAH-specific therapy**
Version identifier of the final study report:	1.0
Date of last version of the protocol:	EXPOSURE – 22 June 2022; EXTRACT – 10 February 2022
EU PAS Register No:	EXPOSURE – EU PAS 19085; EXTRACT – EU PAS 49227
Active substance (INN common name):	Selexipag
Pharmacotherapeutic group (ATC Code):	Antithrombotic agents, platelet aggregation inhibitors excluding heparin (ATC code: B01AC27)
Medicinal product(s):	UPTRAVI®
Product reference:	H0003774
Procedure number:	EMEA/H/C/003774/MEA001.2; EMEA/H/C/003774/II/0035;
Name of Marketing Authorisation Holder(s)	Janssen-Cilag International NV
Joint PASS	No
Research question and objectives	EXPOSURE, a prospective observational cohort study, is conducted to further characterise the safety profile of UPTRAVI and to describe clinical characteristics and outcomes of patients newly treated with UPTRAVI in the international post-marketing setting. A cohort of patients newly treated with any other PAH-specific therapy who were never treated with UPTRAVI is included in this study for the purpose of comparing the incidence of major adverse cardiovascular event (MACE) and all-cause death to patients newly treated with UPTRAVI. 1. To describe, overall and in the subset of patients over the age of 75 years, demographics, disease characteristics and clinical course in patients with PAH, either newly treated with UPTRAVI (UPTRAVI exposed patients), or newly treated with any other PAH-specific therapy who were never treated with UPTRAVI (patients initiating another PAH-specific therapy). 2. To further characterise the UPTRAVI safety profile and estimate the incidence rates during the UPTRAVI exposure period of all-cause death and the following important identified or potential risks: – Hypotension – Anaemia – Hyperthyroidism

- Pulmonary oedema associated with pulmonary veno-occlusive disease
- MACE
- Acute renal failure and renal function impairment
- Bleeding events
- Light-dependent non-melanoma skin malignancy
- Ophthalmological effects associated with retinal vascular system
- Gastrointestinal disturbances denoting intestinal intussusception (manifested as ileus or obstruction)

3. To compare rates of MACE and all-cause death between UPTRAVI exposed patients and patients initiating another PAH-specific therapy, using a propensity score analysis.

EXTRACT, a retrospective medical chart review study was conducted for patients newly treated with UPTRAVI (UPTRAVI-exposed patients) or newly treated with any other pulmonary arterial hypertension (PAH)-specific therapy to complement the EXPOSURE study to fulfil the European Medicines Agency (EMA) PASS requirement on UPTRAVI to meet all the original objectives of EXPOSURE.

1. To describe, overall and in the subset of patients over the age of 75 years, demographics, disease characteristics and clinical course in patients with PAH newly treated with UPTRAVI and patients initiating another PAH-specific therapy.
2. To further characterise the UPTRAVI safety profile and estimate the IRs during the UPTRAVI exposure period of all-cause death and the following important identified or potential risks:
   - Hypotension
   - Anaemia
   - Hyperthyroidism
   - Pulmonary oedema associated with pulmonary veno-occlusive disease
   - MACE
   - Acute renal failure and renal function impairment
   - Bleeding events
   - Light-dependent non-melanoma skin malignancy
   - Ophthalmological effects associated with retinal vascular system
   - Gastrointestinal disturbances denoting intestinal intussusception (manifested as ileus or obstruction)
3. To describe rates of MACE and all-cause death in UPTRAVI exposed patients and patients initiating another PAH-specific therapy.

Countries of study	Preliminary list of countries where the EXPOSURE study is being conducted: Austria, Belgium, Canada, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Italy, Ireland, Lithuania, the Netherlands, Poland, Portugal, Russia, Slovakia, Spain, Sweden,

	Switzerland, the UK, and other countries, as needed, as UPTRAVI becomes commercially available. List of countries where EXTRACT study was conducted: Canada, Lithuania, the Netherlands, Slovakia, Spain, Sweden, and the UK.
Authors	PPD ☎

MARKETING AUTHORISATION HOLDER(S)

Name of Marketing Authorisation Holder:	Janssen-Cilag International NV
Address:	Turnhoutseweg 30 B-2340 Beerse Belgium
Contact Details:	Person authorised for communication on behalf of the applicant: Simone Spreng Associate Director, EMEA Regulatory Liaison Telephone: +41 79 39 38 366 Email: sspreng@its.jnj.com

The list of investigators for each country in which EXPOSURE is to be performed has not yet been finalised. For EXTRACT, the list of investigators is provided in Appendix 4.

Principal Investigator:	Not Applicable
Name:	Not Applicable
Signature:	Not Applicable
Date:	Not Applicable

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CCI [redacted]

CCI [redacted]

CCI [redacted]

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CCI [redacted]

1. ABSTRACT

Name of Sponsor/Company	Actelion Pharmaceuticals Ltd (a Janssen Pharmaceuticals Company of Johnson and Johnson) *
Name of Finished Product	UPTRAVI®
Name of Active Ingredient(s)	Selexipag

* Actelion Pharmaceuticals Ltd ("Actelion") is a global organisation that operates through different legal entities in various countries/territories. Therefore, the legal entity acting as the sponsor for Actelion studies may vary, such as, but not limited to Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the clinical study report to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

Protocol No.: AC-065A401 and 67896049PAH0002

Titles of Studies: Post-authorisation safety study (PASS): observational cohort study of PAH patients newly treated with either Uptravi® (Selexipag) or any other PAH-specific therapy, in clinical practice; and retrospective medical chart review of patients with PAH newly treated with either Uptravi® (selexipag) or any Other PAH-specific therapy. (1.0, 07 March 2024)

Study Names: EXPOSURE '**EXP**loratory **O**bservational **S**tudy of **U**ptravi in **R**eal-lif**E**' and EXTRACT '**EX**ploratory his**T**o**R**ic**A**l **C**ohort s**T**udy'

Sponsor's Responsible Medical Officer: Irina Konourina, MD

Sponsor's Responsible Party: PPD

Keywords : PAH, Selexipag, RWE, Cohort

EU PAS Register Number : EXPOSURE – EU PAS 19085 ; EXTRACT – EU PAS 49227

NCT No.: Not Applicable

Clinical Registry No.: Not Applicable

Marketing Authorisation Holder(s): Janssen Cilag International NV

Names and Affiliations of Principal Investigator(s): Not Applicable

Study Centre(s): EXPOSURE- Austria, Belgium, Canada, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Italy, Ireland, Lithuania, the Netherlands, Poland, Portugal, Russia, Slovakia, Spain, Sweden, Switzerland, and the UK.

EXTRACT- Canada, Lithuania, the Netherlands, Slovakia, Spain, Sweden, and the UK

Publication (Reference): Muller A, Escribano-Subias P, Fernandes CC, et al. Real-World Management of Patients with Pulmonary Arterial Hypertension: Insights from EXPOSURE. Adv Ther. 2024 Jan 13. doi: 10.1007/s12325-023-02730-8. Epub ahead of print.

Study Period: EXPOSURE – 13 September 2017; Ongoing. Data cut-off for this report: 14 July 2023.

EXTRACT – 11 February 2023 to 28 July 2023.

Background and Rationale: Pulmonary arterial hypertension (PAH) is a rare and progressive disease characterised by increased pulmonary vascular resistance that ultimately leads to right heart failure and death. Selexipag (UPTRAVI®) was approved in the EU on 12 May 2016 for the treatment of PAH. Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with

connective tissue disorders, and PAH associated with corrected simple congenital heart disease. Due to the recent approval of UPTRAVI in the market, no long-term real-world post-authorisation data are available to estimate the safety and clinical outcomes of UPTRAVI treatment in clinical practice. By providing real-world data of how UPTRAVI is used in the clinical management of patients with PAH, the **EXP**loratory **O**bservational **S**tudy of **U**PTRAVI in **R**eal-lif**E** (EXPOSURE) will contribute to a greater understanding of UPTRAVI in this post-marketing setting.

Following study initiation, the recruitment of new UPTRAVI users in EXPOSURE was slower than initially projected. EXTRACT, a retrospective medical chart review study was conducted, following PRAC agreement (EMEA/H/C/003774/II/0035), to complement EXPOSURE with retrospectively identified patients with PAH who were newly treated with UPTRAVI before EXPOSURE was launched and a comparator group consisting of patients with PAH newly treated with other PAH-specific therapies. The aim was to fulfil the European Medicines Agency (EMA) Post authorisation safety study (PASS) requirement on UPTRAVI to meet all the original objectives of EXPOSURE.

Research Question and Objectives:

Research Question:

The purpose of EXPOSURE is to further characterise the safety profile of UPTRAVI when used in clinical practice and to describe clinical characteristics and outcomes of patients newly treated with UPTRAVI compared to patients newly treated with any other PAH specific therapy who were never treated with UPTRAVI, in the post marketing setting.

Objectives:

The objectives for EXPOSURE are:

1. To describe, overall and in the subset of patients over the age of 75 years, the demographics, disease characteristics and clinical course in patients with PAH either newly treated with UPTRAVI (UPTRAVI exposed patients), or newly treated with any other PAH-specific therapy who were never treated with UPTRAVI (patients initiating another PAH-specific therapy).

2. To further characterise the UPTRAVI safety profile and estimate the incidence rates (IR) during the UPTRAVI exposure period of all-cause death and the following important identified or potential risks: hypotension, anaemia, pulmonary oedema associated with pulmonary veno-occlusive disease (PVOD), hyperthyroidism, major adverse cardiovascular event (MACE), acute renal failure and renal function impairment, bleeding events, light-dependent non-melanoma skin malignancy, ophthalmological effects associated with the retinal vascular system, and gastrointestinal disturbances denoting intestinal intussusception (manifested as ileus or obstruction).

3. To compare rates of MACE and all-cause death between UPTRAVI exposed patients and patients in the Other PAH-specific therapy, using a propensity score analysis.

The objectives for EXTRACT were aligned to those described above for the EXPOSURE study:

1. To describe, overall and in the subset of patients over the age of 75 years, demographics, disease characteristics and clinical course in patients with PAH newly treated with UPTRAVI and patients initiating another PAH-specific therapy.

2. To further characterise the UPTRAVI safety profile and estimate the IRs during the UPTRAVI exposure period of all-cause death and the following important identified or potential risks: hypotension, anaemia, pulmonary oedema associated with PVOD, hyperthyroidism, MACE, acute renal failure and renal function impairment, bleeding events, light-dependent non-melanoma skin malignancy, ophthalmological effects associated with the retinal vascular system and gastrointestinal disturbances denoting intestinal intussusception (manifested as ileus or obstruction).

3. To describe rates of MACE and all-cause death in UPTRAVI exposed patients and patients initiating another PAH-specific therapy.

Study Design:

EXPOSURE is a prospective observational cohort study conducted at multiples sites in European and non-European countries to document the treatment of PAH with UPTRAVI in a clinical practice setting. The planned observation period for each patient enrolled in the study is at least 18 months or until the earliest of death, withdrawal of consent, loss to follow-up or study end. Only data available from clinical practice were collected.

EXTRACT was a retrospective chart review study in patients with PAH newly treated with UPTRAVI or other PAH-specific therapies. Only data available within standard clinical practice was collected in this study. The enrolment period was from the start of reimbursement of UPTRAVI in a specific country, to the earlier of either 31 days before the respective EXPOSURE site initiation visit or 30 June 2021. The observation period was from the date of initiation of new PAH-specific therapy until death, loss to follow up, or 30 June 2022, whichever was earlier.

Setting:

Participating patients in EXPOSURE are screened for eligibility criteria for either cohort (UPTRAVI or Other PAH therapy cohort) and enrolled after signing of ICF.

For EXTRACT, the participating physician evaluated patient's medical records to determine their eligibility for data collection in the study. Eligible patients were treated with UPTRAVI or other PAH-specific therapies in a routine clinical setting. The study was conducted only at sites and countries where an ICF waiver was accepted by authorities.

Patient Population and Study Size:

For EXPOSURE, key inclusion criteria are patients ≥18 years old, Group I PAH, newly initiating UPTRAVI or any other PAH specific therapy (less than 1 month prior to enrolment, or at enrolment). A precision-based approach for the confidence interval (CI) was used to determine the minimum (Min) number of UPTRAVI exposed patients needed to estimate the IR of MACE within the study and resulted in a target number of 1184 UPTRAVI exposed patients and 1850 patients exposed to any other PAH-specific therapy enrolled, under the assumptions of Min exposure duration 18 months, IR 3.0 per 100 person-years, precision 0.93 per 100 person-years, relative precision 31% and patient retention rate 75% in the UPTRAVI cohort.

Eligibility criteria for EXTRACT were aligned with those described above for the EXPOSURE study. Sample size was determined based on the difference between the overall sample size needed in the UPTRAVI cohort in EXPOSURE and the projected number of patients that could be enrolled in the UPTRAVI cohort in EXTRACT by June 2023, while maintaining a similar ratio with the comparator cohort as in EXPOSURE.

Variables and Data Sources:

Variables recorded in EXPOSURE include demographics, clinical characteristics, laboratory data, medical history, medications, and follow-up clinical data. Data were collected for each patient at initiation of new PAH-specific therapy and throughout the observation period from the existing medical record at any clinical visit on the respective EXPOSURE eCRF.

Variables collected for EXTRACT were same as those for EXPOSURE with few exceptions for laboratory data and medical history. Medication variables were restricted to PAH-specific therapies. The outcomes variables were similar to the follow-up clinical data in EXPOSURE, except for AEs where only new diagnosis or ADRs considered by the reporter to be explicitly causally related to a PAH-specific MAH

product were collected. Data were collected for each patient throughout the observation period based on the existing medical records and recorded into the EXTRACT eCRF.

Statistical Methods:

The SAP v9.0, for EXPOSURE and SAP v2.0 for EXTRACT and the combined EXPOSURE and EXTRACT analysis, describe the planned analysis for this study report. All analyses are exploratory.

Data analysis for EXTRACT followed the same approach as agreed with the PRAC for EXPOSURE. Homogeneity assessment between EXPOSURE and EXTRACT patients was based on patient characteristics at the time of new PAH-specific therapy initiation.

RESULTS:

PARTICIPANTS AND PATIENT CHARACTERISTICS:

Patient disposition

CCI [redacted].

The retrospective EXTRACT study complemented the number of patients by recruiting 173 patients in the UPTRAVI cohort (including 19 'Late Initiators') and 104 patients in the Other PAH therapy cohort. A total of 252 patients, 169 patients in the UPTRAVI cohort and 96 patients in the Other PAH therapy cohort were in the FUP Set. For the patients in the FUP Set, the median duration (range) of the observation period was 32.3 (0.6-64.3) months. The median duration (range) of the first exposure period was 27.0 (0.3-62.2) months for the UPTRAVI cohort and 31.5 (0.4-64.3) months for the Other PAH therapy cohort. A total of 26 patients aged >75 years were enrolled, with 16 patients in the UPTRAVI cohort and 10 patients in the Other PAH therapy cohort in the FUP Set. The median duration (range) of the observation period was 23.8 (2.5-52.3) months and the median duration (range) of the first exposure period was 12.6 (1.0-41.7) months for the UPTRAVI cohort and 18.1 (0.7-39.4) months for the Other PAH therapy cohort.

CCI [redacted]

Demographics at baseline

CCI [redacted]

In EXTRACT, median (range) age was 55 (19-85) years for both cohorts.

CCI [redacted]

Disease characteristics

CCI [redacted]

In EXTRACT, median time (range) since PAH diagnosis was 2.8 (0.0-37.4) years for the UPTRAVI cohort. About half of the patients were diagnosed with IPAH (88 patients, 52.1%). Of 150 patients with data available for WHO FC within 3 months prior to, or at baseline, 119 patients (79.3%) were classified as WHO FC III. In the Other PAH therapy cohort, median time (range) since PAH diagnosis was 1.7 (0.0-33.5) years. Most patients were diagnosed with IPAH (38 patients, [40.0%]). Of the 83 patients with data available for WHO FC within 3 months prior to, or at baseline, 50 patients (60.2%) were classified as WHO FC III. For the subset of patients aged >75 years, median time (range) since PAH diagnosis was longer in the UPTRAVI cohort than in the Other PAH therapy cohort. Most patients were diagnosed with IPAH and CTD-PAH in the UPTRAVI cohort and with CTD-PAH in the Other PAH therapy cohort. Most patients were classified as WHO FC III in both cohorts.

CCI [redacted]

Background PAH-specific therapies

CCI [redacted]

In EXTRACT, at baseline, most patients (137, 81.1%) were receiving triple combination therapy in the UPTRAVI cohort. In the Other PAH therapy cohort, most of the patients were receiving double

combination therapy (71, 74.0%). For the subset of patients aged >75 years most patients were receiving triple combination therapy in the UPTRAVI cohort and double combination therapy in the Other PAH therapy cohort.

CCI [redacted]

Hospitalisation

CCI [redacted].

Overview of IR (per 100 person-years, 95% CI) of All Hospitalisations During the First Exposure period; FUP Set

	UPTRAVI	Other PAH therapy Cohort
CCI [redacted]		
[redacted]		

OUTCOME DATA:

CCI [redacted]

Overview of the Safety Profile: IR of Important Identified and Potential Risks. UPTRAVI Cohort (N = 807);

CCI [redacted]

Overview of the Safety Profile: IR of Important Identified and Potential Risks. UPTRAVI Cohort (N = 807); EXPOSURE

Events	Number of patients included in the analysis[a], n (%)	Number of patients with new event after UPTRAVI initiation[b], n (%)	Exposure (person- years)	IR (per 100 person-years) 95% CI
CCI [redacted]				
Important Potential Risks				
CCI [redacted]				

All-cause Deaths

CCI [redacted]

CCI [redacted]

[redacted].

Overview of the Safety Profile for Patients >75 years old: IR of Important Identified and Potential Risks. UPTRAVI Cohort (N = 101); EXPOSURE

CCI

[redacted]

All-cause Deaths

CCI

[redacted]

UPTRAVI safety profile for important identified and potential risks in EXTRACT

An overview of the safety profile for the UPTRAVI cohort (N = 169) in EXTRACT during the first exposure period is summarised in the table below. UPTRAVI safety profile, during the total exposure period, was consistent with that observed in the first exposure period.

CCI

All-cause Deaths

In the UPTRAVI cohort, the mortality rate (95% CI) was CCI

UPTRAVI safety profile for patients >75 years old in EXTRACT

For patients aged >75 years in the UPTRAVI cohort, CCI

All-cause Deaths

In the UPTRAVI cohort for patients aged >75 years, the mortality rate (95% CI) was CCI per 100 person-years during the first exposure period.

CCI

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CCI [redacted]

Overview of the Safety Profile: IR of Important Identified and Potential Risks. UPTRAVI Cohort (N = 976); combined EXPOSURE and EXTRACT FUP Set (POOLED)

CCI [redacted]

All-cause Deaths

CCI [redacted]

CCI [redacted]

Overview of the Safety Profile for Patients >75 years old: IR of Important Identified and Potential Risks. UPTRAVI Cohort (N = 117); combined EXPOSURE and EXTRACT FUP Set (POOLED)

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

[redacted].

ADVERSE EVENTS/ADVERSE REACTIONS:

CCI [redacted]

[redacted]

UPTRAVI Safety Profile: Any other AEs (occurring in >2% of patients) during the First Exposure Period – Follow-Up Set; UPTRAVI cohort N = 807 (EXPOSURE)

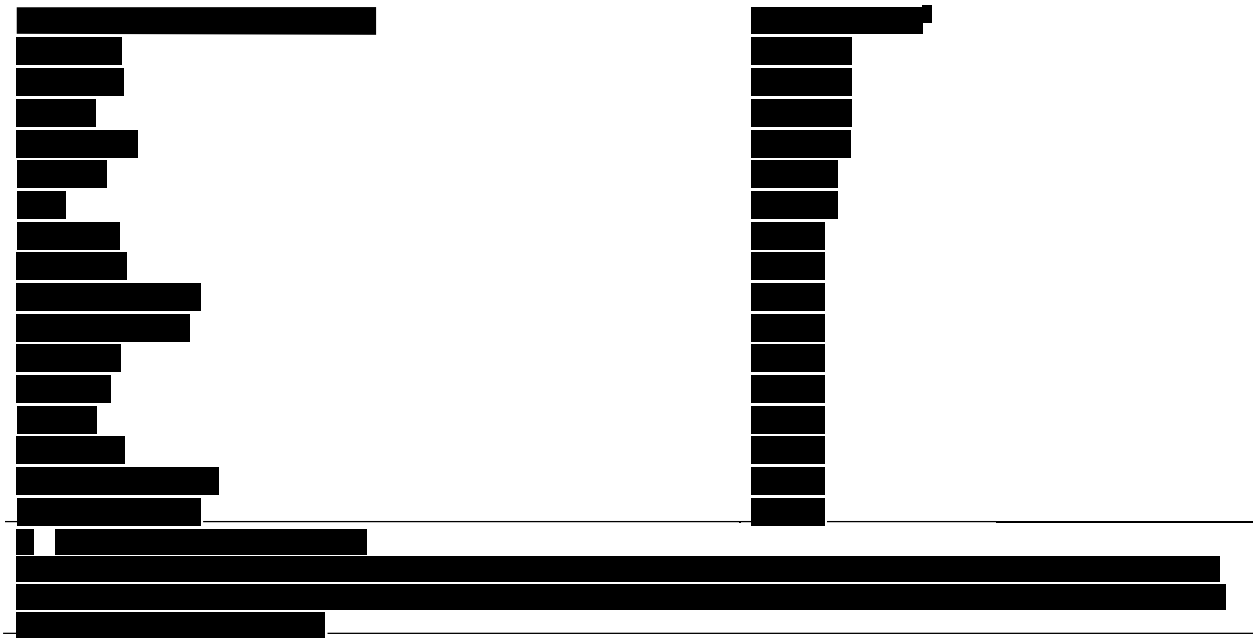
CCI [redacted]

CCI [redacted]

Other ADRs profile in the UPTRAVI cohort in EXTRACT

During the first exposure period, CCI [redacted] in the UPTRAVI cohort and most common ADRs (occurring in >2% of patients) are presented in the Table below. All other ADRs were reported for CCI [redacted] of patients each.

CCI [redacted]



In the subgroup of patients aged >75 years, CCI [redacted] during the first exposure period.

CCI [redacted]

DISCUSSION AND CONCLUSION:

DISCUSSION:

Based on the available data presented in this 7th interim report for EXPOSURE complemented with data from the retrospective EXTRACT study, marked differences are observed between patients enrolled in the UPTRAVI cohort and those enrolled in the Other PAH therapy cohort. When compared to the Other PAH therapy cohort, patients enrolled in the UPTRAVI cohort are diagnosed with PAH for a longer time and initiate UPTRAVI in the context of PAH disease progression mainly as a triple combination therapy (as per the indication in the approved Product Labelling documents). Based on these differences, patients in the UPTRAVI cohort could reasonably be considered to have been enrolled in the study at a more severe and more advanced stage of their PAH disease compared to patients initiating another PAH-specific therapy.

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

CONCLUSIONS:

- Data from EXPOSURE and EXTRACT represent the most comprehensive long-term safety, tolerability and survival dataset collected for patients with PAH newly treated with UPTRAVI and Other PAH specific medications in real world clinical practice. Observing the clinical data of more than 2500 patients and 4000 person-years, including 450 patients over the age of 75 years, with a high and homogeneous quality standard, in the context of a rare disease is a noteworthy achievement.
- The combined dataset of EXTRACT and EXPOSURE has reached a sufficient number of person-years to provide an adequate precision for comparing IR of MACE and all-cause death between patients newly treated with UPTRAVI and patients initiating another PAH-specific therapy.
- The safety profile of UPTRAVI was consistent with the known safety profile established in the pivotal clinical study and reflected in the EU SmPC and other approved product information documents. CCI [redacted]
- [redacted]
- [redacted]

- CCI [redacted]
- [redacted]
- No unexpected or new safety findings that impact the established safety profile of UPTRAVI or its benefit-risk profile in PAH patients including patients over the age of 75 years were identified.
- The combined EXPOSURE and EXTRACT results adequately meet the objectives of this PASS program and hence the MAH would propose conclusion of EXPOSURE. The MAH will submit a final study report via another Type II variation.

2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

6MWD	6-minute walk distance
AE	adverse event
ADR	adverse drug reaction
ATC	anatomical therapeutic code
ATO	average treatment effect for the overlap population
ATT	targeting at treatment effects on the treated group
BMI	body mass index
BNP	brain natriuretic peptide
CHD	congenital heart disease
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CRO	contract research organisation
CTD-PAH	PAH associated with connective tissue disease
DBL	database lock
EC	Ethics Committee
eCRF	electronic case report form
eDC	electronic data capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ENR	enrolled Set
ERA	endothelin receptor antagonist
EU	European Union
EXPOSURE	Exploratory Observational Study of UPTRAVI in Real-life
FC	functional class
FDA	Food and Drug Administration
FUP	follow-up set
GI	gastrointestinal
GPP	Guidelines for Good Pharmacoepidemiology Practices
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IPAH	idiopathic pulmonary arterial hypertension
hPAH	heritable pulmonary arterial hypertension
IR	incidence rate
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ITT	intention-to-treat
LAI	Last available information
LLN	lower limit of normal
MACE	major Adverse Cardiovascular Event(s)
MAH	Marketing Authorisation Holder
Max	maximum
MI	myocardial infarction

Min	minimum
mPAP	mean pulmonary artery pressure
NT-proBNP	N-terminal of the prohormone brain natriuretic peptide
PAH	pulmonary arterial hypertension
PASS	post-authorisation safety study
PBRER	Periodic Benefit-Risk Evaluation Report
PDE5i	phosphodiesterase type 5 inhibitor
PH	pulmonary hypertension
PRAC	Pharmacovigilance Risk Assessment Committee
PSA	propensity score analysis set
PSE	propensity score excluded set
PSUR	Periodic Safety Update Report
PVOD	pulmonary veno-occlusive disease
PVR	pulmonary vascular resistance
RHC	right heart catheterisation
SAP	statistical analysis plan
SD	standard deviation
SGC	soluble guanylate cyclase
SMD	standardised mean difference
SmPC	summary of product characteristics
TSH	thyroid stimulating hormone
UK	United Kingdom
UNK	unknown
WHO	World Health Organisation

Definition of Term(s)

Study	The term "study" indicates the collection of data for research purposes only. The use of this term in no way implies that any interventional treatments or procedures, planned or otherwise, have been provided or performed.
Retrospective non-interventional study	A study that has all information collected from source data or a retrospective database. Normally, there is no new collection of information from the patient, although this may be required to address specific questions. Studies/Programs/Related Research Activities with only one visit can be considered prospective or retrospective bearing in mind this definition and the source of information.
Post-Authorisation Safety Study (PASS)	Any study relating to an authorised medicinal product conducted with the aim of identifying, characterising, or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.

3. INVESTIGATORS

The list of investigators for each country in which EXPOSURE study is performed has not yet been finalised. For EXTRACT, the list of investigators is provided in Appendix 4.

Principal Investigator: Not Applicable

Coordinating Investigator: Not Applicable

Coordinating Investigator: Not Applicable

4. OTHER RESPONSIBLE PARTIES

Details on sponsor and CRO contact information are provided in Appendix 4.

5. MILESTONES

The dates for key milestones for EXPOSURE and EXTRACT are provided in Table 1.

Table 1: EXPOSURE and EXTRACT milestones

Milestone	Planned Date	Actual Date	Comments
EXPOSURE			
Start of data collection	September 2017	13 Sep 2017	
Registration in the EU PAS register (ENCePP)	2017	12 May 2017	
Interim report 1 (iCSR 1 EXPOSURE 2018)	March 2018	20 Mar 2018	
Interim report 2 (iCSR 2 EXPOSURE 2019)	March 2019	25 Mar 2019	
Interim report 3 (iCSR 3 EXPOSURE 2020)	March 2020	23 Mar 2020	
Interim report 4 (iCSR 4 EXPOSURE 2021)	March 2021	25 Mar 2021	
Interim report 5 (iCSR 5 EXPOSURE 2022)	March 2022	25 Mar 2022	
Interim report 6 (iCSR 6 EXPOSURE 2023)	March 2023	20 Mar 2023	
Data cutoff for interim study report 7	June 2023	14 Jul 2023	
Submission of combined report of study results from EXPOSURE (interim report 7) and EXTRACT (final report)	March 2024	By 31 Mar 2024	
End of data collection	at time of PRAC agreement that commitment is fulfilled		
Final report of study results	12 months after PRAC agreement		

Table 1: EXPOSURE and EXTRACT milestones

Milestone	Planned Date	Actual Date	Comments
EXTRACT			
Start of data collection	Q4 2022	11 Feb 2023	
End of data collection	Q2 2023	28 Jul 2023	
Database lock	06 Sep 2023	07 Sep 2023	
Registration in the EU PAS register	At time of PRAC protocol approval	06 Oct 2022	
Submission of combined report of study results from EXPOSURE (interim report 7) and EXTRACT (final report)	March 2024	By 31 Mar 2024	

6. BACKGROUND AND RATIONALE

Pulmonary arterial hypertension (PAH) is a rare and progressive disease characterised by increased pulmonary vascular resistance that ultimately leads to right heart failure and death. Population based estimates of PAH epidemiology in the European population are not available. However, recent estimates from national systematic registries of European countries (the UK and Sweden) may be most indicative of the true prevalence. Using these databases, PAH prevalence ranges between 22.4 and 54.7 patients per million (Leber 2021).

Selexipag (UPTRAVI®) was approved in the EU on 12 May 2016 for the treatment of PAH. Per the EU SmPC (UPTRAVI SmPC 2016), UPTRAVI is indicated for the long-term treatment of PAH in adult patients with WHO FC II–III, either as combination therapy in patients insufficiently controlled with an ERA and a PDE5i, or a PDE5i, or as monotherapy in patients who are not candidates for these therapies. Efficacy has been shown in PAH populations including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease.

The EXPloratory Observational Study of UPTRAVI in Real-lifE (EXPOSURE) is being conducted to describe the clinical characteristics and outcomes of patients with PAH and to compare the incidence of MACE and all-cause death between UPTRAVI exposed and unexposed patients.

This post-authorisation safety study is part of the European UPTRAVI Risk Management Plan. While the benefits and risks of the new treatments are established in large clinical trials, the impact of these new treatments in the real-world setting remains to be determined. By providing real world data on how UPTRAVI is used in the clinical management of patients with PAH, EXPOSURE will contribute to a greater understanding of UPTRAVI in this post-marketing setting.

EXPOSURE provides contemporaneous real-world data on the overall PAH population, including the aged patient population, in clinical practice. The prospective observational follow up of patients newly treated with UPTRAVI (UPTRAVI cohort) allows this study to put the safety profile of UPTRAVI into context, reporting on all-cause death and other important safety risks, including MACE. Additionally, the UPTRAVI cohort is observed along with a cohort of patients newly treated with any other PAH-specific therapy who were never treated with UPTRAVI (Other PAH therapy cohort).

EXPOSURE was initiated several months after UPTRAVI reimbursement was available in the enrolling countries and had a strict enrolment requirement that PAH-specific therapy should have been initiated no more than 30 days prior to ICF signature by patients. These events resulted in a substantial number of patients who initiated UPTRAVI more than 30 days prior to the study start that were not eligible for enrolment in EXPOSURE. As a result, the recruitment of new UPTRAVI users in EXPOSURE was slower than initially projected since the initiation of the study. Thus, the target enrollment of 1184 patients with PAH who initiated UPTRAVI, and 1850 patients with PAH who initiated any other PAH-specific therapy, is unlikely to be met (EMEA/H/C/0003774/MEA/001.9), as the current enrollment is 829 and 1771 patients, respectively.

EXTRACT was a retrospective chart review study of patients with PAH newly treated with UPTRAVI or other PAH-specific therapy. The study was undertaken to complement the EXPOSURE study with retrospectively identified patients with PAH who were newly treated with UPTRAVI (as monotherapy or in combination with other PAH-specific therapy) before EXPOSURE was initiated and a comparator group consisting of patients with PAH newly treated with other PAH-specific therapies. The overall aim was to fulfil the EMA PASS requirement on UPTRAVI to meet all the original objectives of EXPOSURE.

The EXPOSURE study results were reported annually as interim reports. The latest protocol amendment (Amendment 6, Protocol Version 7), which addressed the PRAC comments received in the fourth interim report, was approved by PRAC on 07 July 2022 (EMEA/H/C/003774/II/0035). The EXTRACT retrospective study was completed on 28 July 2023, and final EXTRACT data are herein reported alongside, and in combination with, the data from EXPOSURE with a data cut-off on 14 July 2023.

The first interim report for EXPOSURE is dated 20 March 2018 and key dates for subsequent reports are presented in Table 1. For EXTRACT, as agreed with PRAC, final report of the study is submitted along with the 7th interim report for EXPOSURE (EMEA/H/C/003774/II/0035).

Data from the UPTRAVI cohorts of both studies are also reported in the PBRER/PSUR.

The EXPOSURE and EXTRACT study protocols and amendments (Appendix 1) and latest SAPs (Appendix 9) describe the analyses performed for this combined report of study results from EXPOSURE (interim report 7) and EXTRACT (final report).

7. RESEARCH QUESTION AND OBJECTIVES

7.1. Research Question

The purpose of the EXPOSURE study is to further characterise the safety profile of UPTRAVI when used in clinical practice and to describe clinical characteristics and outcomes of patients newly treated with UPTRAVI, compared to patients newly treated with any other PAH-specific therapy who were never treated with UPTRAVI, in the post-marketing setting. The EXTRACT study was conducted to complement the EXPOSURE study to meet the desired sample size to effectively address the research objectives.

7.2. Objectives

7.2.1. EXPOSURE

The objectives for this study are:

1. To describe, overall and in the subset of patients over the age of 75 years, demographics, disease characteristics, and clinical course in patients with PAH either newly treated with UPTRAVI (UPTRAVI cohort), or newly treated with any other PAH-specific therapy who were never treated with UPTRAVI (Other PAH therapy cohort).
2. To further characterise the UPTRAVI safety profile, and estimate the IRs during the UPTRAVI exposure period, of all-cause death and the following important identified or potential risks:
   - Hypotension
   - Anaemia
   - Pulmonary oedema associated with PVOD
   - Hyperthyroidism
   - MACE
   - Acute renal failure and renal function impairment
   - Bleeding events
   - Light-dependent non-melanoma skin malignancy
   - Ophthalmological effects associated with the retinal vascular system
   - Gastrointestinal disturbances denoting intestinal intussusception (manifested as ileus or obstruction)

3. To compare rates of MACE and all-cause death between patients in the UPTRAVI cohort and patients in the Other PAH therapy cohort, using a propensity score analysis.

7.2.2. EXTRACT

The objectives of EXTRACT were aligned with EXPOSURE.

1. To describe, overall and in the subset of patients over the age of 75 years, demographics, disease characteristics, and clinical course in patients with PAH newly treated with UPTRAVI and patients initiating another PAH-specific therapy.

2. To further characterise the UPTRAVI safety profile and estimate the IRs during the UPTRAVI exposure period of all-cause death and the following important identified or potential risks:
   - Hypotension
   - Anaemia
   - Pulmonary oedema associated with PVOD
   - Hyperthyroidism
   - MACE
   - Acute renal failure and renal function impairment
   - Bleeding events
   - Light-dependent non-melanoma skin malignancy
   - Ophthalmological effects associated with the retinal vascular system
   - Gastrointestinal disturbances denoting intestinal intussusception (manifested as ileus or obstruction)
3. To describe rates of MACE and all-cause death in UPTRAVI exposed patients and patients initiating another PAH-specific therapy

The third objective of EXTRACT differs from the respective EXPOSURE objective in that it is descriptive due to the limited statistical power that was expected to be obtained for a comparative analysis using the EXTRACT database alone.

7.3. Hypothesis

EXPOSURE is primarily a descriptive study. Additionally, there is an objective to compare the rates of MACE and all-cause death between UPTRAVI-exposed patients and patients initiating other PAH-specific therapy.

EXTRACT was a descriptive study.

8. AMENDMENTS AND UPDATES

Amendments and updates to the PRAC-approved EXPOSURE protocol version 4 (11 April 2017) (Appendix 1) after the start of data collection are summarised in Table 2 below. There were no amendments to the EXTRACT protocol (Appendix 1).

Table 2: List of EXPOSURE protocol amendments

Number	Date	Amendment or update	Overall reason
Amendment 6 Version 7	22 Jun 2022	Amendment	• To update the study milestones (Date of final report of study results) due to the lower recruitment rate than initially planned.

Table 2: List of EXPOSURE protocol amendments

Number	Date	Amendment or update	Overall reason
			• To reflect the sample size re-estimation proposed in interim report #4 of Study AC-065A401 as agreed with PRAC. • To reflect participation of non-EU countries in the study, the study acronym definition for EXPOSURE is changed to '**EXP**loratory **O**bservational **S**tudy of **U**ptravi in **R**eal-lif**E**'
Amendment 5 Version 6	11 Jan 2021	Amendment	• To align safety reporting processes to Janssen procedures.
Amendment 4 Version 5	17 Dec 2019	Amendment	• To implement administrative updates associated with the change in the MAH. • Adverse events were documented in the safety database regardless of reporter's causality assessment for patients treated with PAH specific therapies from the MAH (broader scope than initially documented) to appropriately reflect pharmacovigilance activities in EDC system for reporting of collected AEs on the AE form. • Updated the global drug safety contact information. • Aligned cohort names (UPTRAVI and Other cohorts instead of UPTRAVI exposed and unexposed cohorts) per SAP and corrected the definition for calculating the IR.

9. RESEARCH METHODS

9.1. Study Design

9.1.1. Overview of Study Design

EXPOSURE

EXPOSURE is a multicentre, international, prospective, real-world, observational, cohort study conducted at multiples sites in European and non-European countries to document the treatment of PAH in a clinical practice setting. The planned total sample size is 1184 patients with PAH who initiated UPTRAVI less than 1 month prior to enrolment, at enrolment or during observation (UPTRAVI cohort), and 1850 patients with PAH, who initiated any other PAH-specific therapy less than 1 month prior to enrolment or at enrolment (Other PAH therapy cohort). Definitions of both cohorts are given below.

The UPTRAVI cohort included patients who initiated treatment with UPTRAVI less than 1 month prior to or at ICF signature date (ie, enrolment), patients who died within the first month of UPTRAVI initiation (after study site initiation) and before being able to be consented (if permitted by the local ethics committee), and data collected from UPTRAVI initiation for patients enrolled first in the Other PAH therapy cohort and initiating UPTRAVI for the first time during the observation period (see Section 9.4.2.1 for definition) (ie, 'Late Initiators'). Patients belonging to the UPTRAVI cohort who add another new PAH-specific therapy (other than UPTRAVI) during the course of the study, remain in the study in the UPTRAVI cohort. Patients who, at initiation of treatment with UPTRAVI, are already exposed to other PAH-specific therapies, are included in the UPTRAVI cohort from initiation of UPTRAVI.

Other PAH therapy cohort included patients who initiated any other PAH-specific therapy than UPTRAVI less than 1 month prior to, or at ICF signature date, or patients who died within the first month of any other PAH-specific therapy initiation (after study site initiation) and before being able to be consented (if permitted by the local ethics committee). Patients belonging to the Other PAH therapy cohort who add another new PAH-specific therapy (other than UPTRAVI) during the course of the study, remain in the study in the Other PAH therapy cohort. For patients belonging to the Other PAH therapy cohort who initiated UPTRAVI during the course of the study, the period prior to UPTRAVI initiation in the study belongs to the Other PAH therapy cohort.

'Late Initiators' are patients enrolled in the study while initiating any other PAH-specific therapy than UPTRAVI (ie, belonging to the Other PAH therapy cohort) and who initiated UPTRAVI for the first time during the course of the study. These patients were added to one cohort at a time. Per the inclusion criteria, patients initiating another PAH specific therapy are naïve to UPTRAVI/selexipag, therefore patients who discontinue UPTRAVI and initiate any other PAH-specific therapy during the course of the study are not eligible to enter the Other PAH therapy cohort. These patients remained in the study in the UPTRAVI cohort. A patient was never contributing person-time to both the UPTRAVI and the Other PAH therapy cohorts at the same time point during the study. Any event could be counted only once (in the cohort in which the patient is accumulating person-time at the time the event occurs), ie, a 'Late Initiator' will only contribute to 1 cohort at a time.

If a patient initiated 2 or more PAH-specific therapies not including UPTRAVI at study enrolment, then 1 of these therapies was considered as the treatment defining the cohort entry and other treatments are considered as concomitant PAH-specific therapies (for further details refer to Section 3.3 SAP v9.0 [EXPOSURE], Appendix 9).

EXTRACT

EXTRACT was a non-interventional, multicentre, international, retrospective, medical chart review study of patients with PAH newly treated with UPTRAVI or other PAH-specific therapies. The study aimed to enrol at least 391 patients with PAH who had been newly treated with UPTRAVI prior to launch of EXPOSURE study in their respective country to supplement the EXPOSURE data (Figure 1). Of all the sites participating in the EXPOSURE study, sites in 8 countries granted approval for an ICF waiver and participated in the EXTRACT study. At each

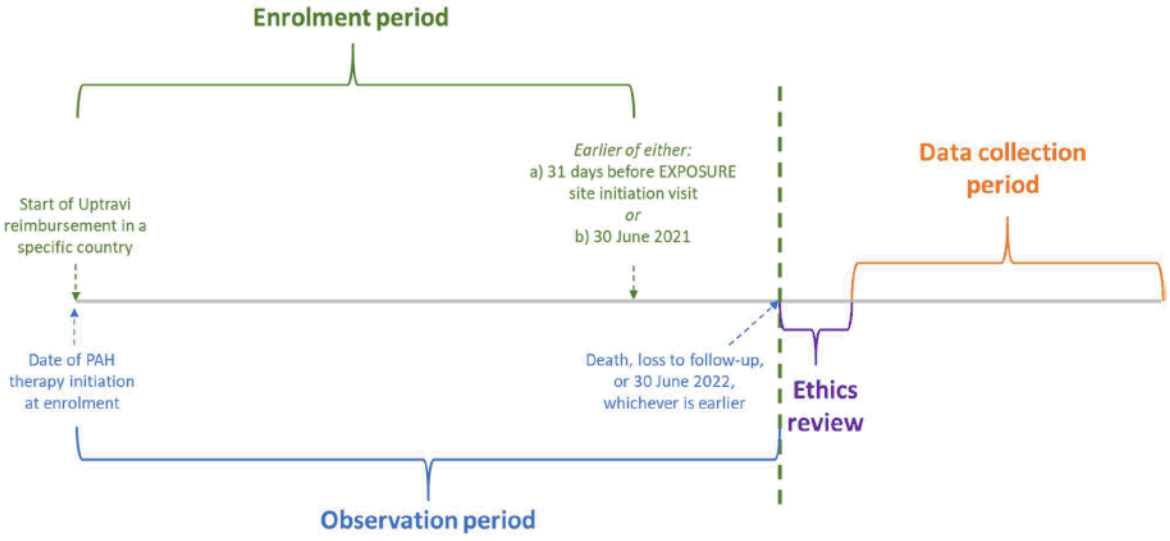
EXTRACT site, the participating physician evaluated patient's medical records to determine their eligibility for data collection in the EXTRACT study. Participants enrolled in EXPOSURE were not considered for EXTRACT recruitment to avoid duplicates.

Only data available within clinical practice were collected. Definitions of the UPTRAVI cohort, Other PAH therapy cohort and 'Late Initiators' were similar to those in EXPOSURE. The enrolment period was from the start of reimbursement of UPTRAVI in a specific country, to the earlier of either:

a) 31 days before the respective EXPOSURE site initiation visit (to avoid enrolment of any patients who were eligible for EXPOSURE to also be enrolled in EXTRACT), or

b) 30 June 2021 (to allow a Min of 12 months of potential follow up after enrolment, as the observation period ended on 30 June 2022)

Figure 1: Diagram of the EXTRACT study design



9.1.2. Changes in Conduct

EXPOSURE

Protocol version 4 (11 April 2017) was the initial protocol approved by the PRAC for the EXPOSURE PASS, before data collection began. Since then, there have been 3 amendments to the PRAC-approved EXPOSURE study protocol (see Section 8 and Appendix 1).

EXTRACT

There were no changes to the planned conduct of the EXTRACT study.

9.2. Setting

EXPOSURE

Initiation of new PAH specific therapy (baseline) is the starting point of the study observation period in both cohorts. A time window of up to 1 month from initiation of the new PAH specific therapy to ICF signature was allowed, to provide patients and site staff sufficient time to discuss study participation (ie, consenting process).

Participating patients were screened for eligibility criteria for either cohort (UPTRAVI or Other PAH therapy cohort) and enrolled after signing of ICF. In cases where the ICF was signed before initiation of new PAH-specific therapy, data collection only started at the time of new PAH treatment initiation.

Eligible patients who died within 1 month of any new PAH treatment initiation, and who were not consented, were included in the study and its analysis if permitted by the local ethics committee. Retrospective data collection was conducted for these deceased patients for the duration of the study, on a continuous basis.

Information on sex, age range, new PAH-specific therapy initiated, and WHO FC were also collected in eligible patients not participating in the study (regardless of non-enrolment reason), depending on local regulation. Details of patients who were not enrolled are provided in the non-enrolment log (Annex 2.2).

Patient data were collected at initiation of a new PAH-specific therapy (ie, baseline) and throughout the observation period (ie, follow-up data) from the existing medical record at any clinic visit.

'Late Initiators' had 2 cohort-specific observation periods (one for the Other PAH-therapy cohort and one for the UPTRAVI cohort) as described in Section 9.4.4.5.1.

The study protocol did not mandate any specific schedule of visits or investigations. Patients were followed by their physician according to clinical practice.

Patient participation in the study could be discontinued at any time for any of the following reasons: withdrawal of consent, lost to follow-up, death, or site closure due to sponsor's decision.

Starting or stopping PAH-specific therapies, including UPTRAVI, per clinical practice during the observation period did not impact data collection for this study.

EXTRACT

Eligible patients were treated with UPTRAVI or other PAH-specific therapies in a routine clinical setting. All treatment decisions were made at the discretion of the treating physician. Starting or stopping PAH-specific therapies during the observation period did not impact data collection for this study. If a patient discontinued treatment before the end of the observational period, all relevant following treatments and assessments were documented.

9.3. Patient Population

EXPOSURE

Enrolment was defined as time of ICF signature or new PAH-specific therapy initiation, whichever occurred the latest.

Patients at each participating site in this study are required to meet the following eligibility criteria:

Inclusion Criteria at Enrolment

- Patients ≥18 years old, and
- Signed patient ICF[a], and
- Group I PAH patients (Simonneau 2013), and
- Newly initiating UPTRAVI or any other PAH specific therapy:
  - less than 1 month prior to enrolment, or
  - at enrolment.

Exclusion Criteria:

- Patients previously exposed to UPTRAVI/selexipag treatment.
- Patients newly initiating any other PAH-specific therapy must not have been previously treated with that same drug.
- Patients enrolled in any ongoing interventional clinical trial.

After study site initiation, all eligible patients initiating a new PAH-specific therapy, including UPTRAVI, are invited to participate in the EXPOSURE study.

Where applicable, the study protocol and amendment(s) were reviewed by the PRAC. The study was conducted in accordance with applicable regulatory requirements.

Personal data for patients participating in this study were limited to those data necessary to investigate the safety and clinical characteristics of the medicinal product under study; these data were collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Additional information on the ethical conduct of this study is contained in the protocol (Appendix 1).

EXTRACT

For the EXTRACT study, the following criteria defined eligibility for data collection:

[a] ICF was provided by the physician and signed by the patient only after the decision is taken by the physician to treat or not treat the patient with UPTRAVI.

Inclusion Criteria at Enrolment:

- Patients ≥18 years old
- Clinically diagnosed with Group I PAH
- Patients whose medical charts were available for data collection during the observation period
- UPTRAVI cohort:
  - Patients who initiated UPTRAVI for the first time
- Other PAH-specific therapy cohort:
  - Prevalent patients (≥ 6 months from first clinically diagnosed PAH)
  - Patients who initiated a PAH-specific therapy other than UPTRAVI for the first time as part of a combination therapy

Exclusion Criteria:

- Patients previously treated with UPTRAVI/selexipag
- Patients who initiated another PAH-specific therapy and had been previously treated with the same drug
- Patients enrolled in EXPOSURE
- Patients enrolled in any ongoing interventional clinical study during the EXTRACT observation period

9.4. Variables

EXPOSURE

The following data are collected for each patient prior to, or at initiation of, a new PAH-specific therapy (ie, baseline) and throughout the observation period from the existing medical record at any clinic visit on the respective eCRF.

- Study specifics (visit date, termination of data entry [date, reason])
- Demographics (age, gender, country)
- Clinical characteristics (PAH classification, aetiology, date of diagnosis and WHO FC at diagnosis, WHO FC, 6MWD, Incremental shuttle walking test, height, weight, RHC, hemodynamics, % predicted carbon monoxide diffusing capacity of the lung, pericardial effusion, vital signs [heart rate, systolic/diastolic blood pressure], transplantation list/pre-transplantation visit, and renal insufficiency)
- Laboratory data (haemoglobin, thyroid hormones [hsTSH, free T3, free T4], NT-proBNP, and BNP)
- Medical history:
  - Cardiovascular/cerebrovascular disease history (history of myocardial ischaemia, MI, cardiac arrest, ischaemic, or haemorrhagic cerebrovascular disorders, carotid and coronary artery revascularisation, or coronary artery revascularisation and unstable angina)

  - Cardiovascular risk factors history (cardiac arrhythmia, cardiac right to left shunts, history of valvular heart disease, cardiomyopathy, carotid and coronary artery arteriosclerosis, or coronary artery arteriosclerosis, high BMI, diabetes mellitus, metabolic syndrome, smoking status, hyperlipidaemia, systemic hypertension, sleep apnoea syndrome, alcoholism, use of illicit drugs)
  - Other relevant medical history (hypotension, anaemia, pulmonary oedema associated with PVOD, hyperthyroidism, renal impairment, bleeding events, light-dependent non-melanoma skin malignancies, ophthalmological effects associated with retinal disorder, intestinal intussusception manifested as intestinal obstruction/ileus) (UPTRAVI cohort only)

- Medication:
  - UPTRAVI treatment (start date, reason for start, dosing regimen, reason for dose reduction, and discontinuation date and reason)
  - Other PAH-specific therapy (history in the previous 12 months, treatment name, dose, start/stop date, reason for start, reason for dose reduction, discontinuation reason)
  - Non-PAH specific therapy (history in the previous 12 months, drug class, start/stop date)
  - Immunosuppressant/immunomodulatory medication (start/stop date, ATC, and indication)

- Follow-up clinical data:
  - Underlying or incident (new) comorbidities at time of the visit (hypotension, anaemia, acute renal failure, and renal function impairment, bleeding event, pulmonary oedema associated with PVOD, hyperthyroidism, light-dependent non-melanoma skin malignancy, ophthalmological effects associated with retinal vascular system, intestinal intussusception manifested as intestinal obstruction or ileus)
  - Hospitalisation (PAH-related or not, admission/discharge dates, reason for hospitalisation)
  - MACE, defined as the occurrence of at least 1 condition falling into any of the below categories:
    - Death from cardiovascular causes (sudden death, fatal MI, fatal stroke, fatal arrhythmia)
    - Non-fatal MI
    - Non-fatal stroke (ischaemic stroke and haemorrhagic stroke, or haemorrhagic stroke)
    - Coronary artery revascularisation
    - Unstable angina
    - Non-fatal cardiac arrest (date of occurrence, occurrence: yes/no)
  - All-cause death (date and cause, PAH-related or not)
  - Other AEs
    - Any other AE while taking UPTRAVI or any Janssen product, irrespective of seriousness and causality

- Any AE leading to discontinuation of a Janssen product
- For females only: child-bearing potential and current pregnancy status

EXTRACT

The EXTRACT study collected data retrospectively for each patient at initiation of UPTRAVI (irrespective of combination therapy status) or other new PAH specific therapy as part of a combination therapy and throughout the observation period from the existing medical chart, if available per clinical practice, and recorded it on an EXTRACT eCRF. The study specifics, demographics, clinical characteristics, laboratory data (except for free T3 and T4) and medical history (except for metabolic syndrome, alcoholism, and use of illicit drugs) variables were the same as those for the EXPOSURE study. Due to the purpose of EXTRACT to complement EXPOSURE to address comparative safety objectives and the limitations of retrospective chart reviews, medication variables were restricted to PAH-specific therapies. The outcomes variables were similar to the follow-up clinical data in EXPOSURE, except for ADRs where any new diagnosis or ADRs considered by the reporter (ie, site personnel who entered patient data into medical chart) to be explicitly causally related to a PAH-specific MAH product, ie, ADRs of a PAH-specific MAH product, were collected.

9.4.1. Outcomes

All outcomes analysed in the EXPOSURE and EXTRACT studies are described in the respective study protocols (Appendix 1).

In this report, outcomes include:

- Occurrence of hospitalisation (PAH-related/not related)
- Occurrence of the following important identified or potential risk events for UPTRAVI (yes/no, according to physician judgement):
  - hypotension
  - anaemia
  - pulmonary oedema associated with PVOD
  - hyperthyroidism
  - acute renal failure, and renal function impairment:
    - by category (acute renal failure/renal function impairment)
    - composite outcome (occurrence of any of the above: yes/no)
  - bleeding events
  - light-dependent non-melanoma skin malignancy
  - ophthalmological effects associated with retinal vascular system
  - intestinal intussusception, manifested as intestinal obstruction/ileus
- Occurrence of any other AEs
- Discontinuation of UPTRAVI and reason for stopping
- Occurrence of MACE, as defined above in Section 9.4.
- Occurrence of all-cause death (PAH-related/PAH-not related/unknown)

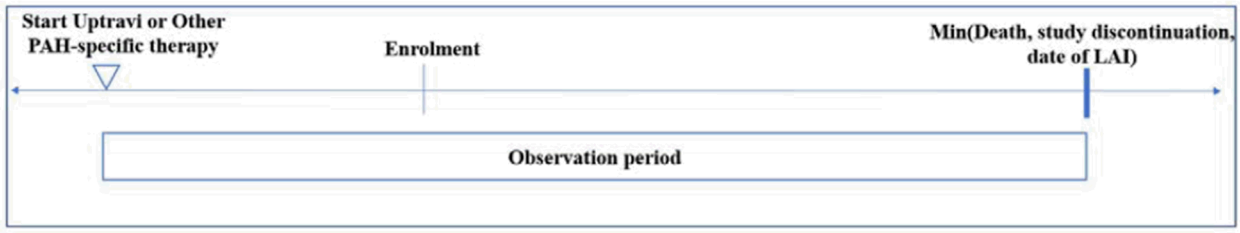
9.4.2. Exposure Definitions and Measures

9.4.2.1. Observation Period

EXPOSURE

For all patients, the observation period is defined as from the date of new PAH specific therapy initiation until the earliest of date of death, date of study discontinuation, or date of last available information (date of LAI prior to data cutoff for this report). The observation period covered all time the patient was observed in the study, regardless of the cohort in which the patient was included for analysis purposes (Figure 2).

Figure 2: Observation Period



EXTRACT

The observation period in the EXTRACT study was from the date of initiation of new PAH-specific therapy until death, lost to follow-up, or 30 June 2022 (the day before planned ethics committee submission for EXTRACT for the first site), whichever was earliest.

9.4.2.2. First Exposure Period

EXPOSURE

For patients in the UPTRAVI cohort, the first exposure period is defined as the time from initiation of UPTRAVI to the earliest of the following events: UPTRAVI discontinuation +7 days, death, date of study discontinuation, or date of last available information. Breaks in UPTRAVI treatment <8 days are included in the first exposure period.

For patients in the Other PAH therapy cohort, the first exposure period is defined as the time from initiation of any other PAH specific therapy to the earliest of the following events: new other PAH therapy discontinuation +7 days, death, date of study discontinuation, or date of last available information. Breaks in the new other PAH specific therapy <8 days were included in the first exposure period (Figure 3).

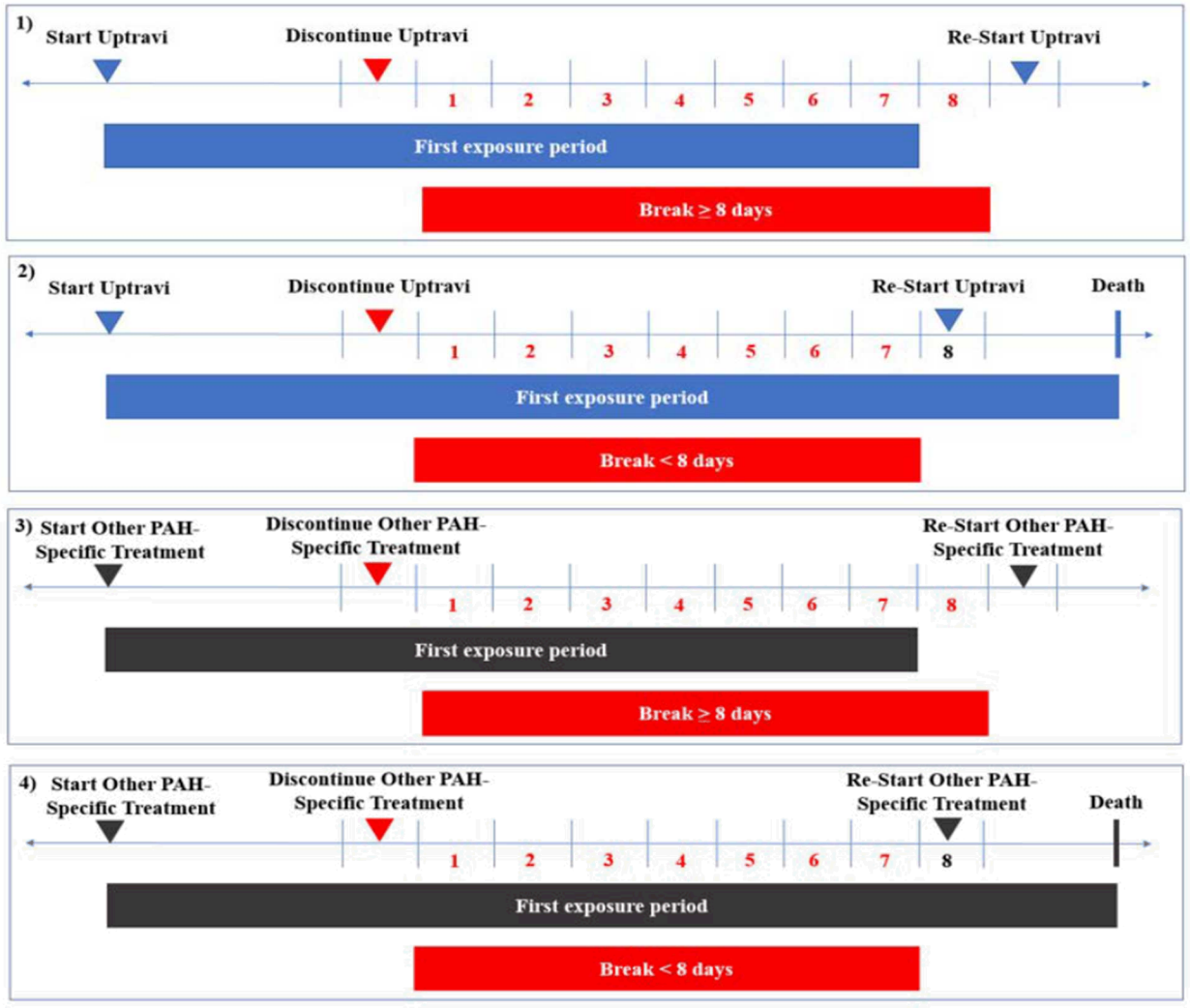
For 'Late Initiators' (ie, patients in the Other PAH therapy cohort who initiated UPTRAVI during the observation period), the first exposure period in the Other PAH therapy cohort is defined as follows:

- If the break between the discontinuation of the new other PAH-specific therapy and initiation of treatment with UPTRAVI was ≥8 days, then the first exposure period in the Other PAH

therapy cohort is calculated as time from initiation of this other PAH-specific therapy to discontinuation of this therapy +7 days.

- If the break between the discontinuation of the new other PAH-specific therapy and initiation of treatment with UPTRAVI was <8 days, then the first exposure period in the Other PAH therapy cohort is calculated as time from initiation of this other PAH-specific therapy until initiation of treatment with UPTRAVI –1 day.
- If UPTRAVI is initiated on top of the other PAH specific therapy, the first exposure period in the Other PAH therapy cohort is calculated as time from initiation of this other PAH specific therapy until initiation of treatment with UPTRAVI –1 day (Figure 4).

Figure 3: First Exposure Period Calculation for UPTRAVI (parts 1 and 2) and Other PAH therapy (parts 3 and 4)



Note: Numbers represent days.

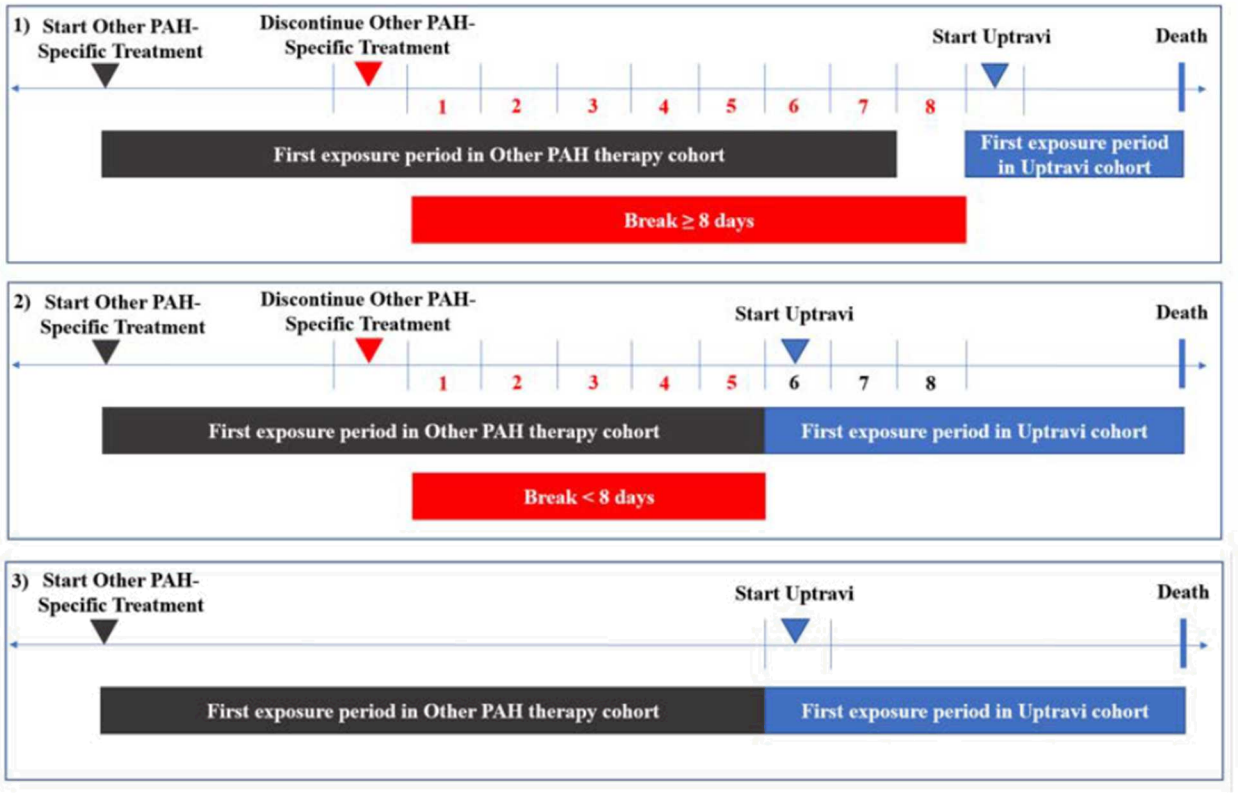
EXTRACT

For patients in the UPTRAVI cohort, the first exposure period is defined as the time from initiation of UPTRAVI to the earliest of the following events: UPTRAVI discontinuation +7 days, death, date of study discontinuation, date of last available information, or 30 June 2022. Breaks in UPTRAVI treatment <8 days are included in the first exposure period.

For patients in the Other PAH therapy cohort, the first exposure period is defined as the time from initiation of any other PAH specific therapy as part of a combination therapy to the earliest of the following events: new other PAH therapy discontinuation +7 days, death, date of study discontinuation, date of last available information, or 30 June 2022. Breaks in the new other PAH specific therapy <8 days were included in the first exposure period.

The first exposure period in the Other PAH therapy cohort for 'Late Initiators' was defined similar to that in EXPOSURE.

Figure 4: First Exposure Period Calculation for 'Late Initiators' for Break in Treatment Between the New other PAH-specific Therapy and UPTRAVI Therapy (≥8 days [1]; break <8 days [2]; UPTRAVI as addition [3])



Note: Numbers represent days.

9.4.2.3. Modified First Exposure Period

EXPOSURE and EXTRACT

The modified first exposure period was used for the ITT analysis in the EXPOSURE and EXTRACT combined analysis.

In EXPOSURE, for patients in the ITT UPTRAVI cohort, the modified first exposure period was defined as time from initiation of UPTRAVI to the earliest of the following events: UPTRAVI discontinuation +7 days, death, study discontinuation, or date of last available information.

In EXTRACT, for patients in the ITT UPTRAVI cohort, the modified first exposure period was defined as time from initiation of UPTRAVI to the earliest among the following events: UPTRAVI discontinuation +7 days, death, study discontinuation, date of last available information, or 30 June 2022.

Breaks in UPTRAVI treatment <8 days were included in the modified first exposure period in both EXPOSURE and EXTRACT studies.

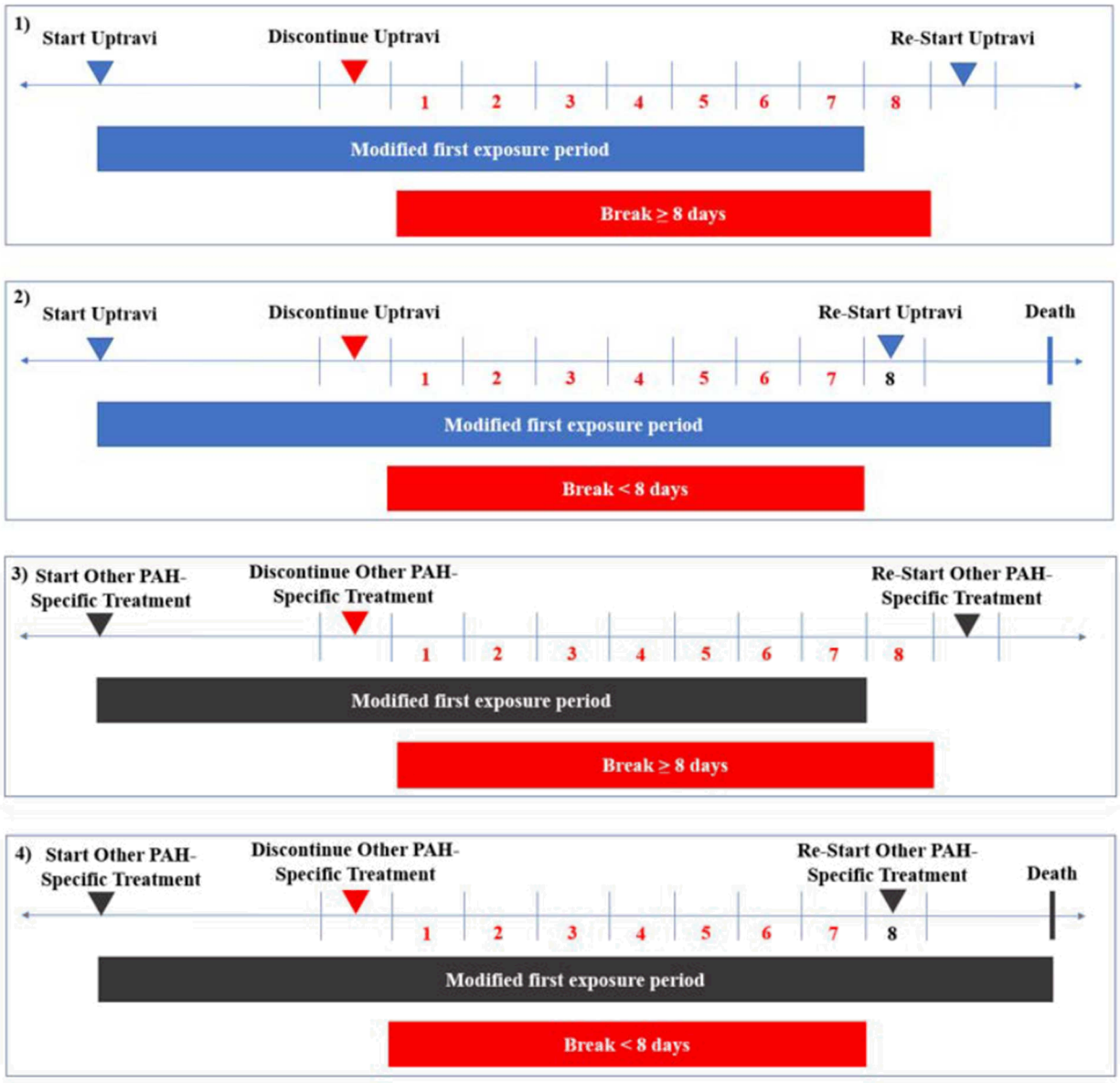
In EXPOSURE, for patients in the ITT Other PAH therapy cohort, the modified first exposure period was defined as the time from initiation of any other PAH-specific therapy to the earliest of the following events: cohort-defining other PAH therapy discontinuation + 7 days, death, study discontinuation, or date of last available information.

In EXTRACT, for patients in the ITT Other PAH therapy cohort, the modified first exposure period was defined as the time from initiation of any other PAH-specific therapy to the earliest of the following events: cohort-defining other PAH therapy discontinuation + 7 days, death, study discontinuation, date of last available information, or 30 June 2022.

Breaks in the cohort-defining other PAH-specific therapy <8 days were included in the modified first exposure period in both EXPOSURE and EXTRACT studies.

The initiation of UPTRAVI during the study did not end the modified first exposure period for patients belonging to the ITT Other PAH therapy cohort (Figure 5).

Figure 5: Modified First Exposure Period Calculation for UPTRAVI (parts 1 and 2) and Other PAH therapy (parts 3 and 4)



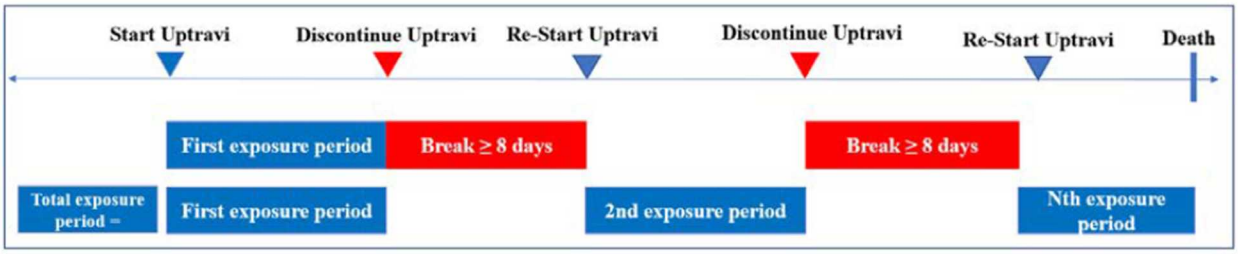
Note: Numbers represent days.

9.4.2.4. Total UPTRAVI Exposure Period

EXPOSURE

To further characterise the UPTRAVI safety profile, the total UPTRAVI exposure period includes all the time periods that a patient received UPTRAVI treatment during the observation period. Breaks in UPTRAVI treatment ≥8 days were excluded from the total UPTRAVI exposure period, while breaks <8 days were included in the total UPTRAVI exposure period. Therefore, the total UPTRAVI exposure period includes the first UPTRAVI exposure period and all subsequent periods that the patient was on UPTRAVI treatment (Figure 6).

Figure 6: Comparison of First and Total Exposure Periods for UPTRAVI



EXTRACT

In EXTRACT, a similar definition of total UPTRAVI exposure period was used as in EXPOSURE.

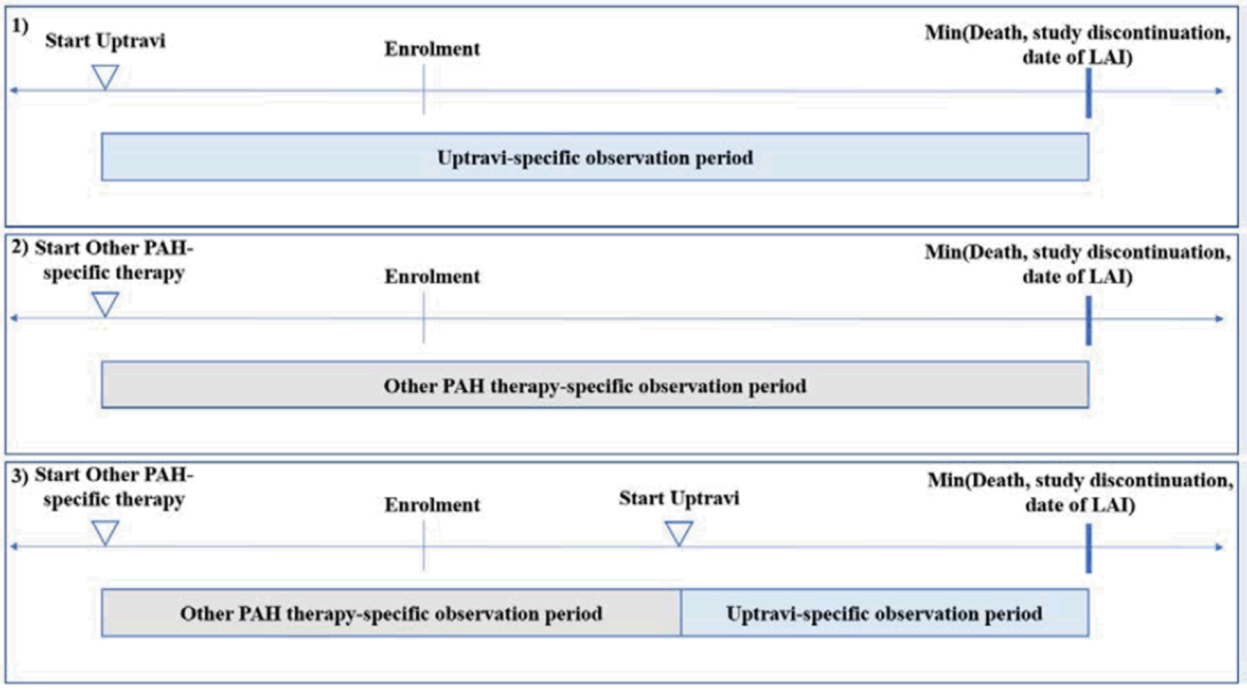
9.4.2.5. Cohort-specific Observation Period

EXPOSURE

A cohort-specific observation period was applied for the 'Late Initiator' patients who switch from the Other PAH therapy cohort to the UPTRAVI cohort during the observation period. The cohort-specific observation period was defined to capture all clinical/safety events that could occur to a 'Late Initiator' patient even outside of his/her exposure period(s) (exposure periods did not cover periods of time when the patient was not under the treatment of interest). For all patients who are not 'Late Initiators', the cohort-specific observation period is the same as the observation period. For 'Late Initiators', the cohort-specific observation period is as follows:

- Start of cohort-specific observation period is defined as the date of the new PAH-specific therapy initiation for the respective cohort (UPTRAVI or Other PAH therapy cohort).
- End of cohort-specific observation period in the UPTRAVI cohort is defined as the earliest of date of death, date of study discontinuation or date of last available information (date of last available information prior to data cut for this interim report).
- End of cohort specific observation period in the Other PAH therapy cohort is defined as date of initiation of UPTRAVI –1 day.

Figure 7: Cohort-specific Observation Period Calculation in non-'Late Initiators' (parts 1 and 2) and 'Late Initiators' (part 3)



'Late Initiators' had 2 cohort-specific observation periods (1 for the Other PAH therapy cohort and 1 for the UPTRAVI cohort) (Figure 7).

EXTRACT

The observation period was from the date of new PAH-specific therapy initiation until death, loss to follow-up, or 30 June 2022 (the day before planned ethics committee submission for EXTRACT for the first site), whichever was earlier. Patients in the Other PAH-specific therapy cohort in the EXTRACT study who initiated UPTRAVI for the first time during the observation period (defined as 'Late Initiator') were followed, from that point forward, as UPTRAVI exposed patients for analysis.

9.4.3. Safety Evaluation

In the EXPOSURE and EXTRACT studies, UPTRAVI is the MAH product under study. Of all other PAH-specific therapies eligible for the study, only the marketed products from the MAH (Veletri®/Caripul®, Opsumit®, Tracleer®/STAYVEER®) are monitored for safety evaluation.

Adverse Events

All serious and non-serious AEs, and special situations following exposure to a PAH-specific marketed products from the MAH (UPTRAVI®, Veletri®/Caripul®, Opsumit®, Tracleer®/STAYVEER®) were recorded in the EXPOSURE eCRF and EXTRACT eCRF and in the patient's source records.

EXPOSURE

Safety was described based on the following data collection:

- UPTRAVI safety profile was described based on the frequency and IR of important identified (hypotension, anaemia and hyperthyroidism) and important potential risks (pulmonary oedema associated with PVOD MACE, renal function impairment/acute renal failure, bleeding event, light-dependent non-melanoma skin malignancy, ophthalmological effects associated with retinal vascular system, gastrointestinal disturbances denoting intestinal intussusception [manifested as ileus or intestinal obstruction]), and all-cause death during all exposure periods.
- Any other AE on UPTRAVI or any other PAH-specific MAH product irrespective of seriousness, and causality
- Any AE leading to discontinuation of UPTRAVI or any other PAH-specific MAH product
- Any AE leading to UPTRAVI dose reduction

EXTRACT

In EXTRACT, UPTRAVI safety profile was described based on the frequency and IR of important identified and important potential risks as listed above for EXPOSURE. Main analysis was performed on the first exposure period (up to first discontinuation; defined as UPTRAVI break >7 days) and total exposure period. For further details on definitions of exposure period, refer to Section 9.4.2. Any new diagnosis or ADRs were collected only if considered explicitly causally related to a PAH-specific MAH product in the medical chart. Frequency of all ADRs related to PAH-specific MAH product were calculated.

Clinical characteristics of patients at the time of UPTRAVI /Other PAH-specific therapy initiation, and the UPTRAVI safety profile were also described in the subset of patients aged >75 years.

Concomitant Medications

After a signed ICF for EXPOSURE was obtained, concomitant medications at the time of enrolment and any changes to those medications during the observation period were recorded into the EXPOSURE eCRF.

Concomitant medications were not collected for EXTRACT.

Safety Variables

Important identified and potential risks for UPTRAVI safety are summarised in Section 9.4.1.

9.4.4. Clinical Outcomes

Data collected for clinical characteristics during observation period are summarised in Section 9.4.

9.5. Data Sources and Measurement

EXPOSURE

The primary data source for this study are the medical records of each patient who provides a signed participation agreement/ICF. Qualified and trained study personnel enter data into the eCRF using eDC via an internet browser-based interface. Data are collected for each patient at initiation of new PAH-specific therapy and throughout the observation period from the existing medical record at any clinical visit on the respective EXPOSURE eCRF.

Where available, the items documented at baseline and during the observational period are summarised in Section 9.4.

EXTRACT

The primary data source for the EXTRACT study were the medical records of each patient. Data were collected retrospectively and entered into the EXTRACT eCRF using eDC via a secure internet-based eDC system.

9.6. Bias

EXPOSURE

EXPOSURE is a prospective non-interventional study with ongoing data entry and cleaning activities, with some data queries and corrections still open at the data cut-off date. The results are subject to the inherent limitations of observational study designs, including potential selection bias, potential bias due to incomplete or missing data, and immortal time bias.

To minimise selection bias during patient recruitment, participating sites are requested to invite consecutive PAH patients who newly initiated a PAH specific therapy and meet the eligibility criteria for either cohort (UPTRAVI/Other PAH therapy cohorts). Potential biases are also presented in the discussion (Section 11).

To account for potential survivor bias in the analysis (eg, either for fatal or non-fatal events during the observation period), only the first period of UPTRAVI/other PAH-specific therapy exposure is included in the UPTRAVI and Other cohorts, respectively.

Methodology to minimise immortal bias is further described in EXPOSURE SAP v9.0 (Appendix 9). To minimise potential immortal time bias, it was requested by the PRAC to include in the study database, where feasible per local regulation, patients who initiated a new PAH specific therapy after study site initiation, but who died within the first month of treatment and were not able to be consented. While all countries and sites were requested to provide this information, many of the ECs refused to include data from recently deceased patients. Enrolment of such patients was possible in 44 sites and rejected for 78 sites, and for 26 sites a decision was pending as of 14 July 2023. The EC refusal reasons are summarised in Ethics Committee Responses (Annex 2.1).

In order to track the number of eligible patients not enrolled into the study, a non-enrolled patient log was completed by each site (see Section 9.2 and the non-enrolment log [Annex 2.2]). The non-enrolment log also includes patients deceased prior to the informed consent being signed.

EXTRACT

The EXTRACT study had inherent limitations of retrospective medical chart review study design, including potential sources of selection or information biases, and confounding. To minimise selection bias, participating sites were encouraged to enrol all patients with PAH initiating a new PAH-specific therapy who met the eligibility criteria, regardless of other previous or concomitant PAH-specific therapy received.

To account for potential survivor bias effect in the analysis from the EXTRACT database (eg, survivor bias either for fatal or non-fatal events during the observation period), only the first exposure period of UPTRAVI/other PAH-specific therapy within the study period was included in the UPTRAVI and the Other cohorts, respectively. The Other PAH-specific therapy cohort also included data prior to UPTRAVI initiation for 'Late Initiators'.

Due to the difference in design between EXTRACT (retrospective) and EXPOSURE (prospective), data quality (eg, missingness, accuracy) might differ between the 2 studies. Poolability of EXTRACT data with EXPOSURE data for comparative analyses is assessed through a homogeneity assessment described in Section 9.9.2.3.

9.7. Study Size

EXPOSURE

A precision-based approach for the CI was used to determine the minimum number of UPTRAVI exposed patients needed to estimate the incidence rate of MACE within the study. A robust estimate of the incidence rate of MACE in PAH is not available from population-based real-world data sources except the contemporaneous and real-world observed data in the EXPOSURE database at the time of protocol development. An incidence of MACE of 3.0 per 100 person-years was observed from the whole study population based on the data cut on 30 November 2020. This was used as an estimate of the background rate of MACE in the general PAH population in real-world settings.

Table 3 shows the sample size re-assessment based on the updated IR. To observe a point estimate of 3.0 per 100 person-years with a 95% CI ranging from 2.07 to 3.93, with a minimum observation time of 18 months, approximately 888 patients in UPTRAVI cohort were needed. For the specified precision, it required 888×1.5 = 1332 person-years. The level of precision of +/–0.93 per 100 person-years (half the width of the CI) equated to a relative precision of 31% of the point estimate. This provided a reasonable margin of error around the point estimate of the assumed background rate of MACE.

Table 3: Number of UPTRAVI patients required to be exposed for a minimum of 18 months in order to achieve various widths of the 95% CI around an IR of 3.0 per 100 person-years

IR	Precision[a]	Relative precision[b](%)	95% Confidence Interval[c]		Study size for UPTRAVI
			Lower bound	Upper bound	Exposed patients[d]
3.0	0.75	25	2.25	3.75	1365.9
3.0	0.81	27	2.19	3.81	1171.0
3.0	0.90	30	2.10	3.90	948.5
3.0	**0.93**	**31**	**2.07**	**3.93**	**888**
3.0	1.05	35	1.95	4.05	696.9
3.0	1.20	40	1.80	4.20	533.5

Source: EXPOSURE Protocol v7.0 Section 9.5 (Appendix 1).
[a] Precision is defined as half the width of the 95% CI.
[b] Relative precision is defined as half the width of the confidence interval and expressed as a percentage of the point estimate IR.
[c] Based on a Normal Approximation.
[d] Observed for a Min of 18 months.

In order to achieve comparable treatment groups, the application of the propensity score methodology might result in patients being excluded from the analysis. According to the distribution of patients initiating another PAH-specific therapy in EXPOSURE as of 30 November 2020 data cutoff, additional 50-60% of patients initiating another PAH-specific therapy would be required for propensity score methodology. Thus, the comparator group would need 1450 patients initiating another PAH-specific therapy followed for at least 18 months. For the specified precision, it required 1450×1.5 = 2175 person-years.

To achieve at least 888 patients receiving UPTRAVI followed for a Min of 18 months, the study target of enrolment would be 1184 UPTRAVI exposed patients for Min of 18 months, assuming a patient retention rate of 75% (Appendix 1). Thus, to ensure the comparable effective sample size in the propensity score weighting analysis, the original target enrolment number in the Other PAH therapy cohort, ie, 1850 patients, should be maintained.

An increased risk for MACE among the UPTRAVI cohort would be indicated if the observed incidence exceeds the upper bound of the 95% CI of the observed background rate in the Other PAH therapy cohort.

The intended precision of +/–0.93 per 100 person-years for incidence rate depends on total person-years. It might also be reached when the actual sample size is different from the target sample size because some patients have much longer exposure duration than 18 months and patients with shorter exposure duration are also included in the analysis, instead of being excluded.

EXTRACT

Sample size in EXTRACT was determined based on the difference between the overall sample size needed in the UPTRAVI cohort in EXPOSURE and the projected number of patients that could be enrolled in that cohort by June 2023 (ie, by the planned end of data collection in

EXTRACT), while maintaining a similar ratio with the Other PAH therapy cohort as in EXPOSURE. No formal sample size calculation was performed for EXTRACT. EXTRACT planned to enrol at least 391 patients in the UPTRAVI cohort, to reach the enrolment target of 1184 UPTRAVI patients in the combined EXPOSURE and EXTRACT dataset. In addition, at least 510 patients were planned to be enrolled in the Other PAH-specific therapy cohort in EXTRACT to serve as an internal comparator to the UPTRAVI cohort.

9.8. Data Management

The original terms used by the investigators in respective AEs fields of the eCRF were assigned preferred terms from MedDRA (Medical Dictionary for Regulatory Activities) for classification and tabulation. The current version of the dictionary database is expected to change over the life of the study. MedDRA v26.0 was used for the EXPOSURE (data cut-off on 14 July 2023) and the EXTRACT (DBL on 06 Sep 2023) studies WhoDD (version WhoDD March 2023) was used to code PAH-specific and concomitant medications that were entered in respective free text field in the eCRF.

9.9. Statistical Methods

Statistical analyses were performed under the authority of the sponsor. Statistical methods are presented in SAP v9.0 for EXPOSURE and in SAP v2.0 for EXTRACT and the EXPOSURE and EXTRACT combined analysis (Appendix 9).

All data analyses are exploratory for EXPOSURE and EXTRACT studies. Selected analyses are tabulated separately for the subgroup of patients aged >75 years (demographics, clinical characteristics, clinical course, UPTRAVI safety profile) and non-European patients (demographics, clinical characteristics, PAH-specific treatment status). A separate tabulation is provided for all-cause death stratified by WHO FC. Homogeneity between EXPOSURE and EXTRACT patients was based on patient characteristics at the time of new PAH-specific therapy initiation. The duration of the observation period was also appraised.

9.9.1. Main Summary Measures

Continuous variables are summarised using the number of patients, number of missing values, mean, median, SD, SE, range (Min, Max), and first and third quartiles.

Categorical variables are summarised using number of patients (n – excluding patients with missing values and patients with value “Unknown”), number of missing values, frequency counts, and percentages. Percentages are based on the number of patients with available values, ie, non-missing and non-unknown data for a given outcome.

9.9.1.1. Safety Analyses

Adverse Events

All documented AEs in EXPOSURE and EXTRACT studies were included in the analysis. For each AE, the percentage of patients who experienced at least 1 occurrence of the given event was summarised.

Where appropriate, additional summaries and listings are provided for those patients who died, discontinued treatment due to an AE, or experienced a severe or a serious adverse event.

The frequencies and percentages of patients with an event prior to or at the initiation of UPTRAVI, ongoing at the initiation of UPTRAVI, and after the initiation of UPTRAVI are presented. Any other AEs were defined as AEs collected in the eCRF "Other Adverse Events" section (questions "Any other AE on UPTRAVI, irrespective of seriousness and causality" and "Main event").

In EXPOSURE, for frequencies, all occurrences marked as "New since last visit?" = "YES" on the eCRF were considered as separate events.

Worsening event rates of safety events of interest for the UPTRAVI safety profile were not available for patients in the EXTRACT study due to the retrospective nature of the data collection.

9.9.1.2. Analysis Sets

EXPOSURE

The following analysis sets are used:

- All Set (ALL): All patients present in the database at the time of the data cut-off (updated annually). No analyses are foreseen for this set, which is only used to provide the overall number of study patients.

Patients belonging to the ALL set, but no other analysis set, for whom it cannot be determined whether they belong to the UPTRAVI or the Other PAH therapy cohort, are presented under the Other PAH therapy cohort in ALL outputs.

- Enrolled Set (ENR): All patients present in the database at the time of the data cut-off (updated annually) with an available PAH-specific therapy initiation date, and who met all the eligibility criteria.

Patients with no baseline information collected (only treatment start date available) are considered as 'Included, not analysed'. These patients were not included in the analyses or in the ENR patient count.

It is possible that a 'Late Initiator' belongs to the ENR set for 1 cohort but does not belong to the ENR set for the other cohort, if some data are missing.

- Follow-Up Set (FUP): All ENR patients who have at least 1 follow-up data point documented (ie, follow-up visit date, death date, hospitalisation start date, medication discontinuation date, medication interruption date, or medication dose change date) after their PAH-specific therapy initiation date.

Each patient had to have at least 1 follow-up data point documented in a specific cohort (during the first exposure period) to be considered in FUP for that cohort. Therefore, it is possible that a 'Late Initiator' belongs to the FUP for one cohort but does not belong to the FUP for the other cohort.

- Extended Follow-Up Set: All patients in the FUP as well as patients excluded from the FUP due to missing baseline data (ie, the ENR included, not analysed patients).

A descriptive subgroup analysis, ie, classification of patients according to important demographic and clinical characteristics was conducted with no hypothesis testing. Subgroup definitions are described in EXPOSURE SAP v9.0 (Appendix 9).

EXTRACT

Definitions of ALL, ENR, FUP Sets in the EXTRACT study were identical to that of EXPOSURE. ALL set included all patients present in the EXTRACT database with an available PAH-specific therapy date. ENR set included all eligible patients present in the database at the time of the DBL on 07 Sep 2023 with an available PAH-specific therapy initiation date.

EXPOSURE and EXTRACT Combined Analysis

In addition to analysis sets defined for EXPOSURE and EXTRACT databases, the following sets were defined for pooled data that were only used for combined analysis.

- **Propensity Score Analysis Set (PSA):** All patients from the FUP Set that contribute to the outcome models in the propensity score (PS) analysis. It is possible that a 'Late initiator' belongs to the PSA set for one cohort but does not belong to the PSA set for the other cohort. Multiple imputation was applied for missing covariates before PS estimation. Therefore, PSA set may differ for each imputed dataset.
- **Propensity Score Excluded Set (PSE):** All patients from the FUP set were included in dataset imputation used in PS analysis. It is possible that a patient in the FUP set did not contribute to the outcome models in the PS analyses due to trimming of the PS or due to other reasons. Only patients in the FUP set who had been discarded from the outcome model estimation for at least 5 out of 10 imputed datasets were included in the PSE set.
- **ITT Follow-Up Set (ITT FUP):** All patients with an available PAH-specific therapy initiation date, and who met all the eligibility criteria and who had at least one follow-up information documented (ie, follow-up visit date, death date, hospitalisation start date, medication discontinuation date, medication interruption date or medication dose change date) after their PAH-specific therapy initiation date.

  Each patient who had at least one follow-up information documented in the specific ITT cohort, ie, either in the ITT UPTRAVI cohort or ITT Other PAH therapy cohort (during the modified first exposure period) were considered in the ITT FUP for that ITT cohort.
- **ITT Propensity Score Analysis Set (ITT PSA):** All patients from the ITT FUP Set that contributed to the outcome models in the PS analysis. Multiple imputation was applied for missing covariates before PS estimation. Therefore, ITT PSA set may differ for each imputed dataset.
- **ITT Propensity Score Excluded Set (ITT PSE):** All patients from the ITT FUP set were included in dataset imputation used in PS analyses. It is possible that a patient in the ITT FUP set did not contribute to the outcome models in the PS analyses due to trimming of the PS or due to other reasons. Only patients in the ITT FUP set who had been discarded from the

outcome model estimation for at least 5 out of 10 imputed datasets were included in the ITT PSE set.

9.9.2. Main Statistical Methods

9.9.2.1. EXPOSURE

The statistical analyses of EXPOSURE data are described in SAP v9.0 (see Appendix 9). All data analyses were exploratory. For this report, all analyses were performed on data collected between 13 September 2017 and the data cut-off date of 14 July 2023. The data cut-off for outputs from the global medical safety database including information about the reported causality assessment is aligned with the cut-off date for this report of 14 July 2023.

9.9.2.1.1. Incidence Rates, Event Rates and Cumulative Event Rates

The IRs were calculated based on the number of patients with a first event after initiation of PAH-specific treatment (numerator) divided by the total duration of the exposure period (denominator) and expressed as events per 100 person-years with associated 95% CIs, based on a generalised linear model assuming a Poisson distribution, and using log (duration of the exposure period) as an offset.

For patients experiencing an event, only the exposure until the first event was included in the calculation of IRs. For patients who did not experience an event, the entire exposure period was included (ie, these patients were right censored at the last day of exposure period) in the calculation of IRs. For the IR analysis during the cohort-specific observation period, patients with no events were right censored at the end of the cohort-specific observation period.

Patients with an ongoing event at initiation of new PAH-specific therapy were excluded from the calculation of IR for that specific event. For the IR of hospitalisation, all patients were considered at risk of hospitalisation and, hence, were included in the IR analyses. For patients hospitalised at baseline, the exposure to the first hospitalisation starts counting from the day after the end date of their baseline hospitalisation.

IRs were calculated for the first exposure period (hospitalisation, UPTRAVI safety profile, MACE, death), the cohort-specific observation period (UPTRAVI safety profile, MACE, death) and observation period (MACE). Additionally, in the UPTRAVI cohort, event rates were calculated similarly as for IRs, but using the total exposure period until the first event, excluding interruption periods.

For hospitalisation, cumulative event rates (ie, including all events during the exposure period) were additionally calculated based on the number of events (numerator) during the exposure period (denominator) and expressed as per 100 person-years with associated 95% CI. For cumulative event rates, the entire exposure period was included as denominator. Cumulative event rates were calculated based on a generalised linear model assuming a negative-binomial distribution and using log (duration of the exposure period) as an offset.

For the UPTRAVI safety profile, annualised event rates were calculated for the first exposure period, the total exposure period, and the cohort-specific observation period. The calculation was done in the same way as the cumulative event rate but presented by 1 person-year.

For the UPTRAVI safety profile, during all the exposure periods, additional annualised treatment emergent event[b] rates were calculated. The calculation was the same as for the annualised event rates, but all the patients were at risk, regardless of an event ongoing at baseline. All new events, as well as worsening events, were considered.

Full details are provided in the EXPOSURE SAP v9.0 (see Appendix 9).

9.9.2.1.2. Time to Event

Time to first event was defined as the time (months) from the date of initiation of new PAH-specific therapy to the date of the first event. Patients who were event-free were censored at the end of the first exposure period (for time to event analysis during the first exposure period) or at their last available information (for time to event analysis during the cohort-specific observation period). Patients with events ongoing at initiation were excluded from the time to event analyses. For hospitalisation events, all patients were included in the analyses. Full details are provided in EXPOSURE SAP v9.0 (see Appendix 9).

9.9.2.1.3. Descriptive Analysis of MACE and All-cause Death

The frequencies and IRs as well as annualised event rates of MACE as composite outcome and by sub-category were calculated in the UPTRAVI and Other PAH therapy cohort patients during the first exposure period. For the UPTRAVI cohort, MACE was further summarised during the UPTRAVI cohort-specific observation period and observation period. Event rates during the total exposure period were only calculated for the UPTRAVI cohort. MACE was summarised for all patients in the FUP set. Additionally, fatal and non-fatal MACE events were summarised separately.

Death was summarised based on the main cause of death question from the follow up EXPOSURE eCRF page. The frequencies and incidence rates (mortality rates) of all-cause death were calculated for the UPTRAVI and Other PAH therapy cohorts during the first exposure period. Mortality rates were calculated during the first and total exposure periods, however mortality rates during the total exposure period were only calculated for the UPTRAVI cohort. In addition, mortality rates stratified by PAH-relatedness were also calculated. For the UPTRAVI cohort, all-cause death was further summarised during the UPTRAVI cohort-specific observation period and observation period.

All-cause death was summarised for all patients in the FUP set. The analysis of all-cause death was additionally stratified by WHO FC (I/II, III/IV, unknown/missing) and treatment combination

[b] Treatment emergent adverse events are undesirable events that are not present prior to medical treatment, or an already present event that worsens either in intensity or frequency following the treatment.

(monotherapy oral, dual combination therapy oral, triple or more combination therapy oral, monotherapy i.v., combination including i.v., unknown information) at the initiation of the new PAH-specific therapy. For patients who died with WHO FC missing at baseline, WHO FC at diagnosis was displayed. All-cause death during the first exposure period was presented for the extended FUP set. The number of patients with all-cause death were summarised by cohort (UPTRAVI and other PAH therapy), period (first exposure period, total exposure period and cohort-specific observation period) and analysis set (FUP, Extended FUP), whichever were applicable.

9.9.2.1.4. Analysis of study treatment exposure

Exposure to UPTRAVI was described in terms of duration, highest dose received during the first 24 weeks, first maintenance dose level, duration of titration period, duration of first maintenance period, number of dose adjustment periods, and number of maintenance doses in all UPTRAVI cohort patients. The duration of the exposure period was summarised by dose and overall.

Exposure to new other PAH-specific therapy was described in terms of duration.

9.9.2.2. EXTRACT

9.9.2.2.1. Incidence Rates, Event Rates and Cumulative Event Rates

IRs, event rates, and cumulative event rate analysis for EXTRACT followed the same statistical methods as applied for the EXPOSURE analysis. Treatment emergent rates were not analysed for EXTRACT data.

9.9.2.2.2. Time to event

Time to first event analysis for EXTRACT was carried out during the first exposure period and followed the same statistical methods as applied for the EXPOSURE time to event analysis.

9.9.2.2.3. Descriptive Analysis of MACE and All-cause Death

Descriptive analysis of MACE for EXTRACT was carried out during the first exposure period and followed the same statistical methods as applied for EXPOSURE. MACE was summarised for all patients in the FUP set.

Death was summarised based on the main cause of death question from the follow up EXTRACT eCRF page and followed the same statistical methods as applied for EXPOSURE. The frequencies and incidence rates (mortality rates) of all-cause death were calculated for the UPTRAVI and Other PAH therapy cohorts during the first exposure period.

9.9.2.2.4. Analysis of study treatment exposure

Exposure to UPTRAVI and new Other PAH-specific therapy were described for EXTRACT using the same statistical methods as applied for EXPOSURE.

9.9.2.3. EXPOSURE and EXTRACT combined analysis

All descriptive analyses performed in the EXPOSURE and EXTRACT studies were also performed on the combined EXPOSURE and EXTRACT dataset.

The comparative analysis with PS addressing the third objective of EXPOSURE (ie, to compare rates of MACE and all-cause death between UPTRAVI exposed patients and patients initiating other PAH-specific therapy; EXPOSURE protocol v7.0 [Appendix 1]), was performed using both EXPOSURE and EXTRACT study data in a combined dataset.

9.9.2.3.1. Homogeneity assessment between EXPOSURE and EXTRACT

Variables included for the homogeneity assessment were age and WHO FC at initiation of therapy, time since diagnosis, renal impairment, PAH classification, comorbidities/medical history, cardiovascular risk factors, and duration of cohort-specific observation period. A clinical appraisal by an MAH group of physicians, scientists, statisticians, and epidemiologists knowledgeable of PAH disease was performed to allow for the inherent fluctuation of the disease phenotype that a formal statistical comparison would not have been able to assess.

9.9.2.3.2. ERS 2022 1-year mortality risk score

The analyses were presented separately for UPTRAVI and Other PAH therapy cohort using the ERS 2022 Risk Score Set, ie, all patients from the FUP set with at least 2 out of 3 components for 1-year mortality risk score calculation available at baseline. Of the 2 components available, 1 needed to be NT-proBNP or BNP and the other was WHO FC or 6MWD. Variables and cut-off values for the ERS 2022 risk score calculation are described in the EXPOSURE and EXTRACT combined analysis SAP v2.0 (Appendix 9).

'Late Initiators' could belong to the ERS 2022 Risk Score Set for the 2 cohorts or only for 1 cohort, depending on the availability of data at the respective baselines. For 'Late Initiators', the ERS 2022 risk score was re-calculated at their UPTRAVI baseline.

9.9.2.3.3. Propensity score analysis of MACE and all-cause death

The covariates listed in Table 4, considered to be prognostic or predictive of the treatment cohort's exposure and outcomes, or outcomes only, were used in the PS model. Two reduced lists of covariates were considered in the respective outcome models. The selection of covariates was based on the clinical assessment of their prognostic values for MACE and all-cause death. This avoids over-fitting in the outcome model (where there are limited numbers of events) and retains power. All baseline variables were described by cohort.

Table 4 shows the list of baseline covariates used for the propensity score, all-cause death, and MACE analyses. Further details about covariates and sub-categories of composite variables are described in the EXPOSURE and EXTRACT combined analysis SAP v2.0 (Appendix 9).

Table 4: Selected baseline covariates included in propensity score and outcome models for all-cause death and MACE

Baseline covariate	Values	Propensity score	All-cause death	MACE
Study	EXPOSURE, EXTRACT	Y	Y	Y
Age at baseline	Continuous	Y	Y	Y
Sex	Male, Female	Y	Y	Y
Country	Canada, Germany, Spain, Others	Y	Y	Y
WHO FC	I/II, III/IV, Missing/Unknown	Y	Y	Y
6MWD	Continuous	Y	Y	
PAH classification	PAH/hPAH/Drug and toxin induced/Associated with HIV, PAH associated with connective tissue disease, PAH associated with congenital heart disease, Other	Y	Y	Y
Time since PAH diagnosis	Continuous	Y	Y	
NT-proBNP/BNP	Normal, Abnormal, Missing/Unknown	Y	Y	Y
RAP	Continuous	Y	Y	
CI	Continuous	Y	Y	
SV02	<60, 60-65, >65, Missing/Unknown	Y	Y	
Pericardial effusion	Yes, No	Y	Y	Y
Specific comorbidities / medical history	1 or more, None, Missing/Unknown	Y	Y	Y
CV risk factors	1 or more, None, Missing/Unknown	Y	Y	Y
Renal impairment at baseline	Yes, No/Unknown	Y	Y	
PAH regimen at baseline	Monotherapy, Dual combination therapy, Triple or more combination therapy, Missing/Unknown	Y	Y	

Source: SAP v2.0 for EXTRACT and the EXPOSURE and EXTRACT combined analysis (Appendix 9).

For both outcomes (MACE, all-cause death), the PS of each individual patient in the UPTRAVI and Other PAH therapy cohorts was calculated using a logistic regression model with a logit link, including all baseline covariates described in Table 4 as independent variables. The weighting approach for estimating the average treatment effect on the treated group (ATT) was used to address confounding factors. An ATT weighting approach allows the inclusion of all patients in the UPTRAVI cohort and gives more weights to the patients in the Other PAH cohort with baseline characteristics similar to the UPTRAVI patients.

To assess the performance of the weighting approach, the mean, SD, and maximum of the weights in each cohort were reported. The effective sample size from both cohorts was also presented. Truncation was applied on patients with weights > 10.

Poisson models including ATT weights calculated from the PS and adjusted for the selected baseline covariates in Table 4 were applied for MACE and all-cause death, respectively.

The two-sided 95% CIs were calculated for the incidence/mortality rate ratio for the UPTRAVI cohort patients compared to the Other PAH therapy cohort patients during their first exposure period. Sandwich variance estimators were used to adjust for possible variance misspecification in

Poisson models of MACE and all-cause death. The advantage of this approach is that the estimate is consistent even if the variance is mis-specified (Diggle 1994).

In addition, for the weighted analyses of MACE and all-cause death, the IR and 95% CI of each cohort were approximated, without covariate adjustment, by the following formula:

- IR per 100 person-years is the average weighted number of patients with event divided by average weighted exposure × 100.
- The precision per 100 person-years is obtained as standard normal distribution quantile at 0.975 × (square root of average weighted number of patients with event divided by average weighted exposure) × 100.
- The 95% CI lower or upper bound is calculated as IR per 100-person-years ± precision per 100 person-years.

These approximated IR estimates were not intended for estimating IR ratio between cohorts as adjustment with covariate was not considered.

9.9.2.3.4. Sensitivity Analysis

To address the impact of right censoring patients from the Other PAH therapy cohort that initiated UPTRAVI during the course of the study (ie, 'Late Initiators'), ITT analyses were also performed as sensitivity analyses for MACE and all-cause death based on ITT FUP Set using the modified first exposure period, ie, from initiation date to end of treatment date +7 days regardless of UPTRAVI late initiation, as well as using the observational period defined in Section 9.4.2. Sensitivity analyses for PS weighting were performed without considering 'Late Initiators'. The PS model for each imputed dataset was repeated for sensitivity analysis based on the ITT FUP set.

Additional sensitivity analyses were performed for both previously described PS analyses (based on FUP and ITT FUP sets) using the average treatment effect for the overlap population (ATO) approach to address confounding factors (Li 2018).

Additional sensitivity analyses using the ATO weighting approach were also performed for all previously described analyses based on the ITT PSA set.

Full details are provided in the EXPOSURE SAP v9.0 and the EXPOSURE and EXTRACT combined analysis SAP v2.0 (see Appendix 9).

9.9.3. Missing Values

Due to the non-interventional nature of EXPOSURE and EXTRACT studies and the retrospective data collection design of the EXTRACT, some study variables were expected to be missing or incomplete and were reviewed on a periodic basis for missing datapoints and incomplete information. Missing data imputations were performed by an independent Statistical Supporting Group (SSG) only on the baseline variables used in the comparative analysis.

Partial missing dates (PAH diagnosis date, date of death, start date of event, start and end dates of hospitalisation, date of discontinuation of new PAH specific therapy, start date of new other PAH

specific therapy) were imputed (Section 5.3 of the EXPOPSURE SAP v9.0 and Section 2.9.3 and Section 3.3.8.2 of the EXPOSURE and EXTRACT combined analysis SAP v2.0 [see Appendix 9]).

All dates that were later than death date after imputation were set equal to death date to avoid inconsistencies between dates. Further details of the rules for handling of missing or incomplete dates are described fully in the Section 5.3 of the EXPOSURE SAP v9.0 and Section 2.9.3 and Section 3.3.8.2 of the EXPOSURE and EXTRACT combined analysis SAP v2.0 (see Appendix 9).

9.9.4. Sensitivity Analyses

Sensitivity analyses performed for 'Late Initiators' are described in Section 9.9.2.3.4.

9.9.5. Amendments to the Statistical Analysis Plan

Changes to the EXPOSURE SAP between v8.0 and v9.0 are detailed in Section 1.5 of the current SAP version (EXPOSURE SAP v9.0 [see Appendix 9]). There were no amendments to the EXPOSURE and EXTRACT combined analysis SAP v2.0 (see Appendix 9).

9.10. Quality Control

The EXPOSURE and EXTRACT studies were conducted in accordance with the International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP) (ISPE 2015) and in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (ENCePP Guide 2015).

9.10.1. EXPOSURE

The accuracy and reliability of the study data were assured by the selection of qualified investigators and appropriate participating sites, review of data collection procedures with the investigator and participating site personnel before the study and remote monitoring and ad-hoc on-site monitoring visits by the sponsor. Guidelines for completion of eCRFs were provided and reviewed with participating site personnel before the start of the study. eCRFs were reviewed by the sponsor for accuracy and completeness and any discrepancies were resolved with the investigator or designee.

A secure, internet-based eDC system was used for data entry. The eDC system contains programmed automatic edit checks to catch data inconsistencies at the time of data entry, resulting in queries to be addressed by the site. The Data Management team conducted an ongoing review of the data to ensure overall consistency and expected level of data quality. Data quality review was performed monthly by the epidemiologist and study physician for implausible values, missing data, assessments not conducted, or incomplete information. The reported AE Forms were reviewed for completeness and missing information eg, regarding causality and outcome were queried.

No source data verification was foreseen; however, monthly monitoring calls were performed by the CRO.

To further minimise the number of patients lost to follow-up, the monthly monitoring calls allowed proactive identification of patients with no data entry for >6 months. For those patients, physicians were contacted to identify the reason for the time gap in data.

As EXPOSURE is an ongoing study, data entry and cleaning activities are ongoing during the study. Before the production of this report, data entry and cleaning activities were closely overseen with an intention to produce a data extract that is as clean as possible. At the time of data cut-off (14 July 2023) for this report, 12 patient visits (5 baseline and 7 follow-up visits) were pending data entry and 30 queries remained open. Data cleaning will be completed at the end of the study.

9.10.2. EXTRACT

The accuracy and reliability of the study data were assured using standard approach similar to that used for EXPOSURE. Periodic monitoring visits or remote monitoring were performed by the sponsor (as applicable) and according to approval requirements provided by regulatory authorities or ECs restricting direct access to source data in view of the ICF waiver granted. Data cleaning activities for EXTRACT were completed at the end of the study prior to the database lock.

10. RESULTS

This CSR is the final report for EXTRACT and the 7th interim CSR for EXPOSURE. Results from EXPOSURE are described in Section 10.1 and from EXTRACT in Section 10.2. Results of the combined EXPOSURE and EXTRACT dataset, including homogeneity assessment for the data from the 2 studies, are described in Section 10.3. Data for the ENR Sets for each analysis are provided in Attachments.

Non-European patients are described in Section 11.4 and patients included in the ITT FUP Set are described in Section 10.3.2.5.

The safety profile and clinical outcome results of the study are summarised in the main text of this report. Additional detailed summary tables are included as attachments.

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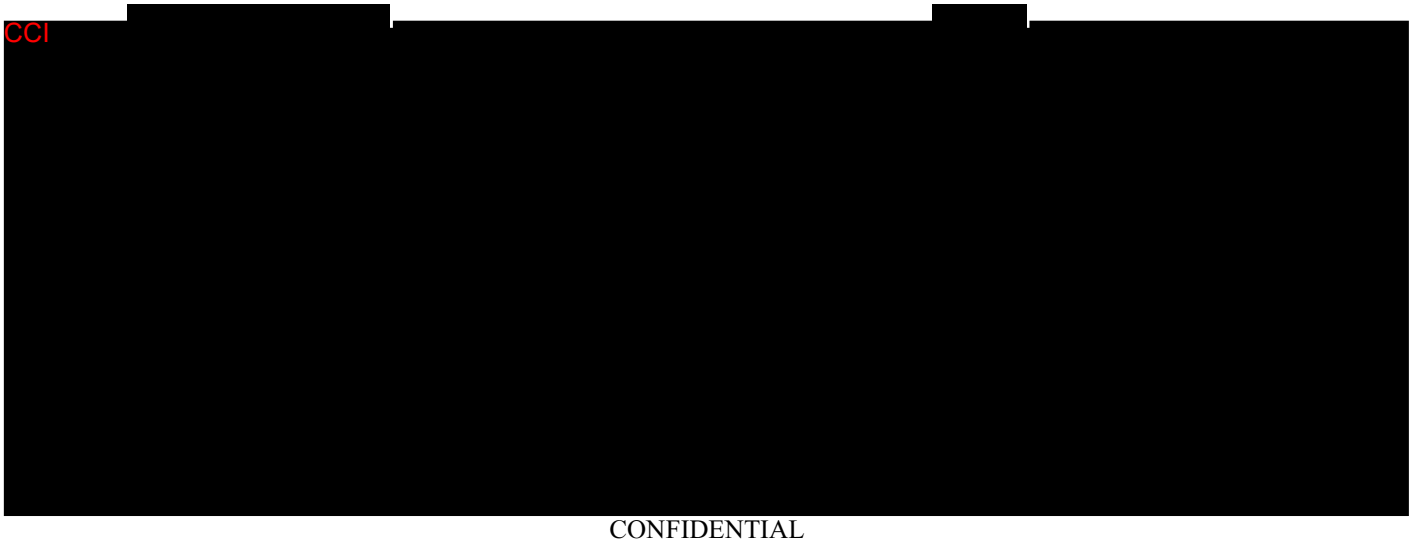

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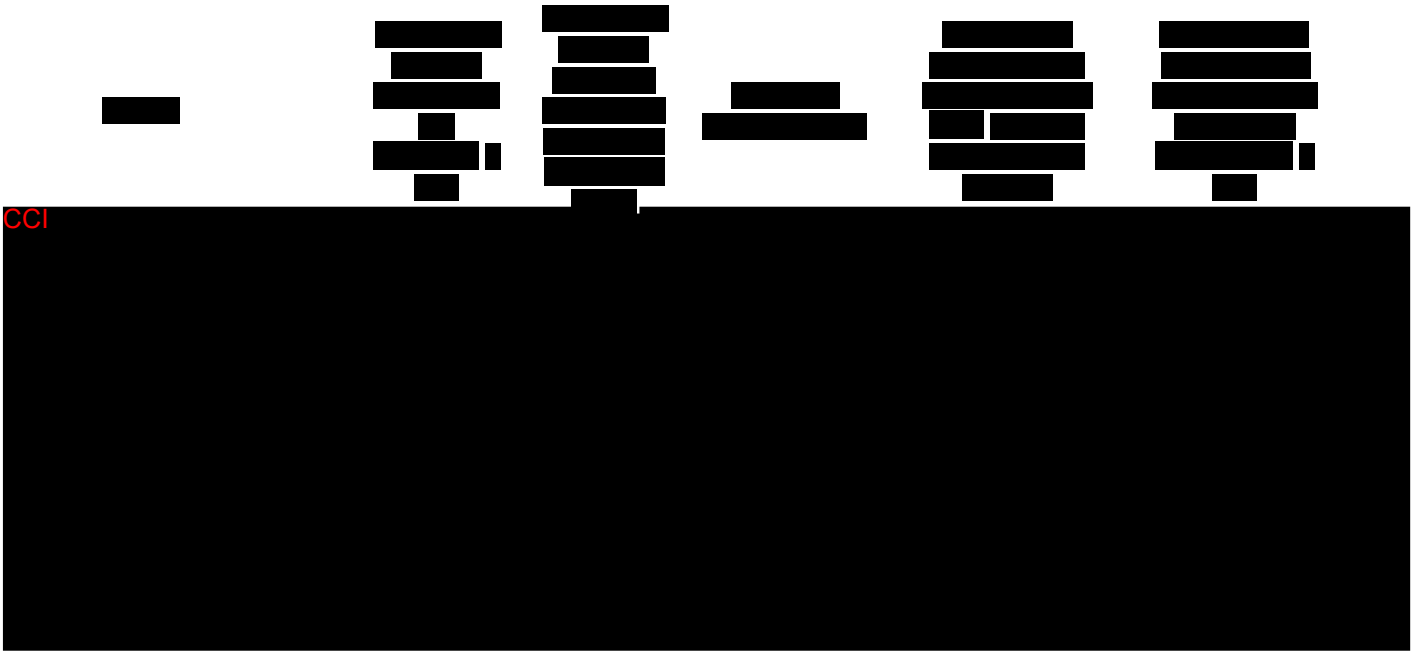

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10.2. EXTRACT

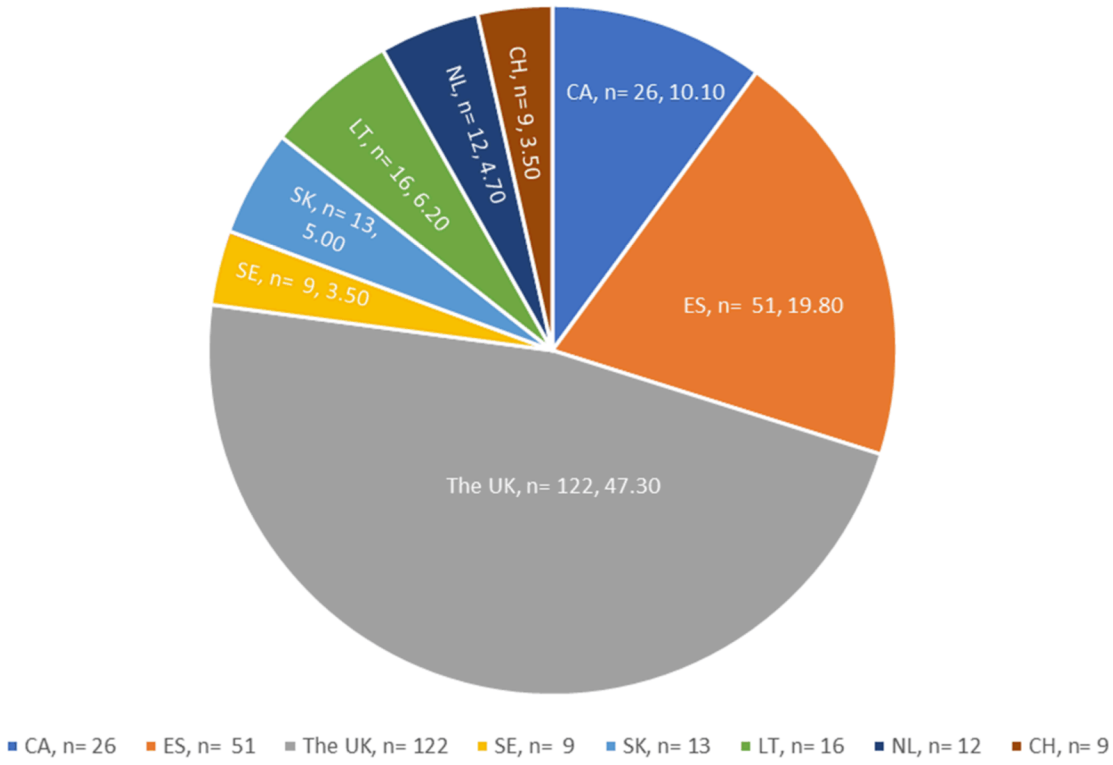
10.2.1. Participants and Treatment Information

This section of the report presents final data for the EXTRACT FUP Set, with the data for the EXTRACT ENR Set presented in the Attachments. Patients aged >75 years at baseline are described in Section 10.2.5.

10.2.1.1. Participants

The EXTRACT study was completed on 28 July 2023. A total of 27 sites in 8 countries (3 sites in Canada, 2 in Lithuania, 2 in the Netherlands, 3 in Slovakia, 11 in Spain, 2 in Sweden, 1 in Switzerland and 3 in the UK) participated in the study (Attachment Table 2.1c_EXTRACT). The number of patients recruited per country is presented in Figure 10.

Figure 10: Patient Recruitment per Country (ENR) – EXTRACT



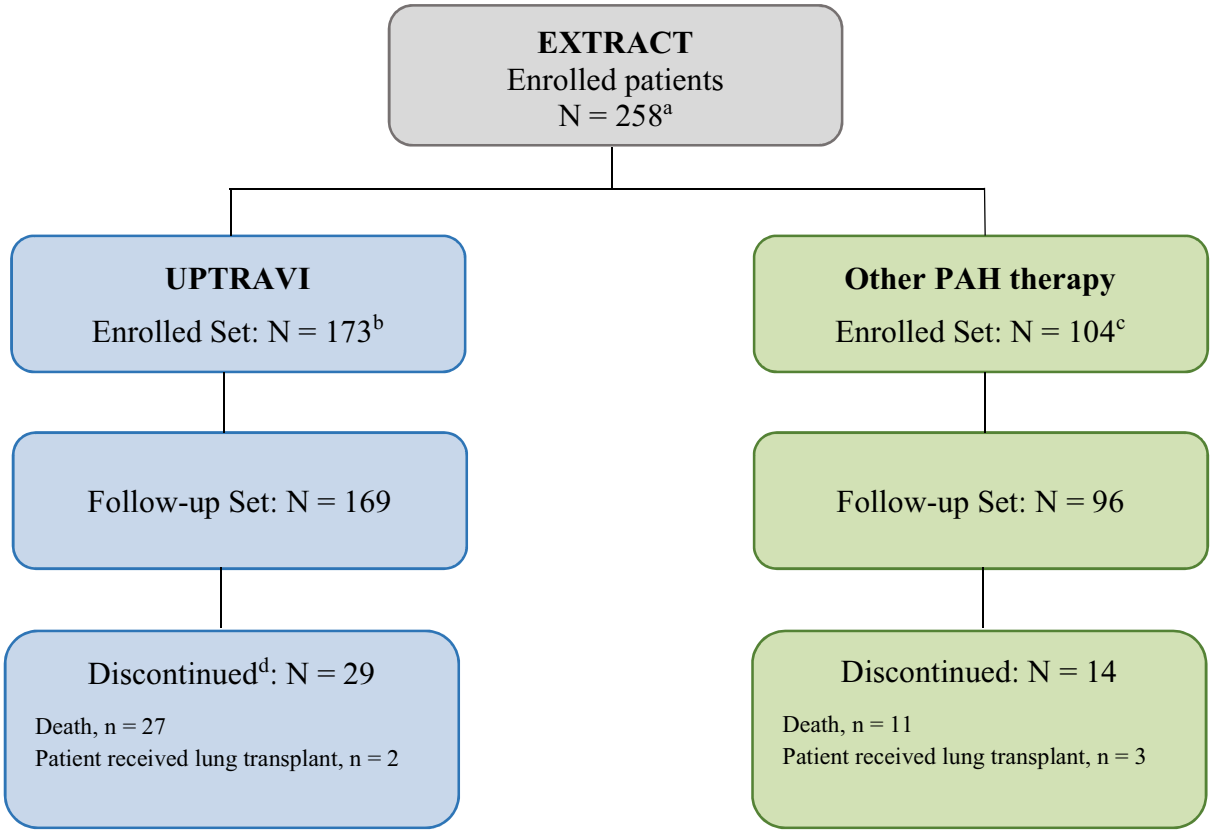
Source: Modified from Attachment Table 2.1c_EXTRACT. CA = Canada; CH = Switzerland; ES = Spain; LT = Lithuania; NL = Netherlands; SE = Sweden; SK = Slovakia; UK = The United Kingdom

10.2.1.2. Patient Disposition and Study Completion Withdrawal Information

A total of 258 patients were enrolled in EXTRACT (ENR Set), of whom 173 patients were enrolled in the UPTRAVI cohort and 104 patients in the Other PAH therapy cohort. A total of 252 patients, 169 patients in the UPTRAVI cohort and 96 patients in the Other PAH therapy cohort had at least 1 follow-up information documented (FUP Set) (Figure 11 and Attachment Table 1.1_EXTRACT).

Of note, 19 patients enrolled in the study as initiators of Other PAH-specific therapy than UPTRAVI, initiated UPTRAVI during the observation period (corresponding to 11.0% of the UPTRAVI cohort). All 19 patients, subsequently named ‘Late Initiators’, had UPTRAVI follow-up information (Attachment Table 1.2a_EXTRACT).

Figure 11: Patient disposition and Analysis Sets – EXTRACT



Source: Modified from Attachment Table 1.1_EXTRACT and Attachment Table 1.2a_EXTRACT.
a: Patients enrolled as of data cut–off date of 14 July 2023. 'Late Initiators' are included in both the UPTRAVI and Other PAH therapy cohorts, but only counted once in the total number of patients.
b: Includes 19 'Late Initiators' with follow up information.
c: Includes 24 'Late Initiators': 16 with follow up information and 8 without.
d: 'Late Initiators' and their reasons for study discontinuation are only included in the UPTRAVI cohort. All study discontinuations are presented, regardless of whether they occurred on or off treatment.
Note: For 1 patient, an error was noted in the treatment initiation date that will be corrected in the following report.

For the 252 patients with follow-up data, the median duration (range) of the observation period was 32.3 (0.6-64.3) months (Attachment Table 1.3a_EXTRACT). The median duration (range) of the first exposure period was 27.0 (0.3-62.2) months for the UPTRAVI cohort and 31.5 (0.4-64.3) months for the Other PAH therapy cohort (Attachment Table 5.1.1a_EXTRACT and Attachment Table 5.2.1a_EXTRACT).

Overall, 6 patients (3.4%) in the UPTRAVI cohort and 8 patients (5.1%) in the Other PAH therapy cohort did not have any follow-up information at the time of DBL (reasons are presented in Attachment Table 1.4_EXTRACT). Additional 4 patients in the UPTRAVI cohort were excluded from the FUP Set because the first exposure period could not be derived for these patients. In total, the FUP Set had 169 patients (94.4%) remained in the UPTRAVI cohort and 96 patients (61.5%) in the Other PAH therapy cohort.

10.2.2. Descriptive Data

10.2.2.1. Demographic and Baseline Characteristics

10.2.2.1.1. Demographics

Demographic characteristics for the UPTRAVI and the Other PAH therapy cohorts in the FUP Set are shown in Table 35. Most patients in both cohorts were female and the median (range) age was 55 (19-85) years.

Table 35: Demographics at Initiation of New PAH-specific Therapy – Follow-Up Set; EXTRACT

Time Point Variable (Unit) Characteristic/Statistic	UPTRAVI N = 169	Other PAH therapy N = 96	Total[a] N = 252
At initiation of new PAH-specific therapy			
Sex, n (%)[b]			
Male	40 (23.7)	22 (22.9)	58 (23.0)
Female	129 (76.3)	74 (77.1)	194 (77.0)
Age (years)			
Mean (SD)	54.0 (16.4)	55.1 (16.4)	54.1 (16.5)
Median	55	55	55
Min, Max	19, 85	19, 85	19, 85
Age (years), n (%)[b]			
18 - 64	117 (69.2)	62 (64.6)	172 (68.3)
65 - 75	36 (21.3)	24 (25.0)	55 (21.8)
> 75	16 (9.5)	10 (10.4)	25 (9.9)

Source: Modified from Attachment Table 2.1a_EXTRACT.

a: 'Late Initiators' are included in both the UPTRAVI and Other PAH therapy cohorts, but only counted once in the total groupwhere information at initiation of first PAH therapy in study is presented. For 'Late Initiators' who have follow-up data only for 1 of the 2 cohorts, data from that cohort are presented in the total column.

b: Percentages are based on the available values within the given variable (n).

10.2.2.1.2. Disease Characteristics

In the UPTRAVI cohort, the median time (range) since PAH diagnosis was 2.8 (0.0-37.4) years. About half of the patients were diagnosed with IPAH. A total of 38 patients (22.5%) were diagnosed with PAH associated with CTD (CTD-PAH) and 26 patients (15.4%) were diagnosed with PAH associated with CHD (CHD-PAH). (Table 36).

In the Other PAH therapy cohort, the median time (range) since PAH diagnosis was 1.7 (0.0 to 33.5) years. Most patients were diagnosed with IPAH. A total of 27 patients (28.4%) were diagnosed with CTD-PAH and 20 patients (21.1%) were diagnosed with CHD-PAH. (Table 36).

Table 36: Clinical Characteristics: PAH at Diagnosis and At Initiation of a New PAH-specific Therapy –Follow-Up Set; EXTRACT

Time Point Variable (Unit) Characteristic/Statistic	UPTRAVI N = 169	Other PAH therapy N = 96	Total[a] N = 252
At initiation of new PAH-specific therapy			
Time since PAH diagnosis (years)			
Number of patients with available data	154	81	223
Mean (SD)	4.59 (5.51)	4.49 (6.09)	4.55 (5.75)
Median	2.8	1.7	2.5
Min, Max	0.0, 37.4	0.0, 33.5	0.0, 37.4
Missing	15	15	29
PAH aetiology, n (%)[b]			
Number of patients with available data	169	95	251
Idiopathic PAH	88 (52.1)	38 (40.0)	121 (48.2)
Heritable PAH	10 (5.9)	2 (2.1)	12 (4.8)
Drug and toxin induced	5 (3.0)	1 (1.1)	5 (2.0)
PAH associated with	65 (38.5)	53 (55.8)	111 (44.2)
Connective tissue disease	38 (22.5)	27 (28.4)	58 (23.1)
Systemic sclerosis/scleroderma	25	15	37
Systemic lupus erythematosus	2	3	4
Rheumatoid arthritis	2	1	2
Sjogren's syndrome	2	3	5
Polymyositis/Dermatomyositis/ Antisynthetase syndrome/Psoriasis /Psoriatic arthritis	1	1	1
Mixed connective tissue disease	0	1	1
Undifferentiated connective tissue disease	2	2	4
Overlap syndrome	0	0	0
Inflammatory bowel disease/ Crohn's disease/Ulcerative colitis	0	0	0
Raynaud's disease/phenomenon	1	1	1
Digital ulcers	0	0	0
Antiphospholipid antibody syndrome	0	0	0
Unknown	3	0	3
HIV infection	0	0	0
Portal hypertension	0	6 (6.3)	6 (2.4)
Congenital heart diseases	26 (15.4)	20 (21.1)	46 (18.3)
Eisenmenger's syndrome	7	9	16
Left-to-right shunts	9	3	12
PAH with coincidental congenital heart disease	5	8	13
Post-operative PAH	4	0	4
Schistosomiasis	1 (0.6)	0	1 (0.4)
Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis	1 (0.6)	1 (1.1)	2 (0.8)
Missing	0	1	1

Source: Modified from Attachment Table 2.2.1a_EXTRACT.

a: 'Late Initiators' are included in both UPTRAVI and Other PAH therapy cohorts, but only counted once in total group where information at initiation of first PAH therapy in study is presented. For 'Late Initiators' who have follow-up data only for one of the 2 cohorts, data from that cohort is presented in total column.

b: Percentages are based on the available values within the given variable (n).

In the UPTRAVI cohort, 150 patients (89.8%) had WHO FC assessed within 3 months prior to or at baseline. Of 150 patients with reported WHO FC, 119 patients (79.3%) were classified as WHO FC III (Table 37). For 6MWD, data within 3 months prior to or at baseline was available for 68patients, with a reported median (range) of 382 (40-600) m. For 8 (7.0%) patients, the 6MWD was not assessed due to PAH and for 38 (33.3%) patients due to other reason not related to PAH (Table 37 and Attachment Table 2.2.3.1a_EXTRACT). Results of RHC performed within 12 months prior to or at baseline were available for 79 patients (48.8%) (Attachment Table 2.2.5.1a_EXTRACT).

In the Other PAH therapy cohort, 83 patients (86.5%) had WHO FC assessed within 3 months prior to, or at baseline. Of 83 patients with reported WHO FC, 50 patients (60.2%) were classified as WHO FC III (Table 37). For 6MWD, data within 3 months prior to or at baseline was available for 58 patients, with a reported median (range) of 375 (167-638) m. For 5 (5.2%) patients, the 6MWD was not assessed due to PAH and for 33 (34.4%) patients due to other reason not related to PAH (Table 37 and Attachment Table 2.2.3.1a_EXTRACT). Results of RHC performed within 12 months prior to or at baseline were available for 49 patients (51.0%) (Attachment Table 2.2.5.1a_EXTRACT).

Table 37: Clinical Characteristics: WHO FC and 6MWD at Initiation of New PAH-specific Therapy-Follow-Up Set; EXTRACT

Time Point Variable (Unit) Characteristic/Statistic	UPTRAVI N = 169	Other PAH therapy N = 96
At initiation of new PAH-specific therapy		
Was WHO FC assessed within past 3 months? n (%)[a]		
Yes	150/167 (89.8)	83/96 (86.5)
No	17/167 (10.2)	13/96 (13.5)
Missing	2	0
If yes, most recent WHO FC		
I	4 (2.7)	5 (6.0)
II	23 (15.3)	24 (28.9)
III	119 (79.3)	50 (60.2)
IV	4 (2.7)	4 (4.8)
6MWD, (m)		
Number of patients with available data[b]	68	58
Mean (SD)	370.7 (127.4)	381.7 (119.7)
Median	382	375
Range	40, 600	167, 638

Source: Modified from Attachment Table 2.2.2.1a EXTRACT and Attachment Table 2.2.3.1a EXTRACT.
a: The percentages are based on the available values within the given variable (n).
b: Number of patients with available values (ie, known values) assessed within 3 months prior to or at initiation of therapy.

Echocardiography and pulmonary function test assessments at baseline for the FUP Set are presented in Attachment Table 2.2.5.1a_EXTRACT.

A total of 24 patients (15.3%) in the UPTRAVI cohort had renal function impairment at baseline. Of these, creatinine clearance data were reported for 22 patients, with the vast majority being assessed as abnormal (n = 20 [90.9%]) as per physician's judgement. Of these 20 patients with an abnormal creatinine clearance[k], 7 patients (35.0%) were assessed as mild, 10 patients (50.0%) as moderate, and 3 patients (15.0%) as severe at baseline (Attachment Table 2.2.8a_EXTRACT).

In the Other PAH therapy cohort, 23 patients (24.2%) had renal function impairment at baseline. Of these, 22 patients (95.7%) were assessed as abnormal as per physician's judgement. Of these patients with an abnormal creatinine clearance, 8 patients (36.4%) were assessed as mild, 10 patients (45.5%) as moderate, 4 patients (18.2%) as severe at baseline (Attachment Table 2.2.8a_EXTRACT).

10.2.2.2. Medical History

Cardiovascular/cerebrovascular disease history prior to or at baseline reported for the UPTRAVI cohort and the Other PAH therapy cohort is summarised in (Table 38).

Table 38: Medical History: Cardiovascular/Cerebrovascular Disease History Prior to, or at Initiation of a New PAH specific Therapy – Follow-Up Set; EXTRACT

Time Point Variable (Unit) Characteristic	UPTRAVI N = 169	Other PAH therapy N = 96
Prior to, or at initiation of new PAH-specific therapy		
Myocardial ischaemia, n (%)	6/154 (3.9)	2/91(2.2)
Myocardial infarction, n (%)	1/4 (25.0)	1/2 (50.0)
Unstable angina, n (%)	0/4	1/2 (50.0)
Cardiac arrest, n (%)	0/168	0/96
Revascularisation procedure, n (%)	6/168 (3.6)	1/95 (1.1)
Coronary	6 (3.6)	1 (1.1)
Carotid	1 (0.6)	1 (1.1)
Unknown/Missing	1	1
Ischaemic cerebrovascular disorder, n (%)	3/165 (1.8)	1/95 (1.1)
Unknown/Missing	4	1
If yes, resulted in ischaemic stroke? n (%)	3 (100)	0
Unknown	0	1
Haemorrhagic stroke, n (%)	0/168	0/95
Unknown	1	1

[k] abnormal creatinine clearance: mild (60-89 mL/min); moderate (30-59 mL/min); and severe (15-29 mL/min).

Table 38: Medical History: Cardiovascular/Cerebrovascular Disease History Prior to, or at Initiation of a New PAH specific Therapy – Follow-Up Set; EXTRACT

Time Point Variable (Unit) Characteristic	UPTRAVI N = 169	Other PAH therapy N = 96

Source: Modified from Attachment Table 2.5.1a_EXTRACT.
Note: Percentages are based on the available values within the given variable.
Note: For 'Late Initiators', the latest occurrence before initiation of UPTRAVI is displayed for the UPTRAVI cohort.

The most reported cardiovascular risk factors (n >20%) prior to or at initiation of UPTRAVI were being a former smoker and having a BMI >30 kg/m^2. (Table 39).

For patients in the Other PAH therapy cohort, the most reported risks (n >20%) were being a former smoker, systemic hypertension and having a BMI >30 kg/m^2. (Table 39).

Table 39: Medical History: Cardiovascular Risk Factor History Prior to or at Initiation of a New PAH specific Therapy – Follow Up Set; EXTRACT

Time Point Variable (Unit) Characteristic	UPTRAVI N = 169	Other PAH therapy N = 96
Prior to, or at initiation of new PAH-specific therapy		
Carotid and/or coronary arteriosclerosis, n (%)	153	86
Yes	14 (9.2)	8 (9.3)
Coronary	14 (9.2)	6 (7.0)
Carotid	2 (1.3)	3 (3.5)
Cardiac arrhythmia, n (%)	24/166 (14.5)	10/92 (10.9)
Cardiac right to left shunt, n (%)	14/165 (8.5)	13/91 (14.3)
Valvular heart disease, n (%)	10/165 (6.1)	3/94 (3.2)
Cardiomyopathy, n (%)	6/164 (3.7)	5/91 (5.5)
Diabetes mellitus, n (%)	20/167 (12.0)	8/96 (8.3)
Type 2	20 (100)	8 (100)
Hyperlipidaemia, n (%)	16/163 (9.8)	13/94 (13.8)
Systemic hypertension, n (%)	30/164 (18.3)	24/96 (25.0)
Sleep apnoea syndrome, n (%)	15/157 (9.6)	8/88 (9.1)
BMI > 30 kg/m^2, n (%)	31/115 (27.0)	17/75 (22.7)
Smoker, n (%)		
Number of patients with available data	117	68
Current	11 (9.4)	8 (11.8)
Former	37 (31.6)	17 (25.0)
Never	69 (59.0)	43 (63.2)

Table 39: Medical History: Cardiovascular Risk Factor History Prior to or at Initiation of a New PAH specific Therapy – Follow Up Set; EXTRACT

Time Point Variable (Unit) Characteristic	UPTRAVI N = 169	Other PAH therapy N = 96

Source: Modified from Attachment Table 2.5.2a_EXTRACT.
Note: Percentages are based on the available values within the given variable.
Note: For 'Late Initiators', the latest occurrence before initiation of UPTRAVI is displayed for the UPTRAVI cohort.

Other relevant medical history, for the UPTRAVI cohort only, was recorded prior to or at baseline. There were 8 patients (4.80%) with systemic hypotension (7, ongoing condition at baseline), 21 patients (13.0%) with anaemia (16, ongoing condition at baseline), 1 patient (0.6%) with pulmonary oedema associated with PVOD, 2 patients (1.2%) with hyperthyroidism (1, ongoing condition at baseline) and 3 patients (1.8%) of non-melanoma skin malignancy. Of 7 patients (4.3%) who reported bleeding events, minor bleeding was reported for 5 patients (71.4%) and major bleeding[1] was reported for 3 patients (42.9%) (Attachment Table 2.5.3a_EXTRACT).

10.2.2.3. Prior and Concomitant PAH specific Medications

In the UPTRAVI cohort, 3 patients (1.8%) were receiving UPTRAVI as monotherapy, 14 patients (8.3%) in the context of a double combination therapy, 137 patients (81.1%) as triple combination therapy, and 10 patients (5.9%) were receiving concomitantly (ie, at least 1 day of overlap) >3 PAH-specific therapies, including UPTRAVI, at baseline (Table 40).

In the Other PAH therapy cohort 14 patients (14.6%) were treated with monotherapy (ie, the other PAH-specific therapy initiated at baseline), 71 patients (74.0%) with double combination therapy, and 10 patients (10.4%) with triple combination therapy. Among the double combination therapies, ERA + PDE5i was the most common treatment option (64.6%) at baseline. None of the patients was receiving concomitantly >3 PAH-specific therapies at baseline (Table 40).

Table 40: PAH-Specific Treatment Status at Initiation of New PAH-Specific Therapy – Follow-Up Set; EXTRACT

Time Point Variable (Unit) Characteristic	UPTRAVI cohort N = 169	Other PAH therapy cohort N = 96
At or during 30 days after the initiation of new PAH-specific therapy		
Monotherapy, n (%)[a]	**3 (1.8)**	**14 (14.6)**
ERA	0	4 (4.2)
PDE5i	0	10 (10.4)
Prostacyclin and its analogues	0	0
Prostacyclin receptor agonist (Selexipag)	3 (1.8)	0
SGC stimulator	0	0

[1] Major bleeding is defined as any clinically over bleeding associated with a decrease in haemoglobin of ≥ 20 g/L, a transfusion of ≥ 2 units of packed red blood cells or whole blood, bleeding at a critical site, or with hospitalisation or a fatal outcome. All other bleeding events are classified as minor.

Table 40: PAH-Specific Treatment Status at Initiation of New PAH-Specific Therapy – Follow-Up Set; EXTRACT

Time Point Variable (Unit) Characteristic	UPTRAVI cohort N = 169	Other PAH therapy cohort N = 96
Double combination therapy, n (%)[a]	**14 (8.3)**	**71 (74.0)**
ERA + PDE5i	0	62 (64.6)
ERA + Prostacyclin and its analogues	0	3 (3.1)
ERA + Prostacyclin receptor agonist	6 (3.6)	0
ERA + SGC stimulator	0	2 (2.1)
PDE5i + Prostacyclin and its analogues	0	4 (4.2)
PDE5i + Prostacyclin receptor agonist	6 (3.6)	0
PDE5i + SGC stimulator	0	0
Prostacyclin and its analogues + Prostacyclin receptor agonist	2 (1.2)	0
SGC stimulator + Prostacyclin and its analogues	0	0
SGC stimulator + Prostacyclin receptor agonist	0	0
Triple combination therapy, n (%)[a]	**137 (81.1)**	**10 (10.4)**
ERA + PDE5i + Prostacyclin and its analogues	0	10 (10.4)
ERA + PDE5i + Prostacyclin receptor agonist	136 (80.5)	0
ERA + PDE5i + SGC stimulator	0	0
ERA + Prostacyclin and its analogues + Prostacyclin receptor agonist	0	0
ERA + SGC stimulator + Prostacyclin and its analogues	0	0
ERA + SGC stimulator + Prostacyclin receptor agonist	1 (0.6)	0
PDE5i + Prostacyclin and its analogues + Prostacyclin receptor agonist	0	0
PDE5i + SGC stimulator + Prostacyclin and its analogues	0	0
PDE5i + SGC stimulator + Prostacyclin receptor agonist	0	0
Other combination therapy (>3 therapies), n (%)[a]	**10 (5.9)**	**0**
Patients with unknown concomitant medication information, n (%)[a]	**5 (3.0)**	**1 (1.0)**

Source: Modified from Attachment Table 2.7.1.3a_EXTRACT.
a: The percentages are based on N.
Note: For all entries in UPTRAVI cohort, Prostacyclin receptor agonist refers to UPTRAVI (selexipag).

10.2.2.4. Laboratory Data

Of 169 patients in the UPTRAVI cohort, NT-proBNP was assessed in 143 patients (84.6%) at baseline. Of these, 64 patients (67.4%) had an abnormal value, as per physician's judgement. (Table 41).

Of the 96 patients in the Other PAH therapy cohort, 80 patients (83.3%) had NT-proBNP value available at initiation of new PAH-specific therapy. Of these, 40 patients (71.4%) had an abnormal value, as per physician's judgement. (Table 41).

Table 41: NT-proBNP and BNP at Initiation of New PAH-Specific Therapy – Follow-Up Set; EXTRACT

Time Point Variable (Unit) Characteristic/Statistics	UPTRAVI N = 169	Other PAH therapy N = 96
At initiation of new PAH-specific therapy		
NT-proBNP, n (%)		
Yes[a]	143 (84.6)	80 (83.3)
Normal[b]	31 (32.6)	16 (28.6)
Abnormal[b]	64 (67.4)	40 (71.4)
Missing	48	24
If abnormal, NT-proBNP (ng/L)		
Mean (SD)	3184.08 (5529.33)	3101.90 (5725.47)
Median	1106.0	1434.0
Min, Max	156.0, 35000.0	116.0, 32000.0
BNP, n (%)		
Yes	136 (80.5)	80 (83.3)
If yes, BNP, n (%)[b]	30	14
Normal	11 (36.7)	6 (42.9)
Abnormal	19 (63.3)	8 (57.1)
Missing	106	66
If abnormal, BNP (ng/L)		
Mean (SD)	369.13 (344.64)	220.88 (160.71)
Median	296.0	182.5
Min, Max	19.0, 1418.0	40.0, 568.5

Source: Modified from Attachment Table 2.4.3a_EXTRACT.
a: Percentages are based on N.
b: Percentages are based on the available values within the given variable (n).

10.2.2.5. Treatment Duration

10.2.2.5.1. UPTRAVI Cohort

Median (range) UPTRAVI exposure during the first exposure period was 27 (0.3-62.2) months, for a total of 322 person-years (Attachment Table 5.1.1a_EXTRACT). About 68.3% (n = 112) had at least 12 months of exposure and 61.0% (n = 100) had at least 18 months. CCI [redacted]

Median (range) of UPTRAVI exposure during the total exposure period was 27.4 (0.4-62.4) months, for a total of 350 person-years (Attachment Table 5.1.2a_EXTRACT).

10.2.2.5.2. Other PAH Therapy Cohort

Median (range) exposure to any other newly initiated PAH-specific therapy during the first exposure period was 31.5 (0.4-64.3) months, for a total of 223 person-years (Attachment Table 5.2.1a_EXTRACT). Approximately 71.0% (n = 68) had at least 12 months of exposure and 63.5% (n = 61) had at least 18 months.

10.2.3. Outcome Data

All clinical outcomes analysed in the EXTRACT study are presented in Section 10.2.4.

10.2.4. Main Results

10.2.4.1. Hospitalisation

Hospitalisations during the first exposure period for the FUP Set are presented in Table 42.

In the UPTRAVI cohort, total number of hospitalisations were CCI [redacted]

[redacted]

In the Other PAH therapy cohort, total number of hospitalisations were 82 of which 3 hospitalisations were ongoing at baseline and 79 hospitalisations occurred after baseline. Of the 73 hospitalisations after baseline assessed for PAH relatedness, 24 (32.9%) were PAH-related as per physician's judgement. The most common reason (n ≥5) for hospitalisation after baseline was disease progression/PAH worsening reported in 8 patients (10.1%) (Table 42 and Attachment Table 2.3.1a_EXTRACT).

In the Other PAH therapy cohort, the hospitalisations IR (95% CI) per 100 person-years for all types of hospitalisations, PAH related hospitalisations and for hospitalisations not related to PAH was 24.22 (16.18, 34.57), 8.78 (5.12, 14.06) and 12.16 (7.50, 18.45), respectively (Table 43).

Table 42: Hospitalisation During the First Exposure CCI [redacted] **Up Set; EXTRACT**

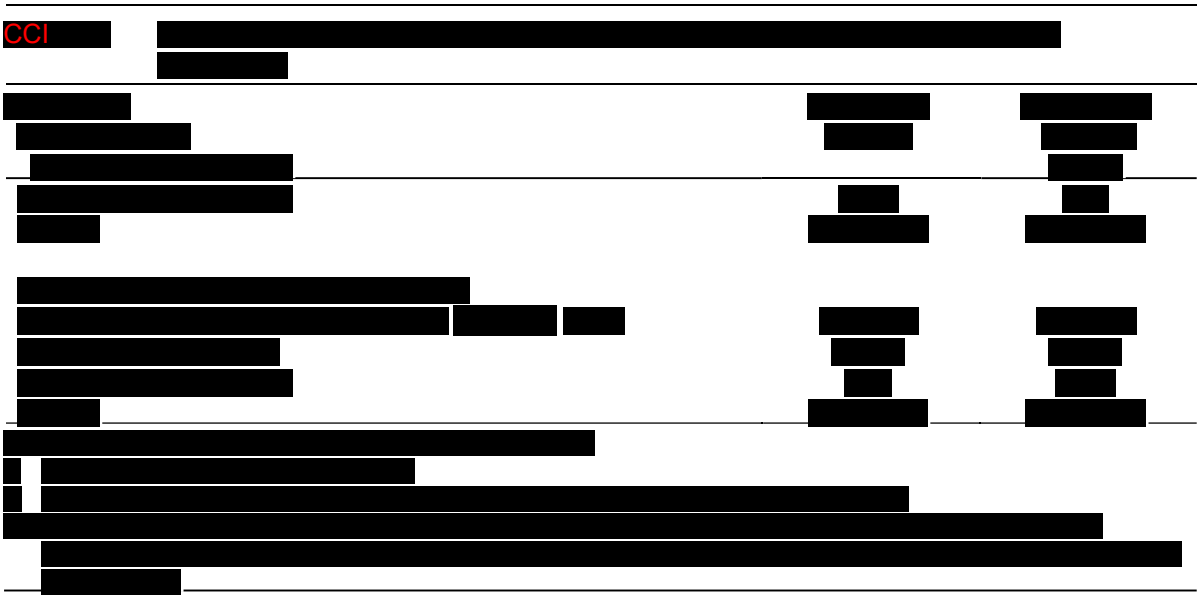
Time Point Variable (Unit) Characteristic/Statistic	[redacted]	Other PAH therapy N = 96
During the first exposure period		
Total number of hospitalisations, n (%)[a]		82
Hospitalisation ongoing at baseline		3 (3.7)
Hospitalisations after baseline		79 (96.3)

Table 42: Hospitalisation During the First Exposure Up Set; EXTRACT

Time Point Variable (Unit) Characteristic/Statistic	Other PAH therapy N = 96
Total number of hospitalised patients, n (%)	96
Never hospitalised	55 (57.3)
Hospitalised only at baseline	2 (2.1)
Hospitalised only after baseline	38 (39.6)
Hospitalised at baseline and after baseline	1 (1.0)
If hospitalised after baseline, was the hospitalisation PAH-related? n (%)[a]	73
Yes	24 (32.9)
No	49 (67.1)
Unknown	6
If hospitalised after baseline, what is the main reason for hospitalisation? n (%)[a]	79
Disease progression/PAH worsening	8 (10.1)
Right heart failure	4 (5.1)
Cardiac arrest	0
Myocardial infarction	1 (1.3)
Unstable angina	1 (1.3)
Stroke	0
Arrhythmia	2 (2.5)
Left heart failure	2 (2.5)
Coronary arterial revascularisation	1 (1.3)
Other[b,c]	60 (75.9)

Source: Modified from Attachment Table 2.3.1a_EXTRACT.
a: All hospitalisation events are included (1 patient could have more than 1 hospitalisation event).
b: Includes various reasons with no obvious pattern or trend and less than 5 events per reason.
c: Includes hospitalisation for cardiac catheterisation.
Note: For reason of hospitalisation, several reasons per hospitalisation can be collected; denominator for percentage calculation is the number of hospitalisations.
Note: Percentages are based on the available values within the given variable (n).

CCI



10.2.4.2. UPTRAVI Safety Profile

The following sections present information collected for study objective 2 to further characterise the UPTRAVI safety profile (Section 7.2.2) in the UPTRAVI cohort as collected in the EXTRACT eCRF.

UPTRAVI safety profile for important identified risks

10.2.4.2.1. Systemic Hypotension

For patients in the UPTRAVI cohort, a new systemic hypotension event during the first exposure period was reported for CCI events per 100 person-years. In total, CCI had systemic hypotension reported as an ongoing condition in the medical history at baseline (initiation of therapy). (Attachment Table 3.1.1.1a_EXTRACT).

10.2.4.2.2. Anaemia

For patients in the UPTRAVI cohort, a new event of anaemia was reported for CCI CCI per 100 person-years (Attachment Table 3.1.2.1a_EXTRACT). Haemoglobin level assessment at the time of new anaemia event was CCI (Attachment Table 3.1.2.4a_EXTRACT). In total, CCI had anaemia reported as an ongoing condition in the medical history at baseline (initiation of therapy) (Attachment Table 3.1.2.1a_EXTRACT) and CCI had abnormal low[m] haemoglobin documented at baseline (Attachment Table 2.4.1a_EXTRACT).

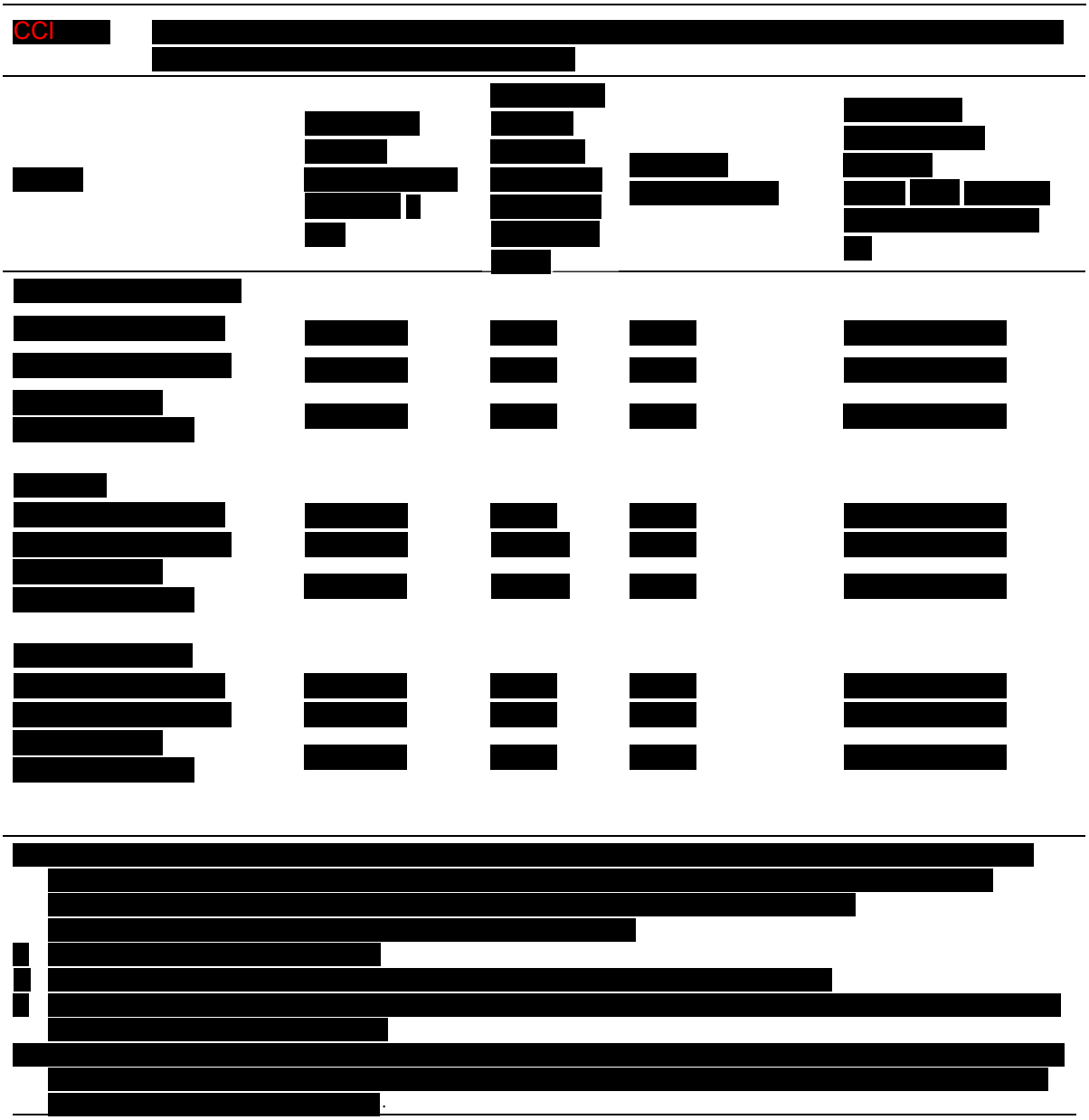
[m] (≥100 g/L and < LLN or <100 g/L)

10.2.4.2.3. Hyperthyroidism

For patients in the UPTRAVI cohort, a new event of hyperthyroidism during the first exposure period was reported for CCI) events per 100 person-years. In total, CCI had hyperthyroidism reported as an ongoing condition in the medical history at baseline (initiation of therapy). (Attachment Table 3.1.4.1a_EXTRACT).

10.2.4.2.4. Overview of the UPTRAVI safety profile for important identified risks

An overview of the UPTRAVI safety profile for important identified risks for UPTRAVI cohort (N = 169) is presented in Table 44.



UPTRAVI safety profile for important potential risks

10.2.4.2.5. Renal Impairment/Acute Renal Failure

During the first exposure period, for patients in the UPTRAVI cohort, a new event of renal impairment or acute renal failure was reported for[CCI [redacted]]), Attachment Table 3.1.5.1a_EXTRACT. In total, 24/157 patients (15.3%) had renal function impairment as an ongoing condition in the medical history at baseline (prior to or at initiation of therapy) and based on abnormal creatinine clearance, [CCI [redacted]] had renal function impairment documented at baseline, of which [CCI [redacted]] had mild renal impairment; [CCI [redacted]] had moderate renal impairment and [CCI [redacted]] had severe renal impairment (Attachment Table 2.2.8a_EXTRACT).

10.2.4.2.6. Bleeding Events

For patients in the UPTRAVI cohort, a new bleeding event was reported for [CCI [redacted]] events per 100 person-years. A total of 5 patients reported bleeding events after UPTRAVI initiation, 4 patients had bleeding events that were considered minor, and 1 patient had bleeding event that was considered major[n], Attachment Table 3.1.6.1a_EXTRACT.

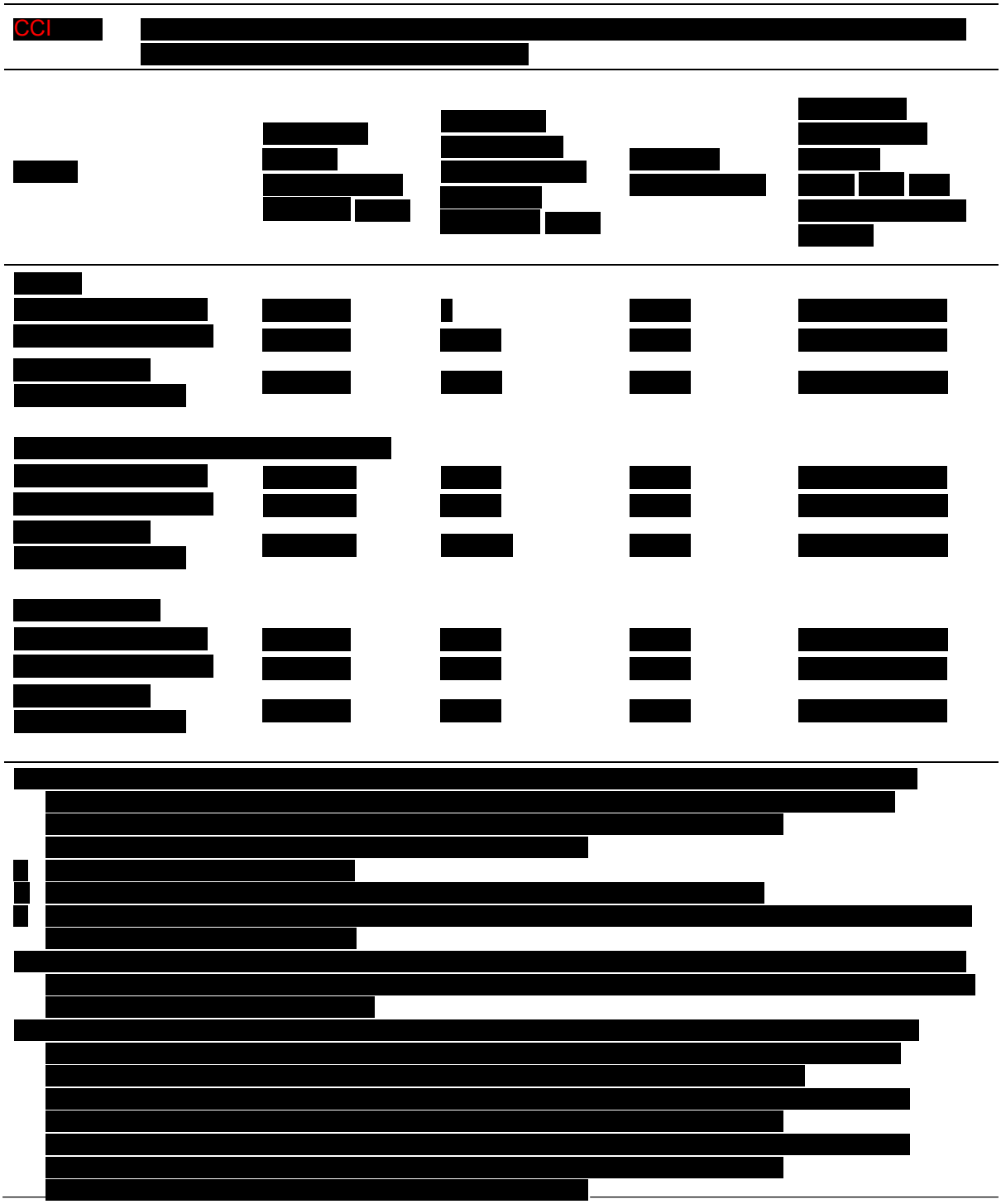
10.2.4.2.7. Other Important Potential Risks

During the first exposure period, [CCI [redacted]] was reported in the UPTRAVI cohort with follow-up information (Attachment Table 3.2.1e_EXTRACT, Attachment Table 3.1.3.1a_EXTRACT, Attachment Table 3.1.7.1a_EXTRACT, Attachment Table 3.1.8.1a_EXTRACT, Attachment Table 3.1.9.1a_EXTRACT).

10.2.4.2.8. Overview of the UPTRAVI safety profile for important potential risks

An overview of the UPTRAVI safety profile for important potential risks for UPTRAVI cohort (N = 169) is presented in Table 45.

[n] Major bleeding is defined as any clinically over bleeding associated with a decrease in haemoglobin of ≥ 20 g/L, a transfusion of ≥ 2 units of packed red blood cells or whole blood, bleeding at a critical site, or with hospitalisation or a fatal outcome. All other bleeding events are classified as minor.



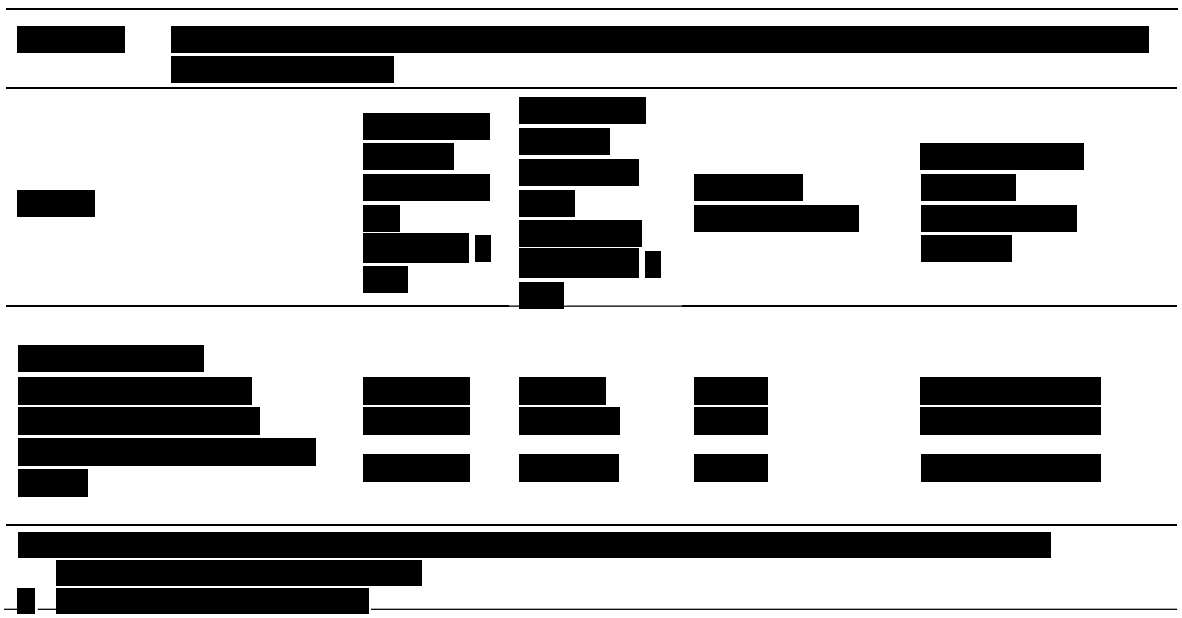
10.2.4.3. All-cause Deaths

10.2.4.3.1. Overall Assessment

During the first exposure period, CCI per 100 person-years. The main causes of death were CCI

CCI

CCI



10.2.4.3.2. Assessment According to World Health Organisation Functional Class

CCI

10.2.5. Other Analyses- Results for Patients >75 Years at Baseline

Data for patients over the age of 75 years at baseline are presented in the following sections for the FUP Set. Data for the ENR Set are available in Attachments.

10.2.5.1. Patient Disposition and Analysis Sets for Patients Aged >75 Years

In the EXTRACT study, 26 patients aged >75 years (10.0%) were enrolled with 16 patient (61.5%) in the UPTRAVI cohort (including 1 Late-Initiator) and 10 (38.4%) patients in the Other PAH therapy cohort (ENR Set). All patients aged >75 years in both cohorts had at least 1 follow-up information documented (including 1 Late-Initiator in the UPTRAVI cohort; FUP Set; Attachment Table 1.2b_EXTRACT and Attachment Table 2.1b_EXTRACT). The median duration (range) of the observation period was 23.8 (2.5-52.3) months (Attachment Table 1.3b_EXTRACT). The median duration (range) of the first exposure period was 12.6 (1.0-41.7) months for the UPTRAVI cohort and 18.1 (0.7-39.4) months for the Other PAH therapy cohort (Attachment Table 5.1.1b_EXTRACT and Attachment Table 5.2.1b_EXTRACT).

In total, 6 patients (37.5%) in the UPTRAVI cohort and 4 patients (40.0%) in the Other PAH therapy cohort (ENR Set) discontinued from the study due to death (Attachment Table 1.2b_EXTRACT).

10.2.5.2. Descriptive Data for Patients Aged >75 Years

10.2.5.2.1. Demographics

In the UPTRAVI cohort (FUP Set), most patients were females (56.3%) and median (range) age at baseline was 79 (76-85) years (Attachment Table 2.1b_EXTRACT).

In the Other PAH therapy cohort, all patients were females and median (range) age at baseline was 80 (76-85) years (Attachment Table 2.1b_EXTRACT).

10.2.5.2.2. Disease Characteristics

For the UPTRAVI cohort, at baseline, the median time (range) since PAH diagnosis was 2.6 (0.0-13.4) years. Half of the patients were diagnosed with IPAH and 6 patients (37.5%) with CTD-PAH. (Table 48).

For the Other PAH therapy cohort, at baseline, the median time (range) since PAH diagnosis was 1.2 (0.0-3.1) years and the majority of patients had CTD-PAH (7 patients [77.8%]) (Table 48).

Table 48: Clinical Characteristics for Patients Aged >75 years: PAH at Diagnosis and at Initiation of New PAH-Specific Therapy – Follow-Up Set; EXTRACT

Time Point Variable (Unit) Characteristic/Statistic	UPTRAVI N = 16	Other PAH therapy N = 10	Total[a] N = 26
At initiation of new PAH-specific therapy			
Time since PAH diagnosis (years)			
Mean (SD)	3.82 (3.65)	1.21 (0.88)	2.82 (3.15)
Median	2.6	1.2	1.5
Min, Max	0.0, 13.4	0.0, 3.1	0.0, 13.4
PAH classification, n (%)[b]	16	9	25
Idiopathic PAH	8 (50.0)	2 (22.2)	10 (40.0)
Heritable PAH	1 (6.3)	0	1 (4.0)
Drug and toxin induced	0	0	0
PAH associated with	7 (43.8)	7 (77.8)	14 (56.0)
Connective tissue disease	6 (37.5)	7 (77.8)	13 (52.0)
Systemic sclerosis/scleroderma	4	5	9
Systemic lupus erythematosus	0	0	0
Rheumatoid arthritis	0	0	0
Sjogren's syndrome	0	2	2
Polymyositis/Dermatomyositis/ Antisynthetase syndrome/Psoriasis /Psoriatic arthritis	0	0	0
Mixed connective tissue disease	0	0	0
Undifferentiated connective tissue disease	1	0	1
Overlap syndrome	0	0	0
Inflammatory bowel disease/ Crohn's disease/Ulcerative colitis	0	0	0
Raynaud's disease/phenomenon	0	0	0
Digital ulcers	0	0	0

Table 48: Clinical Characteristics for Patients Aged >75 years: PAH at Diagnosis and at Initiation of New PAH-Specific Therapy – Follow-Up Set; EXTRACT

Time Point Variable (Unit) Characteristic/Statistic	UPTRAVI N = 16	Other PAH therapy N = 10	Total[a] N = 26
Antiphospholipid antibody syndrome	0	0	0
Unknown	1	0	1
HIV infection	0	0	0
Portal hypertension	0	0	0
Congenital heart diseases	0	0	0
Eisenmenger's syndrome	0	0	0
Left-to-right shunts	0	0	0
PAH with coincidental congenital heart disease	0	0	0
Post-operative PAH	0	0	0
Schistosomiasis	1 (6.3)	0	1 (4.0)
Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis	0	0	0
Missing	0	1	1

Source: Modified from Attachment Table 2.2.1b_EXTRACT.
a: 'Late Initiators' are included in both the UPTRAVI and Other PAH therapy cohorts, but only counted once in the total group where information at initiation of first PAH therapy in study is presented. For 'Late Initiators' who have follow-up data only for 1 of the 2 cohorts, data from that cohort are presented in the total column.
b: Percentages are based on the available values within the given variable (n).

In the UPTRAVI cohort, WHO FC assessed within 3 months prior to or at baseline was known for 13 patients, all but one were classified as WHO FC III (Table 49).

In the Other PAH therapy cohort, the WHO FC assessed within 3 months prior to or at baseline was known for 8 patients. Of these, 6 patients (75.0%) were classified as WHO FC III (Table 49).

Table 49: Clinical Characteristics for Patients Aged >75 years: WHO FC at Initiation of New PAH-Specific Therapy – Follow-Up Set; EXTRACT

Time Point Variable (Unit) Characteristic	UPTRAVI N = 16 n (%)	Other PAH therapy N = 10 n (%)
At initiation of new PAH-specific therapy		
Was WHO FC assessed within past 3 months?[a]		
Yes	13 (81.3)	8 (80.0)
No	3 (18.8)	2 (20.0)
If yes, most recent WHO FC[b]		
I	0	0
II	1 (7.7)	0
III	12 (92.3)	6 (75.0)
IV	0	2 (25.0)

Source: Modified from Attachment Table 2.2.2.1b_EXTRACT.
a: Percentages are calculated based on N.
b: Percentages are based on the available values within the given variable (n).

Echocardiography and pulmonary function test assessments at baseline for the FUP Set are presented in Attachment Table 2.2.5.1b_EXTRACT.

A total of 6 patients (40.0%) in the UPTRAVI cohort had renal function impairment at baseline, all assessed as abnormal[o] as per physician's judgement. Renal impairment was moderate for all but 1 patient who had a severe renal impairment at baseline. Renal function impairment at baseline for the FUP Set are presented in Attachment Table 2.2.8b_EXTRACT.

In the Other PAH therapy cohort, 6 patients (60.0%) had renal function impairment at baseline, all assessed as abnormal as per physician's judgement. Of these 6 patients, renal impairment was moderate for half of the patients, while the remaining half had severe renal impairment at baseline. Renal function impairment at baseline for the FUP Set are presented in Attachment Table 2.2.8b_EXTRACT.

10.2.5.2.3. Medical History

For patients in the UPTRAVI cohort, reported cardiovascular/cerebrovascular disease history prior to or at baseline included myocardial ischaemia for 1 patient (myocardial infarction, 1 patient) and revascularisation procedure (3 patients, all received coronary revascularisation) (Attachment Table 2.5.1b_EXTRACT).

Among 10 patients in the Other PAH therapy cohort, 1 reported previous ischaemic cerebrovascular disorder (Attachment Table 2.5.1b_EXTRACT).

The most frequently reported cardiovascular risk factors (n >20%) prior to or at baseline for patients in the UPTRAVI cohort were systemic hypertension (5, 35.7%), being a former smoker (4, 33.3%), hyperlipidaemia (4, 25.0%) and coronary arteriosclerosis (3, 21.4%) (Attachment Table 2.5.2b_EXTRACT).

For patients in the Other PAH therapy cohort, the most frequently reported risks (n >20%) were systemic hypertension (4, 40.0%), being a former smoker (3, 37.5%) and carotid and coronary arteriosclerosis, or coronary arteriosclerosis (2, 22.2%) (Attachment Table 2.5.2b_EXTRACT).

Other relevant medical history, for the patients in the UPTRAVI cohort only prior to, or at baseline included anaemia and hyperthyroidism (1 patient each and both conditions were ongoing at baseline) (Attachment Table 2.5.3b_EXTRACT).

10.2.5.2.4. Concomitant PAH specific Medications

Patients in the UPTRAVI cohort were predominantly receiving triple combination therapy (14patients [87.5%]). One patient each was receiving double combination therapy and other combination therapy (>3). No patient was receiving monotherapy (Attachment Table 2.7.1.3b_EXTRACT).

[o] abnormal creatinine clearance: mild (60-89 mL/min); moderate (30-59 mL/min); and severe (15-29 mL/min).

Among 10 patients in the Other PAH therapy cohort, most of the patients were receiving double combination therapy (6 patients) and 4 patients were receiving monotherapy (Attachment Table 2.7.1.3b_EXTRACT). No patient was receiving triple combination therapy or other combination therapy (>3).

10.2.5.2.5. Laboratory Data

Of 16 patients in the UPTRAVI cohort, NT-proBNP was assessed in 13 patients at baseline. Ten patients had an abnormal value (median [range]) 2503.5 (437.0, 11670.0) ng/L, as per physician's judgement (Attachment Table 2.4.3b_EXTRACT).

Of 10 patients in the Other PAH therapy cohort, 8 patients had an NT-proBNP value available at baseline. Five patients had an abnormal value (median [range]) 1865.0 (116.0, 2189.0) ng/L (Attachment Table 2.4.3b_EXTRACT).

10.2.5.2.6. Treatment Duration

10.2.5.2.6.1. UPTRAVI Cohort

Median (range) UPTRAVI exposure during the first exposure period was 12.6 (1.0-41.7) months, for a total of 22 person-years (Attachment Table 5.1.1b_EXTRACT). More than half of the patients (n = 9, 56.3%) had at least 12 months of exposure and 43.8% (n = 7) had at least of 18 months. In total, CCI [redacted]

Median (range) of UPTRAVI exposure during the total exposure period was 12.6 (1.0-41.7) months, for a total of 22 person-years (Attachment Table 5.1.2b_EXTRACT).

10.2.5.2.6.2. Other PAH Therapy Cohort

Median (range) exposure to any other newly initiated PAH-specific therapy during the first exposure period was 18.1 (0.7-39.4) months, for a total of 15 person-years (Attachment Table 5.2.1b_EXTRACT). More than half of the patients (n = 6, 60.0%) had at least 12 months of exposure and half (n = 5) had at least of 18 months.

10.2.5.3. Outcome Data for Patients Aged >75 Years

10.2.5.3.1. Hospitalisation

Hospitalisations during the first exposure period for patients aged >75 years (FUP Set) are presented in this section.

CCI [redacted]

CCI [redacted]

In the Other PAH therapy cohort, total number of hospitalisations was 10, all occurred after baseline. Of 8 hospitalisations assessed for PAH relatedness, 4 were assessed as PAH related per physician's judgement. The most common reason (≥2 patients) for hospitalisation after baseline was disease progression/PAH worsening (2, 20.0%) (Attachment Table 2.3.1b_EXTRACT).

CCI [redacted]

10.2.5.3.2. UPTRAVI Safety Profile

The following sections present information on IRs of events of interest for the UPTRAVI safety profile as captured in the EXTRACT eCRF for patients aged >75 years in the UPTRAVI cohort only. Other ADRs for patients aged >75 years are presented in Section 10.2.6.2.

UPTRAVI safety profile for important identified risks in patients aged >75 years during the first exposure period

10.2.5.3.2.1. Anaemia

For patients in the UPTRAVI cohort, a new anaemia event during the first exposure period was reported for CCI [redacted] events per 100 person-years. In total, CCI [redacted] had anaemia reported as an ongoing condition in the medical history at baseline (initiation of therapy) (Attachment Table 3.1.2.1b_EXTRACT) and CCI [redacted] had abnormal low[p] haemoglobin documented at baseline (Attachment Table 2.4.1b_EXTRACT).

10.2.5.3.2.2. Other Important Identified Risks

During the first exposure period, CCI [redacted] was reported in the UPTRAVI cohort in patients aged >75 years with follow-up data. (Attachment Table 3.1.1.1b_EXTRACT and Attachment Table 3.1.4.1b_EXTRACT).

10.2.5.3.2.3. Overview of the UPTRAVI safety profile for important identified risks for patients aged >75 years

For patients in the UPTRAVI cohort, CCI [redacted] during the total exposure period and the cohort-specific observation period, respectively. (Attachment Table 3.1.2.2b_EXTRACT, Attachment Table 3.1.2.3b_EXTRACT).

[p] (≥100 g/L and < LLN or <100 g/L)

CCI [redacted] Attachment Table 3.1.1.1b_EXTRACT, Attachment Table 3.1.1.2b_EXTRACT, Attachment Table 3.1.1.3b_EXTRACT, Attachment Table 3.1.4.1b_EXTRACT, Attachment Table 3.1.4.2b_EXTRACT and Attachment Table 3.1.4.3b_EXTRACT).

UPTRAVI safety profile for important potential risks for patients aged >75 years

During the first exposure period, CCI [redacted]s (as described in previous sections) was reported in the UPTRAVI cohort in patients aged >75 years with follow-up data (Attachment Table 4.1.1.1b_EXTRACT, Attachment Table 3.1.3.1b_EXTRACT, Attachment Table 3.1.5.1b_EXTRACT, Attachment Table 3.1.6.1b_EXTRACT, Attachment Table 3.1.7.1b_EXTRACT, Attachment Table 3.1.8.1b_EXTRACT, Attachment Table 3.1.9.1b_EXTRACT).

10.2.5.3.2.4. Overview of the UPTRAVI safety profile for important potential risks for patients aged >75 years

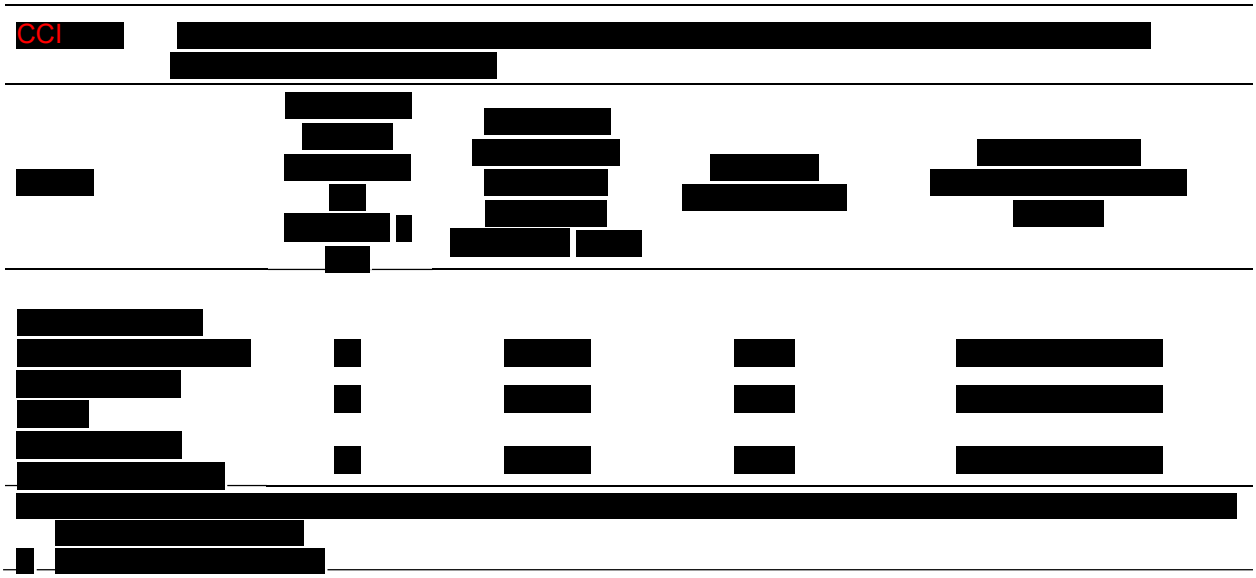
CCI [redacted] was reported during all exposure periods in the UPTRAVI cohort. (Attachment Table 3.1.3.1b_EXTRACT, Attachment Table 3.1.3.2b_EXTRACT, Attachment Table 3.1.3.3b_EXTRACT, Attachment Table 3.2.1f_EXTRACT, Attachment Table 3.2.1b_EXTRACT, Attachment Table 3.2.1d_EXTRACT, Attachment Table 3.1.5.1b_EXTRACT, Attachment Table 3.1.5.2b_EXTRACT, Attachment Table 3.1.5.3b_EXTRACT, Attachment Table 3.1.6.1b_EXTRACT, Attachment Table 3.1.6.2b_EXTRACT, Attachment Table 3.1.6.3b_EXTRACT, Attachment Table 3.1.7.1b_EXTRACT, Attachment Table 3.1.7.2b_EXTRACT, Attachment Table 3.1.7.3b_EXTRACT, Attachment Table 3.1.8.1b_EXTRACT, Attachment Table 3.1.8.2b_EXTRACT, Attachment Table 3.1.8.3b_EXTRACT, Attachment Table 3.1.9.1b_EXTRACT, Attachment Table 3.1.9.2b_EXTRACT and Attachment Table 3.1.9.3b_EXTRACT).

10.2.5.4. All-cause Deaths

Of the 16 patients in the UPTRAVI cohort aged >75 years with follow-up data, CCI [redacted]

CCI [redacted]

An overview of mortality rate for patients aged >75 years old in the UPTRAVI cohort is provided in Table 50.



10.2.6. Adverse Reactions

The events relevant for UPTRAVI safety profile, including incident and worsening events, occurring during the first exposure period are presented in Section 10.2.4.2 and for patients aged >75 years in Section 10.2.5.3.2.

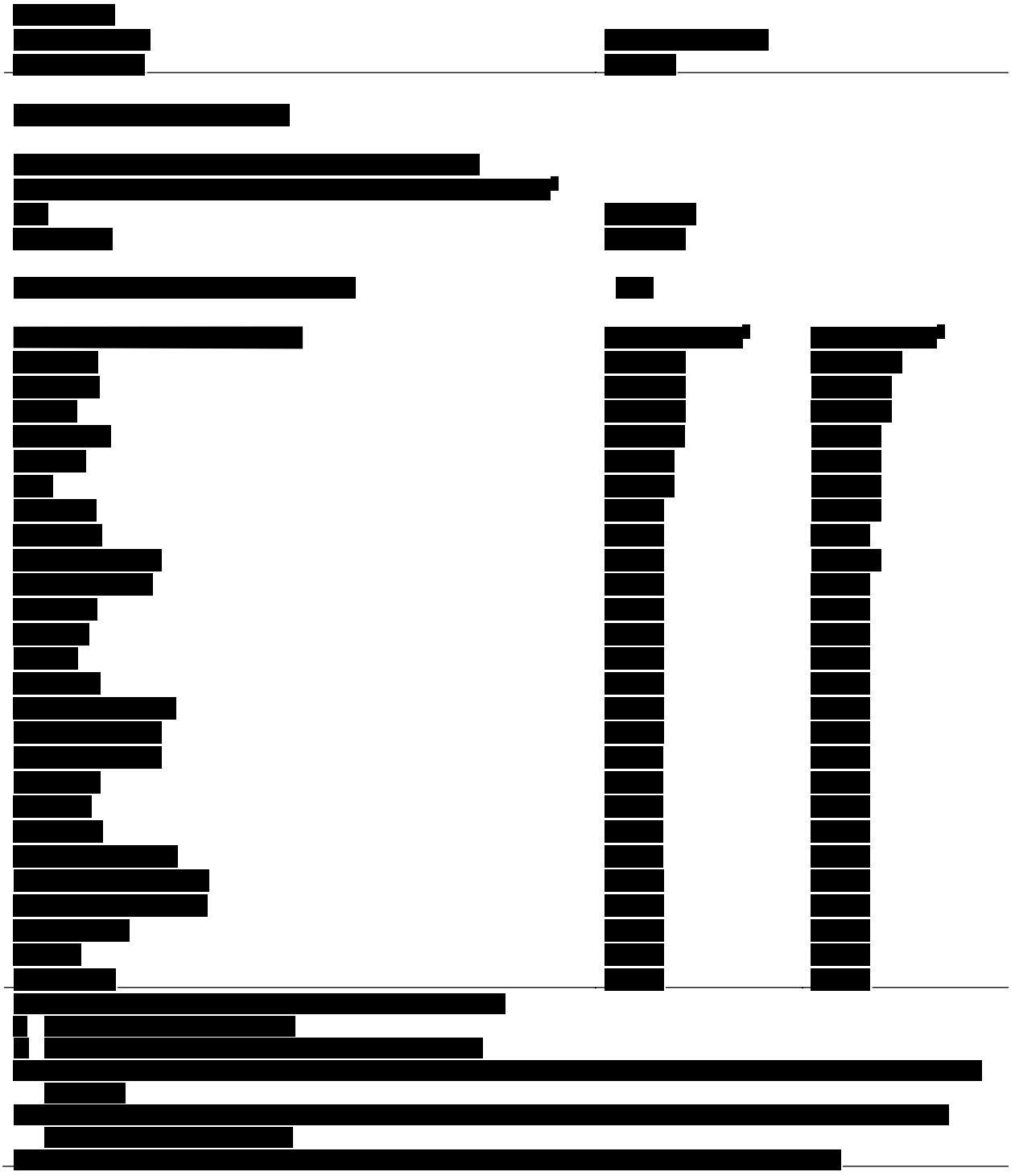
10.2.6.1. Overall Analysis of Other Adverse Reactions

During the first exposure period, CCI in the UPTRAVI cohort. The most common ADRs (n >1%) are presented in Table 51. All other ADRs were reported for 1 patient each (Attachment Table 3.3.3.1a_EXTRACT).

During the total exposure period, CCI in the UPTRAVI cohort. The ADR profile during the total exposure period was similar to that for the first exposure period. (Attachment Table 3.3.3.2a_EXTRACT).

Any other ADRs occurring during the cohort-specific observation period are provided in Attachment Table 3.3.3.3a_EXTRACT.

CCI [redacted]



10.2.6.2. Adverse Reactions for Patients Aged >75 Years

During the first exposure period, CCI [redacted] in the UPTRAVI cohort aged >75 years with follow-up data. CCI [redacted] All other ADRs were reported for 1 patient each (Attachment Table 3.3.3.1b_EXTRACT).

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(Attachment Table 3.3.3.2b_EXTRACT). Any other ADRs occurring during the cohort-specific observation period are provided in Attachment Table 3.3.3.3b_EXTRACT.

10.3. EXPOSURE AND EXTRACT Combined Analysis

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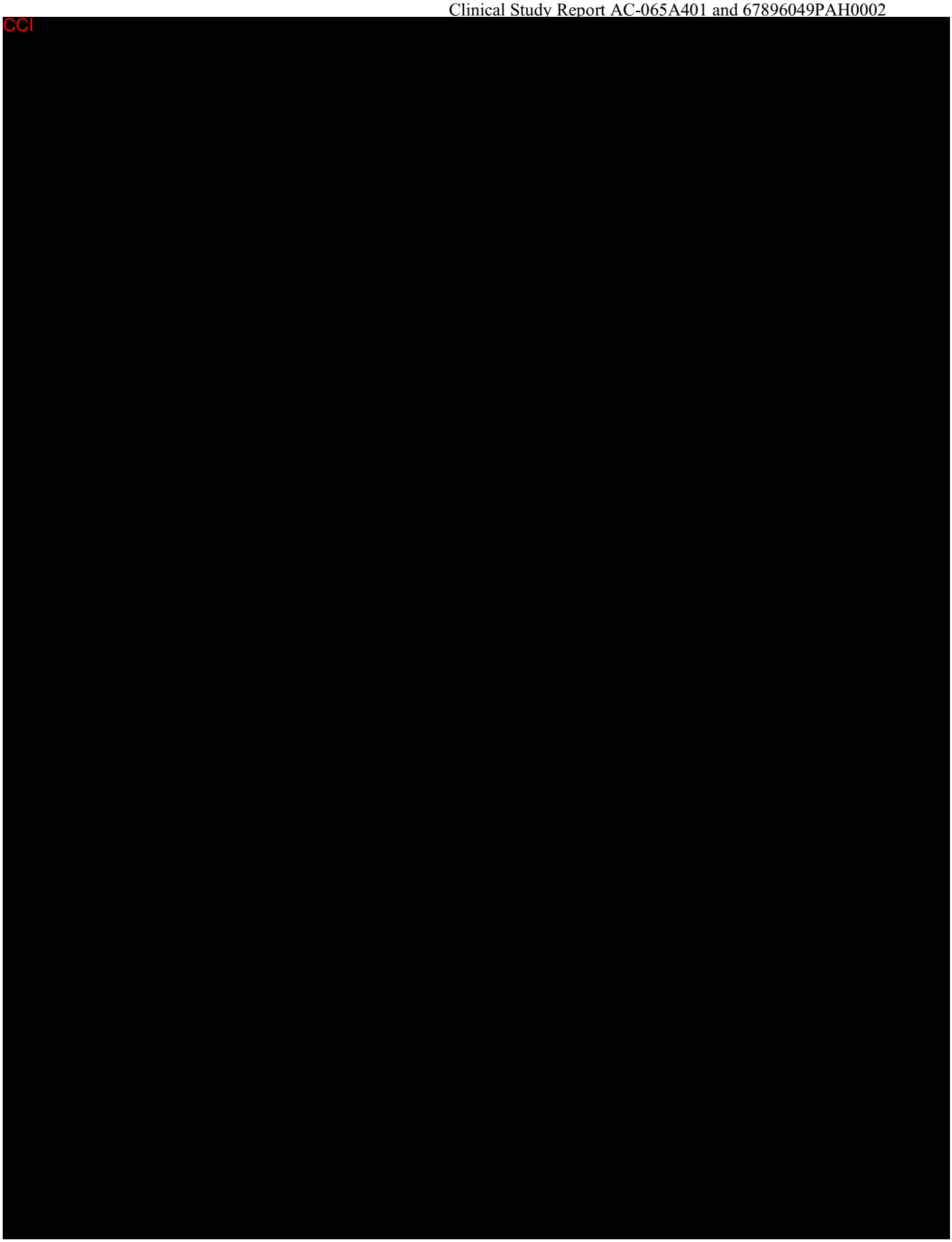

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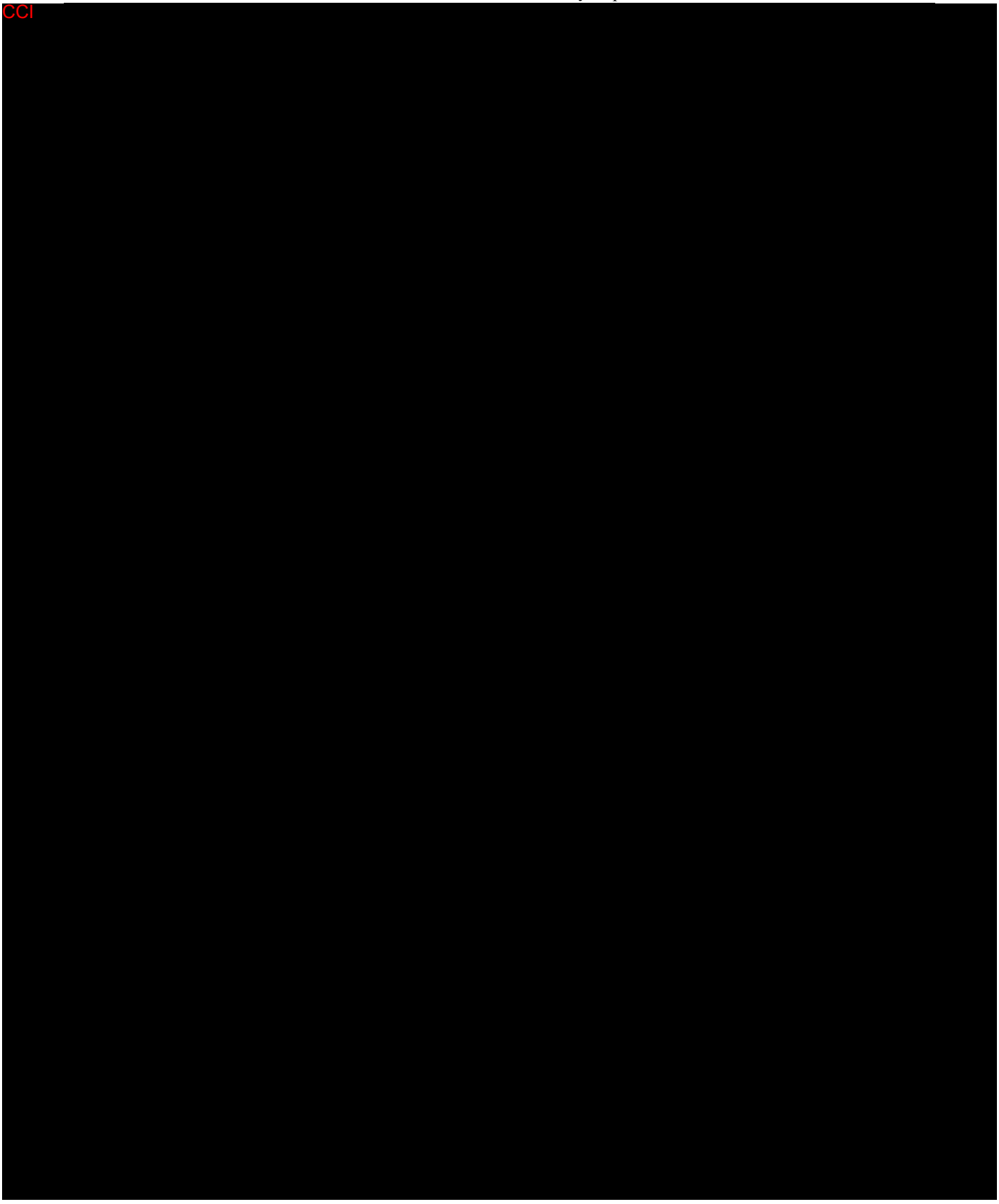

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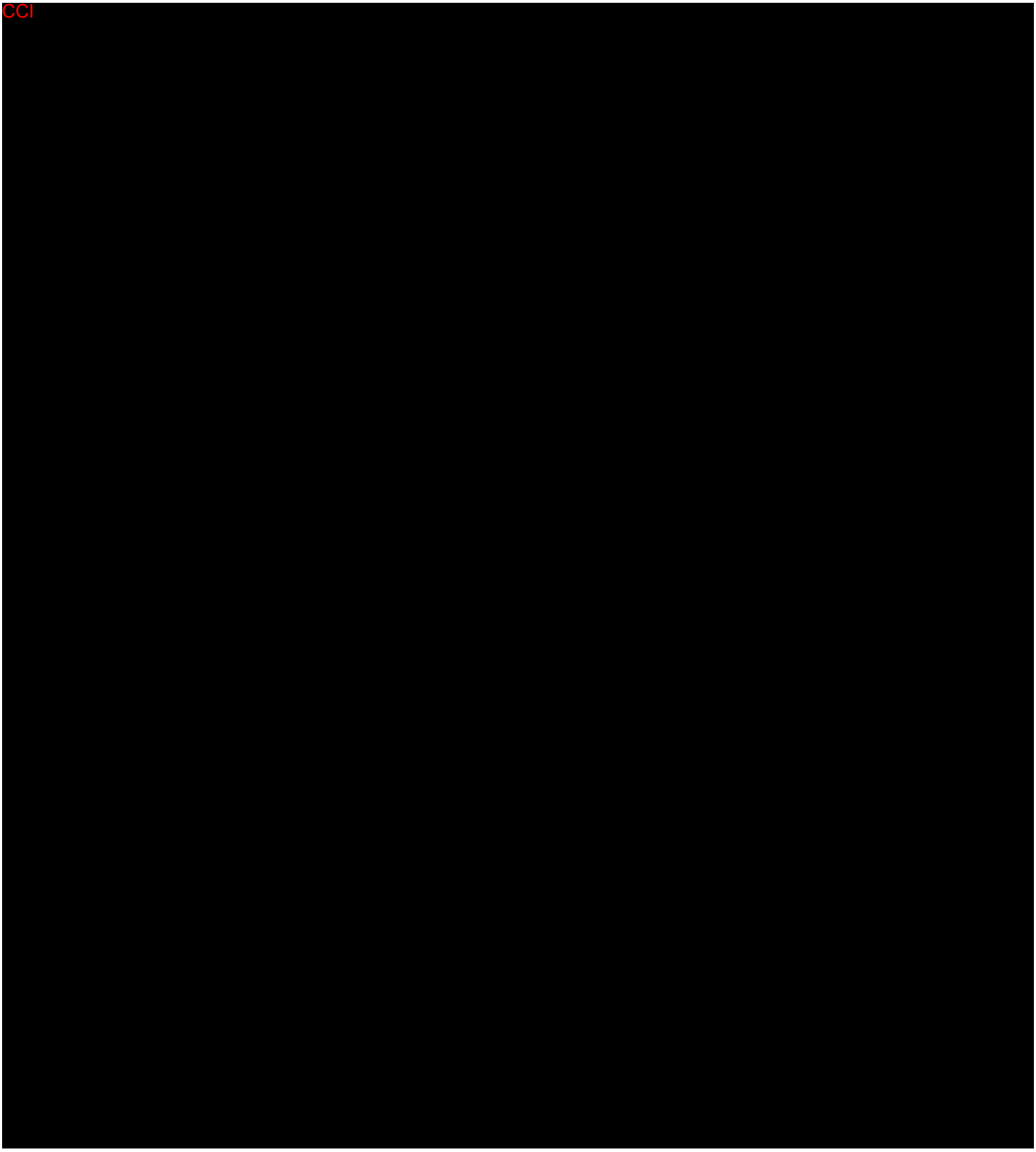

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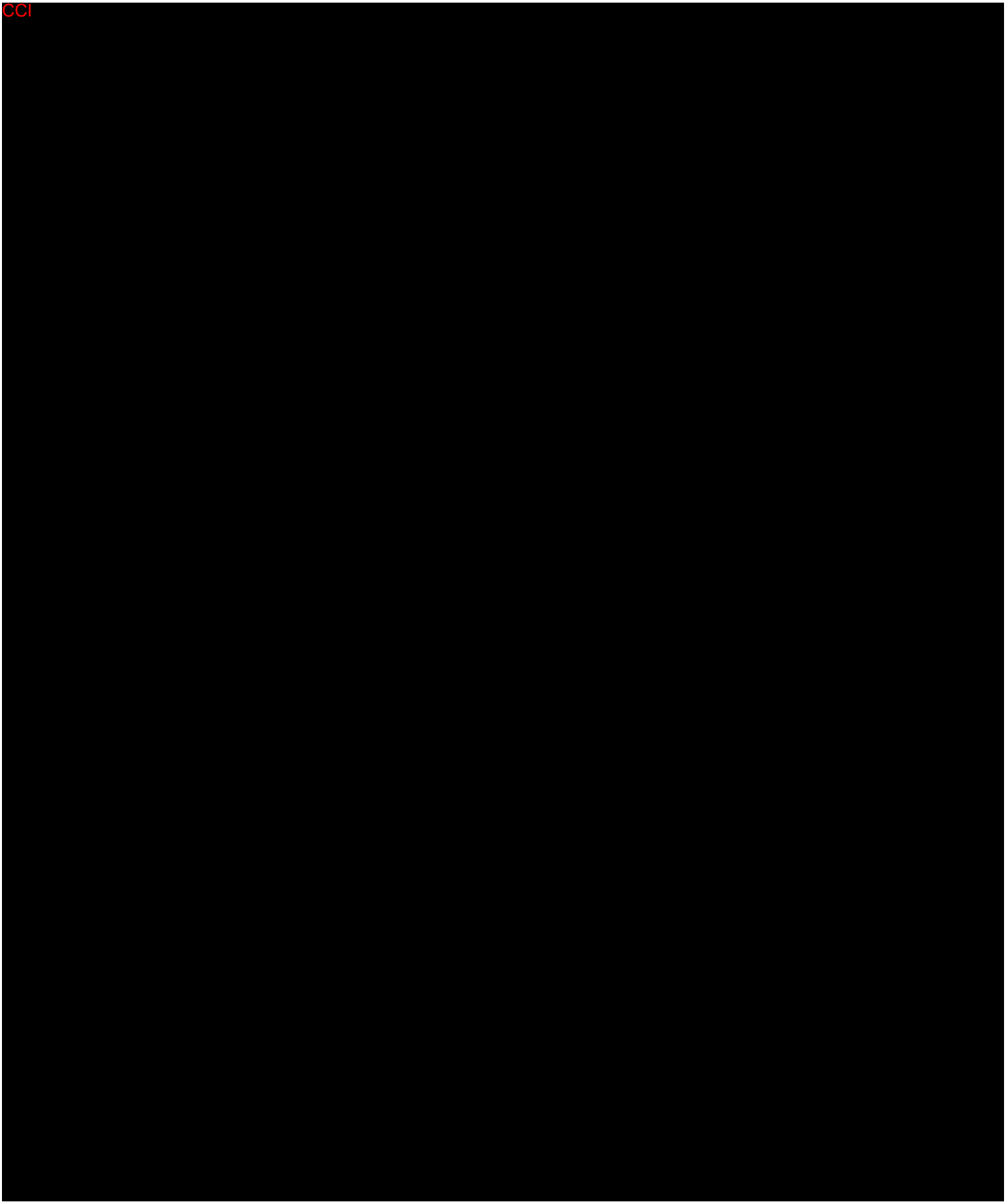

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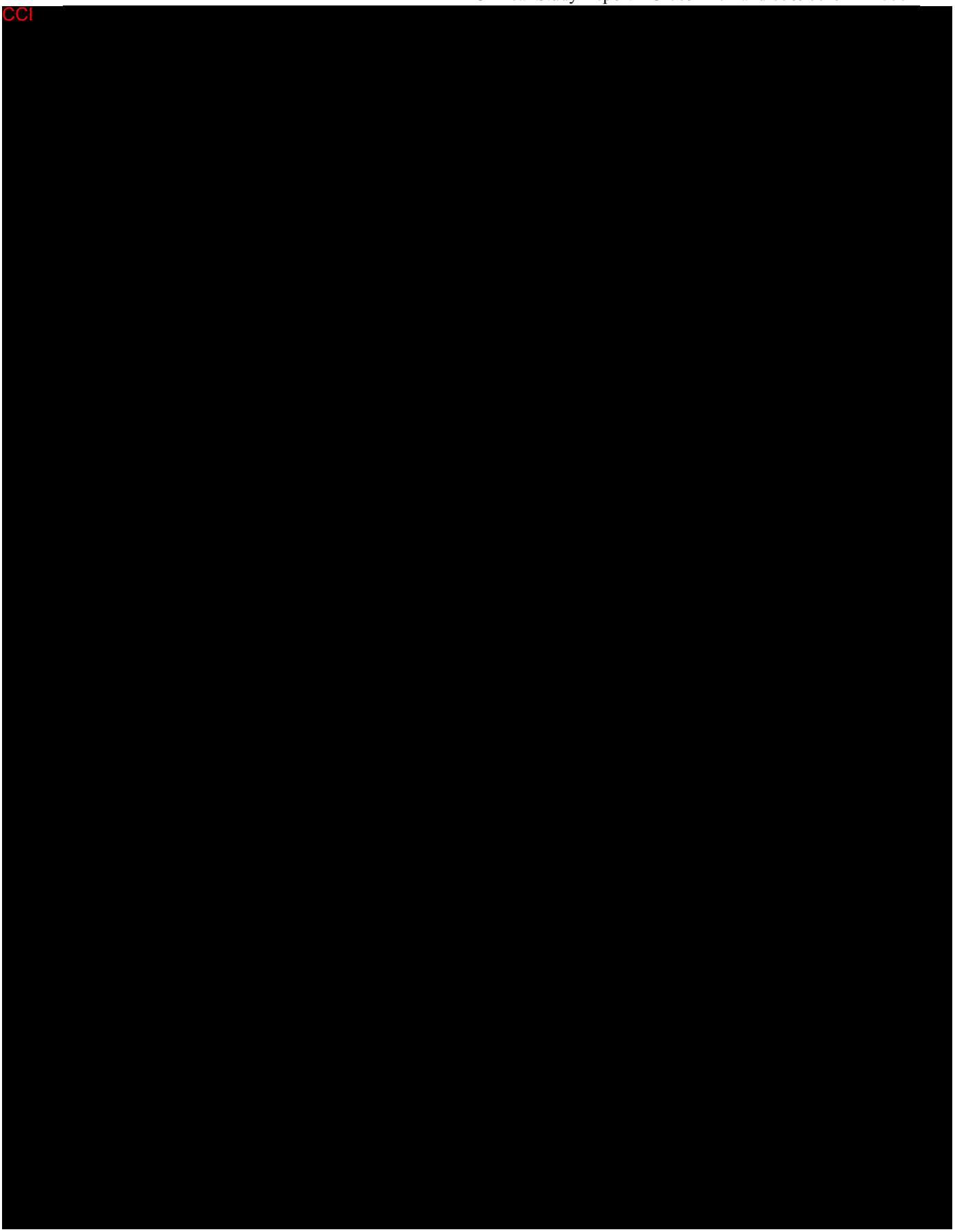

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11. DISCUSSION

11.1. Key Results

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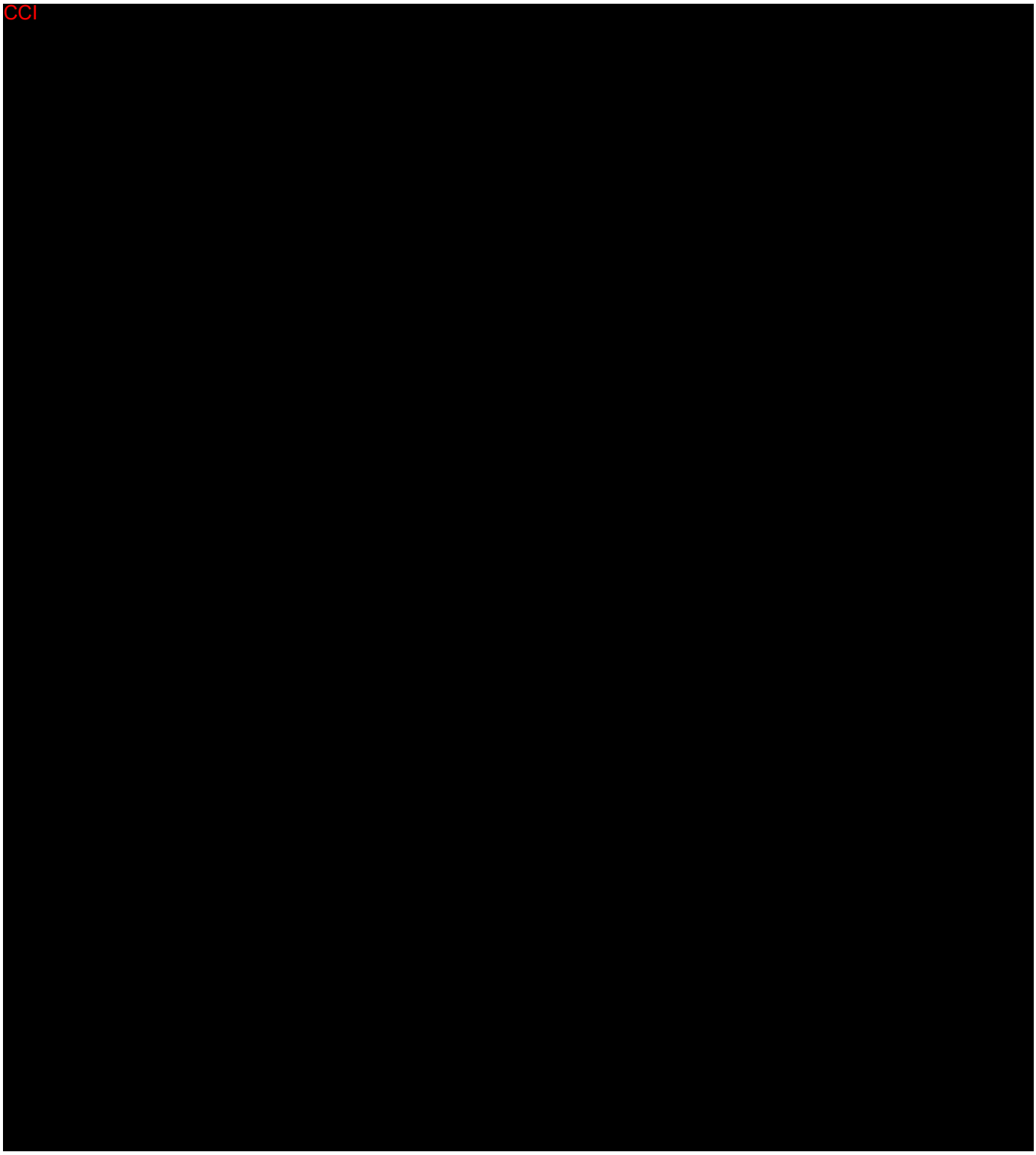

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11.2. Limitations

As with all ongoing observational prospective and retrospective studies, there are several limitations to consider when evaluating the data.

Selection bias

The reasons for an eligible patient not being enrolled in EXPOSURE are recorded to capture any potential systematic bias in nonparticipation (Annex 2.2). As of the time of this 7th interim report for EXPOSURE and final report for EXTRACT, 456 eligible patients were not enrolled and recorded in the non-enrolment log per study investigators. However, based on MAH review of the non-enrolment log, accounting for the level of imprecision due to aggregated data structure, around 182 of these patients were found to be ineligible and should have not been recorded in the log. The two main reasons for ineligibility were refusal to participate/consent and enrolment in an interventional clinical trial. Due to the aggregated structure of the non-enrolment log, all 456 patients were considered for the description of demographic characteristics. The majority (59.3%) were between 50-75 years old, and 72 patients (15.8%) were aged >75 years. Most of the patients (60.4%) were in WHO FC III and there were more females than males (66.9% females and 33.1% males). There was no difference in demographic data between eligible patients not enrolled in

EXPOSURE and those enrolled; therefore, no major selection bias has been observed at this stage of the study.

Immortal time bias

To minimise potential immortal time bias, it was requested by the PRAC to enrol in EXPOSURE, where feasible per local regulation, patients who initiated a new PAH-specific therapy after study site initiation, but who died within the first month of treatment and were not able to be consented. However, although all countries and sites were asked to include data from these patients, a significant number of the ECs rejected this aspect of study design (78 sites over 14 countries [Section 9.6]). Analysis of the non-enrolment log (Annex 2.2) shows that there have been 4 deaths among the recorded non-enrolled patients to date.

Missing data

The database has a variable amount of missing data, which is expected due to the non-interventional nature of the studies, the patient medical chart as the main source of information, the ongoing collection of the data for EXPOSURE, and the retrospective nature of EXTRACT. As the EXPOSURE study is observational, no visits, examinations or interventions can be mandated, and information is collected as part of the normal medical care at the site or country. The eCRF uses online data quality checks upon data entry to reduce the risk of missing information. If variables believed to have a high impact on the study are identified as missing (eg, PAH-specific therapy initiation date, UPTRAVI safety profile, all-cause hospitalisations, all-cause deaths), queries are raised to the study site to retrieve missing information. In the retrospective medical chart review study, EXTRACT, all possible efforts have been made in a similar manner to obtain a high-quality dataset. While retrospective studies have usually a high rate of missing data, the EXTRACT variables had very close proportions of missingness to EXPOSURE variables, emphasising the high quality of this retrospective dataset. For key dates, imputation rules have been implemented in the SAPs (Appendix 9) to account for incomplete information.

Role of the 'Late Initiators'

As defined in the SAPs (Appendix 9), the 'Late Initiators' were included in both cohorts based on the PSA Set using the separate treatment exposures as well as baseline parameters for the main propensity score analysis. However, this approach may lead to informative censoring when 'Late Initiators' are discontinued from the Other PAH cohort (patients may have initiated UPTRAVI due to a deterioration of PAH while on another treatment). By including 'Late Initiators', the sample sizes, number of events and corresponding exposure time were increased in the UPTRAVI cohort. To understand the effect of the 'Late Initiators', the sensitivity propensity score analysis based on ITT PSA Set was performed. Per definition, an ITT analysis is following the patients using their first treatment group allocation, regardless of subsequent treatments initiated during the observation period. Given that the number of 'Late Initiators' is growing, results from the main analysis are to be interpreted in context of the ITT analysis results to further assess the role of Late-Initiators in these analyses. ATT analysis on the main Set (PSA) including 'Late Initiators' can be considered as the most conservative with regards to potential events in patients treated with UPTRAVI during the study observation period. In this CSR, 254 'Late Initiators' were included

in the comparative analyses in the combined EXPOSURE and EXTRACT FUP set. PS results in the weighted ATT population report a consistent pattern in favour of patients treated with UPTRAVI, for MACE and all-cause death, both in the main and the ITT analyses. For both outcomes, MACE IR ratio and mortality rate ratio had an even more favourable trend (albeit 95% CI for IR ratio include 1) for UPTRAVI patients when using the PSA ITT Set compared with the PSA Set.

Weighting method

Because of the large heterogeneity between the UPTRAVI cohort and the Other PAH cohort, ATT and ATO focus on specific subgroups of the EXPOSURE population.

The ATT approach includes all patients from the UPTRAVI cohort and assigns more weight to patients from the Other PAH therapy cohort who are similar to UPTRAVI patients. The resulting cohorts have comparable baseline characteristics. For instance, in the Other PAH cohort, most patients in the unweighted population were treated with monotherapy (41%) or double combination therapy (50%), while most of the patients in the weighted population were treated with triple combination therapy (81%).

The ATO approach assigns more weight to patients with similar prognostic factors and overlapping propensity scores between the 2 cohorts. For instance, in the FUP Set, the majority of patients in the UPTRAVI cohort before weighting were treated with triple combination therapy (84%), while after weighting the majority of the patients were treated with double (45%) or triple (41%) combination therapy; in the Other PAH therapy cohort, the majority of patients before weighting were treated with monotherapy (42%) or double combination therapy (50%), while in the weighted population, the majority of the patients were treated with double combination therapy (45%) or triple combination therapy (41%).

Both weighting approaches are focusing on a subset of patients within the whole study population. The ATT population contains all the patients treated with UPTRAVI and a weighted number of patients that correspond to around 47% of patients from the Other PAH therapy cohort who, per their baseline characteristics, could have been treated with UPTRAVI. The ATO population is a middle ground between the 2 original cohorts. The resulting weighted number of patients (ie, the sum of patients multiplied by their weight) is approximately 24% of the original size of the UPTRAVI cohort and 14% of the Other PAH therapy cohort. Given the focus of the EXPOSURE and EXTRACT studies on safety events for UPTRAVI patients, the ATT weighting approach leads to a more clinically relevant population.

Data homogeneity

For this report, following agreement with PRAC (EMEA/H/C/003774/II/0035) to conduct a retrospective medical chart review (EXTRACT) to complement EXPOSURE recruitment, results are based on a combined dataset of the 2 studies. EXTRACT eligibility criteria and data collection structure have been designed as closely as possible to EXPOSURE to allow the recruitment of similar patients and data pooling between the 2 studies. A homogeneity assessment was conducted on baseline variables and critically appraised by an MAH group of physicians, scientists,

statisticians, and epidemiologists knowledgeable of PAH disease. Patients treated with UPTRAVI in EXTRACT were very similar to the first UPTRAVI patients enrolled in EXPOSURE (ie, slightly younger patients, diagnosed with PAH for a longer time and with a lower comorbidity burden compared to patients enrolled at a later stage), reflecting physicians' cautious behaviour with regards to the new drug at the time of its availability on the country markets. Based on this assessment, it was concluded that, overall, while some differences were noted in the patient characteristics between the 2 studies, these did not preclude the pooling of the data from the 2 studies.

11.3. Interpretation

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11.4. Generalizability

In EXPOSURE and EXTRACT, a large proportion of patients have been recruited in Germany and Spain (25.6% and 17.8%, respectively) (Attachment Table 2.1c_POOLED). This is an expected finding, as Germany and Spain were among the first European countries to have UPTRAVI authorised and reimbursed and to join the EXPOSURE study. Additionally, Germany and Spain are 2 of the most populous countries in Europe and, therefore, the total number of patients with PAH and hence the available pool for study recruitment, is much higher than in other participating countries. Enrolment trends by country were closely monitored, ensuring a good generalisability of the study database to the European PAH population.

The study protocol specifies that the study population characteristics will be compared with the overall European PAH population to assess how the study population reflects the characteristics of patients with PAH in Europe.

Patient characteristics in the combined EXPOSURE and EXTRACT FUP Set (ie, in both the UPTRAVI cohort and the Other PAH therapy cohort) are broadly similar to those in the Comparative Prospective Registry of Newly Initiated Therapies for PH (COMPERA, Annual Report 2023). For the combined EXPOSURE and EXTRACT data and COMPERA, the mean age was 59.9 years and 62.4 years, respectively; and the proportion of females was 69.7% and 64.3%, respectively. The proportion of patients with WHO FC II and III PAH at therapy initiation was 94.3% in the UPTRAVI cohort and 90.1% in the Other PAH therapy cohort in the combined EXPOSURE and EXTRACT FUP Set compared to 83.0% (NYHA class II and III) in COMPERA; and mean 6MWD at PAH therapy initiation was 365.0 m in the UPTRAVI cohort and 326.6 m in the Other PAH therapy cohort in the combined EXPOSURE and EXTRACT FUP Set compared to 314 m in COMPERA (Attachment Table 2.2.3.1a_POOLED).

Comparability of combined EXPOSURE and EXTRACT data with those from European PH registries is limited as data are reported at PAH diagnosis rather than at PAH-specific therapy initiation. However, similarities are observed between EXPOSURE and EXTRACT patients, and patients from the European PH registries including the Swedish registry (SPAHR Report 2022), the Polish registry (Kopeć 2020), the Greek registry (Arvanitaki 2019), the UK National Audit report (NHS England 2023), the Latvian registry (Skride 2018), and the French registry (Boucly 2022). Combined EXPOSURE and EXTRACT FUP Set includes 69.7% female patients, within the range reported in the EU registries (60.0 - 73.0). Combined EXPOSURE and EXTRACT FUP Set patients had a mean age of 59.9 years similar to the EU registries (51.8 - 65.0 years) (Attachment Table 2.1a_POOLED). The proportion of patients with WHO FC II and III at diagnosis was 90.8% in the UPTRAVI cohort and 88.9% in the Other PAH therapy cohort in the combined EXPOSURE and EXTRACT FUP Set (Attachment Table 2.2.2.1a_POOLED) compared to 89.0% - 91.4% in the EU registries. Despite some variation in the CHD-PAH proportion (11.1% in the combined EXPOSURE and EXTRACT FUP Set vs 1.0% - 38.0% in the EU registries), the majority of patients within EXPOSURE and EXTRACT and the EU registries are classified as IPAH (51.4% vs 33.0 - 58.0%) (Attachment Table 2.2.1a_POOLED).

In total, 342 patients (127 patients in the UPTRAVI cohort and 256 patients in the Other PAH therapy cohort) were enrolled from non-EU countries as part of the recruitment maximisation initiative (Attachment Table 2.1f_POOLED). Despite some gender variations (72.2% vs 69.7% females in non-EU patients vs overall study database) and proportion of IPAH aetiology (41.8% vs 51.4%), demographics and clinical characteristics for non-EU patients were generally similar to those for the overall study database (Attachment Table 2.1f_POOLED and Attachment Table 2.2.1f_POOLED) and therefore do not impact the generalisability of the study results to Europe.

12. OTHER INFORMATION

No additional or complementary information is available. All specific aspects of the study have been addressed in previous sections.

13. CONCLUSION

- Data from EXPOSURE and EXTRACT represent the most comprehensive long-term safety, tolerability and survival dataset collected for patients with PAH newly treated with UPTRAVI and Other PAH specific medications in real world clinical practice. Observing the clinical data of more than 2500 patients and 4000 person-years, including 450 patients over the age of 75 years, with a high and homogeneous quality standard, in the context of a rare disease is a noteworthy achievement.
- The combined dataset of EXTRACT and EXPOSURE has reached a sufficient number of person-years to provide an adequate precision for comparing IR of MACE and all-cause death between patients newly treated with UPTRAVI and patients initiating another PAH-specific therapy.
- The safety profile of UPTRAVI was consistent with the known safety profile established in the pivotal clinical study and reflected in the EU SmPC and other approved product information documents. CCI [redacted]
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- No unexpected or new safety findings that impact the established safety profile of UPTRAVI or its benefit-risk profile in PAH patients including patients over the age of 75 years were identified.
- The combined EXPOSURE and EXTRACT results adequately meet the objectives of this PASS program and hence the MAH would propose conclusion of EXPOSURE. The MAH will submit a final study report via another Type II variation.

14. REFERENCES

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Interim Report #1 AC-065A401 (UPTRAVI) (D-18.053). Post-authorisation safety study (PASS): observational cohort study of PAH patients newly treated with either UPTRAVI® (selexipag) or any other PAH-specific therapy, in clinical practice. **EXPOSURE** (**E**uro**P**ean **O**bservational **S**tudy of **UPTRAVI** in **R**eal-lif**E**). Version 1.0. Actelion Pharmaceuticals; 20 March 2018.

Interim Report #2 AC-065A401 (UPTRAVI) (D-19.085). Post-authorisation safety study (PASS): observational cohort study of PAH patients newly treated with either UPTRAVI® (selexipag) or any other PAH-specific therapy, in clinical practice. **EXPOSURE** (**E**uro**P**ean **O**bservational **S**tudy of **UPTRAVI** in **R**eal-lif**E**). Version 1.0. Actelion Pharmaceuticals; 25 March 2019.

Interim Report #3 AC-065A401 (UPTRAVI) (D-20.080). Post-authorisation safety study (PASS): observational cohort study of PAH patients newly treated with either UPTRAVI® (selexipag) or any other PAH-specific therapy, in clinical practice. **EXPOSURE** (**E**uro**P**ean **O**bservational **S**tudy of **UPTRAVI** in **R**eal-lif**E**). Version 1.0. Actelion Pharmaceuticals; 23 March 2020.

Interim Report #4 AC-065A401 (UPTRAVI). Post-authorisation safety study (PASS): observational cohort study of PAH patients newly treated with either UPTRAVI® (selexipag) or any other PAH-specific therapy, in clinical practice. **EXPOSURE** (**E**uro**P**ean **O**bservational **S**tudy of **UPTRAVI** in **R**eal-lif**E**). Version 1.0. Actelion Pharmaceuticals; 25 March 2021.

Interim Report #5 AC-065A401 (UPTRAVI). Post-authorisation safety study (PASS): observational cohort study of PAH patients newly treated with either UPTRAVI® (selexipag) or any other PAH-specific therapy, in clinical practice. **EXPOSURE** (**EXP**loratory **O**bservational Study of **UPTRAVI** in **R**eal-lif**E**). Version 1.0. Actelion Pharmaceuticals; 25 March 2022.

Interim Report #6 AC-065A401 (UPTRAVI). Post-authorisation safety study (PASS): observational cohort study of PAH patients newly treated with either UPTRAVI® (selexipag) or any other PAH-specific therapy, in clinical practice. **EXPOSURE** (**EXP**loratory **O**bservational Study of **UPTRAVI** in **R**eal-lif**E**). Version 1.0. Actelion Pharmaceuticals; 20 March 2023.

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Study protocol amendment 5 version 6, AC-065A401 (UPTRAVI). Post-authorisation safety study (PASS): observational cohort study of PAH patients newly treated with either UPTRAVI® (selexipag) or any other PAH-specific therapy, in clinical practice. **EXPOSURE** (**EuroPean O**bservational **S**tudy of **UPTRAVI** in **R**eal-lif**E**). Version 6. Actelion Pharmaceuticals Ltd; 11 January 2021.

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ANNEX 1: STAND-ALONE DOCUMENTS

The following appendices are either included with the report or are available on request.

1	Protocol and Amendments
2	Sample Case Report Form(s)
3	List of IECs or IRBs and Sample Consent Forms
4	List and Description of Investigators and Sites
5	Signature of Sponsor's Responsible Party (located at the end of this document) Signature of Principal or Coordinating Investigator(s) (not applicable)
6	Listing of Patients Receiving Test Drug(s) from Specified Batch (not applicable)
7	Randomisation Scheme (not applicable)
8	Audit Certificates (not applicable)
9	Documentation of Statistical Methods and Interim Analysis Plans
10	Documentation of Interlaboratory Standardisation Methods and Quality Assurance Procedures if Used (not applicable)
11	Publications Based on the Study
12	Important Publications Referenced in the Report (not applicable)
13	Data Listings (not applicable)

ANNEX 2: ADDITIONAL/SUPPORTING INFORMATION

Annex 2.1: ETHICS COMMITTEE RESPONSES
Annex 2.2: NON-ENROLLMENT LOG
CCI [redacted]

Annex 2.1: ETHICS COMMITTEE RESPONSES

Clinical Study Number: AC-065A401

Responses to request for inclusion of data from patients who initiated a new PAH-specific therapy after study site initiation, died within the first month of treatment and were not able to be consented, are summarised below as of 14 July 2023.

Country	Number of Sites		Reason for Agreement/Refusal
	Agreed	Refused	
Austria	0	4/4	[Refusal] Only in case of a signed ICF from a patient, data of the deceased should be collected. It is not allowed for relatives to consent instead.
Belgium	0	2/2	[Refusal]: Only in case of a signed ICF from a patient, data of the deceased be collected. It is not allowed for relatives to consent instead.
Canada	4/7	1/7	[Agreement] Since collecting data retrospectively from deceased patients was approved in the protocol, you do not need to submit any further documentation. You are able to proceed with the collection of this data as outlined in the protocol. [Refusal]: IRB confirmed will not allow data collection for deceased patients. [Pending] Feedback from 2 sites; not received as of 14 July 2023.
Czech Republic	0	1/1	[Refusal]: IRB confirmed that patient consent is required for follow-up in a non-interventional study.
Denmark	0	1/1	[Refusal] According to § 10 Section 1, the data can be collected without consent if this is done solely for the purpose of performing statistical or scientific studies of essential significance for the society and if the processing is necessary for the conduct of the investigations. The changes do not give rise to comments from Datatilsynet. Datatilsynet must, for the sake of the matter, draw attention to the fact that the permission of Datatilsynet is given in the light of the rules in the Personal Data Act, which will be replaced by the rules in the Data Protection Regulation in May 2018. Datatilsynet therefore allows the processing of personal data to continue on previously defined terms.'
Estonia	-	-	[Pending] Feedback from 1 site not received as of 14 July 2023.
Finland	0	2/2	[Refusal] During the phone call to Ethics Committee of the Hospital District of Southwest Finland the retrospective data collection process of EXPOSURE study was explained: "Eligible patients who died within less than 1 month of treatment and were not able to be consented, will be included in the study database, where permitted by local regulation." Ethics Committee wasn't able to answer if this is permitted in Finland. They asked to contact lawyer. Lawyer of Pharma Industry Finland was not able to mention any local regulation that allows data collection of subject mentioned above. Based on above information it was concluded that it is not allowed in Finland to collect data of the deceased patients.

Country	Number of Sites		Reason for Agreement/Refusal
	Agreed	Refused	
France	0	6/6	[Refusal] It is not possible as no "non-opposition" form would have been signed by the patient previously
Germany	26/27	0/27	[Agreement] The legal background is that a presumed will cannot be assumed. The Data Protection Law which requests an ICF does not apply for deceased persons. It remains to look at the general personality right. If it is ensured that the recipient of the pseudonymized data cannot draw back on the identity of the deceased patient, then in the opinion of the CEC Berlin no violation of the personality rights occurs, so that the data for deceased persons can be forwarded without ICF. [Pending] Feedback from 1 site not received as of 14 July 2023.
Greece	7/9	2/9	[Refusal] The Scientific Council of the Hospital does not approve the retrospective data collection for eligible patients who die within less than 1 month of treatment and were not able to be consented.
Italy	-	20/20	[Refusal]: It is not allowed.
Lithuania	-	-	[Pending] Feedback from 2 sites not received as of 14 July 2023.
Netherlands	0	3/3	[Refusal] Both from the perspective of the Data Protection Law and from the perspective of the health care professional/provider's duty of confidentiality there are legal obstacles to the use of data from the deceased patient in the situation you have described. These obstacles cannot be taken away in the ways you have described or in any other way. After the patient has died, his/her relatives can no longer act as proxy for the patient in order to give consent for participation of the patient in the study and they also can no longer act as a proxy for the patient in order to lift the duty of confidentiality. Therefore inclusion of the patient in the study and/or use of his/her data in the study is not allowed. In the Dutch system this cannot be amended by Independent Review Boards or other independent bodies (e.g., courts). For the use of patient data this can be circumvented, only in very exceptional circumstances, but this does not apply to inclusion of patients in interventional studies. For the exceptional circumstances in which data of deceased patients can be used, I refer you to the text of article 23, paragraph 2 of the Data Protection Law and article 7:458 of the Civil Code.
Poland	-	-	[Pending] Feedback from 7 sites not received as of 14 July 2023.
Portugal	0	2/2	[Refusal] Country regulation do not allow data collected from deceased patient without consent.
Russia	-	-	[Pending] Feedback from 12 sites not received as of 14 July 2023. Country was closed as on 14 July 2023.

Country	Number of Sites		Reason for Agreement/Refusal
	Agreed	Refused	
Slovakia	0	4/4	[Refusal] According to Slovak law Act on Drug 362/2011 (A subject shall be enrolled in a clinical trial on the basis of his/her consent to take part in the clinical trial. The subject's consent shall be given voluntarily following a thorough explanation of the objectives, purpose, consequences, and risks associated with the clinical trial in which the subject is asked to take part, and after signing such explanation (further referred to as "informed consent form") by the subject. § 30 Protection of Subjects b) the subject or, if the subject is legally incapable of giving informed consent, his/her legal representative understands, following discussion with the investigator, the objectives, risks, and disadvantages of the clinical trial, and the conditions under which the clinical trial is to be conducted, and his/her right to withdraw from the clinical trial at any time and without any consequences; c) the rights of subjects are guaranteed with respect to their physical and mental integrity, as well as their right for privacy and protection of personal data in accordance with a special regulation.
Spain	0	27/27	[Refusal] Data collection from patients who died and have not been consented, is not permitted by the Spanish legislation. Order of SAS SAS/3470/2009, 16 Dec 2009 requires signed ICF before data collection.
Sweden	0	3/3	[Refusal] Collection of data not allowed if consent is not given/signed. Relatives of a deceased cannot be consented instead but only consulted.
Switzerland	1/2	-	[Agreement] EC approval received from EC. [Pending] Feedback from 1 site not received as of 14 July 2023.
United Kingdom	6/6	0	[Agreement] The UK EC has confirmed the text relating to data collection from deceased patients as per the protocol has been approved.

CEC=central ethics committee; EC=ethics committee; ICF=informed consent form; UK=United Kingdom

Clinical Study Number: 67896049PAH0002

Responses to request for inclusion of data from patients who initiated a new PAH-specific therapy after study site initiation, died within the first month of treatment and were not able to be consented, are summarised below as of 28 July 2023.

Country	Number of Sites		Reason for Agreement/Refusal
	Agreed	Refused	
Canada	4/4	-	[Agreement] Reviewed and approved. This research study is to be conducted by the investigator noted. Consent can be waived as the conditions in Section 50(1)(b) of the Health Information Act have been met.
Czech Republic	-	1/1	[Refusal]: Reasons for EC opinion: Currently applicable laws do not make it possible to carry out this project without the patient's informed consent. The applicant also points to the fact that it can only be conducted in countries where the legislation allows for it; this is not possible in the Czech Republic.
France	1/1	-	[Pending] Review timelines too long to have receive approval within recruitment period as per protocol requirements.
Germany	-	3/3	[Refusal]: ICF waiver not allowed. Need ICF to be in place for all participants to provide consent.
Italy	-	11/11	[Refusal]: ICF waiver not allowed. Need ICF to be in place for all participants who are alive. Authorization from Garante of Privacy regarding the ICF waiver required for participants who are not alive.
Lithuania	2/2	-	[Agreement] Reviewed and approved.
Netherlands	2/2	-	[Agreement] Reviewed and approved.
Poland	-	5/5	[Refusal]: CEC did not approve study. LEC's for other sites not submitted because of CEC non approval. ICF waiver not allowed.
Slovakia	3/3	-	[Agreement] Reviewed and approved.
Spain	10/10	-	[Agreement] Reviewed and approved
Sweden	3/3	-	[Agreement] Reviewed and approved.
Switzerland	1/1	-	[Agreement] Reviewed and approved.
United Kingdom	3/3	-	[Agreement]

CEC=central ethics committee; EC=ethics committee; ICF=informed consent form; UK=United Kingdom

Annex 2.2: NON-ENROLLMENT LOG

As of the time of this 7th interim report for EXPOSURE and final report for EXTRACT, 456 eligible patients were not enrolled and recorded in the non-enrolment log per study investigators. However, based on MAH review of the non-enrolment log, accounting for the level of imprecision due to aggregated data structure, around 182 of these patients were found to be ineligible and should have not been recorded in the log. The two main reasons for ineligibility were refusal to participate/consent and enrolment in an interventional clinical trial. Due to the aggregated structure of the non-enrolment log, all 456 patients were considered for the description of demographic characteristics. The majority (59.3%) were between 50-75 years old, and 72 patients (15.8%) were aged >75 years. Most of the patients (60.4%) were in WHO FC III and there were more females than males (66.9% females and 33.1% males). There was no difference in demographic data between eligible patients not enrolled in EXPOSURE and those enrolled; therefore, no major selection bias has been observed at this stage of the study.

Annex 2.3: CLINICAL QUALITATIVE ASSESSMENT OF ALL-CAUSE DEATHS AND MAJOR ADVERSE CARDIOVASCULAR EVENTS

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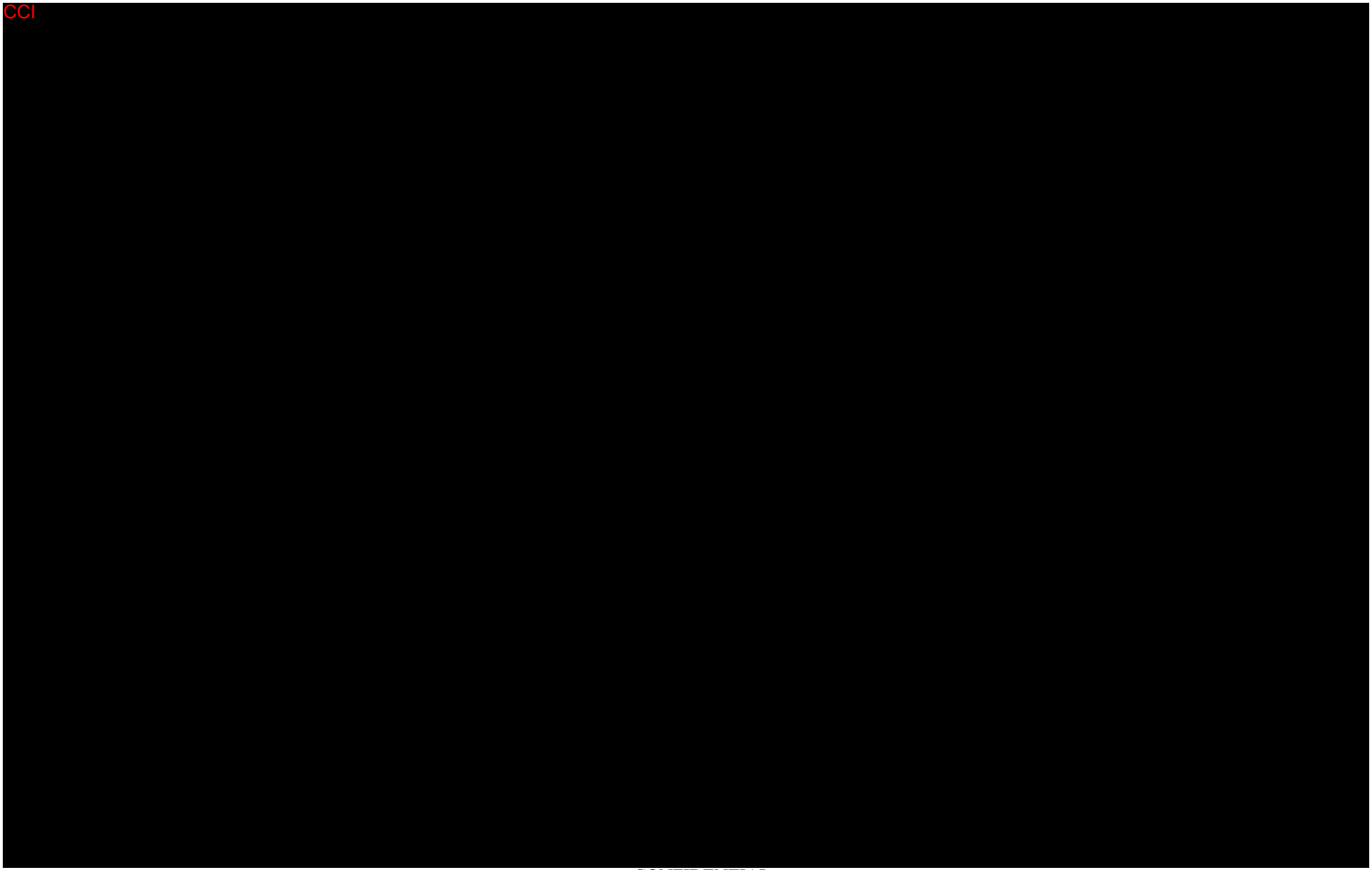

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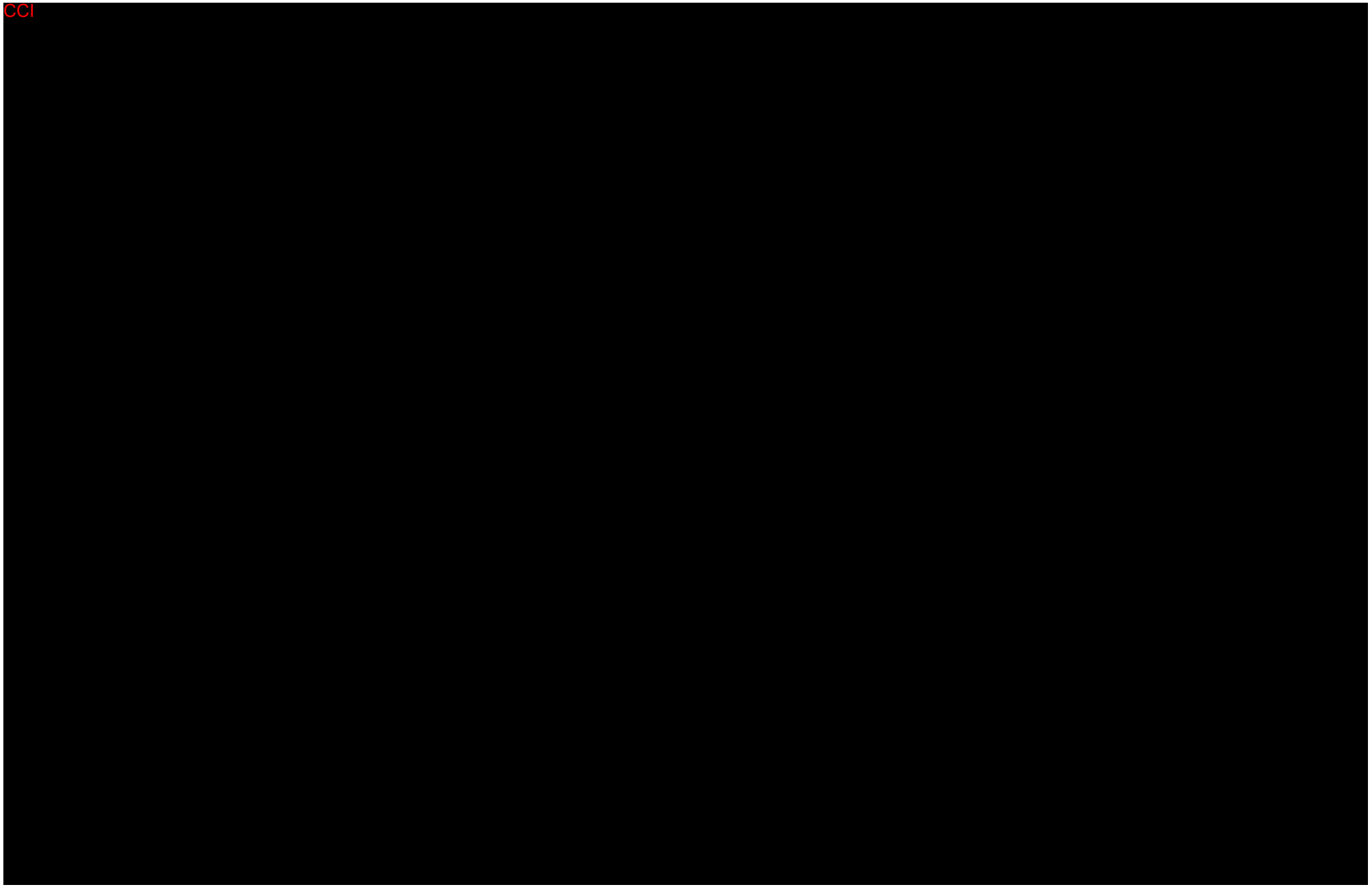

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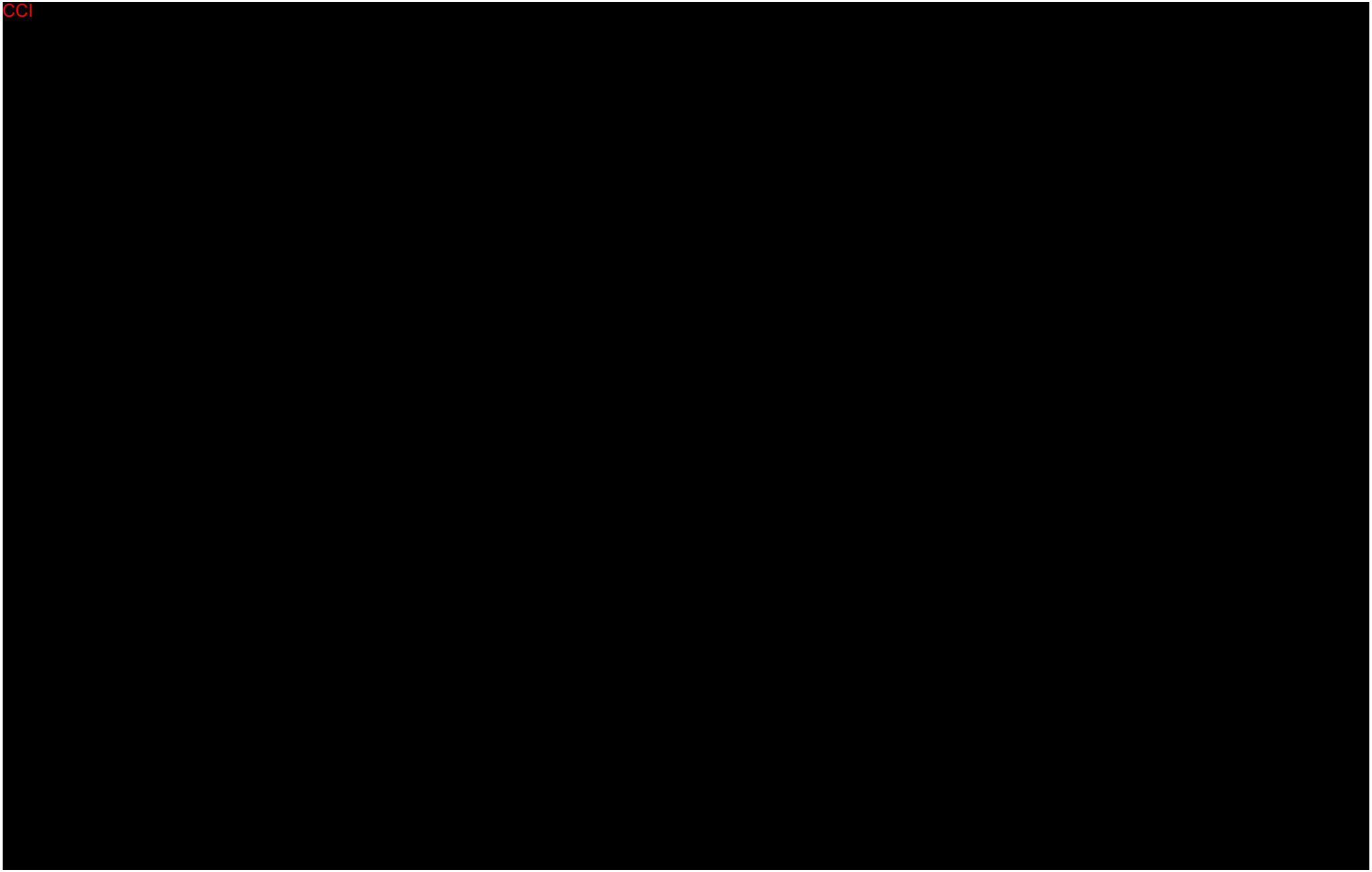

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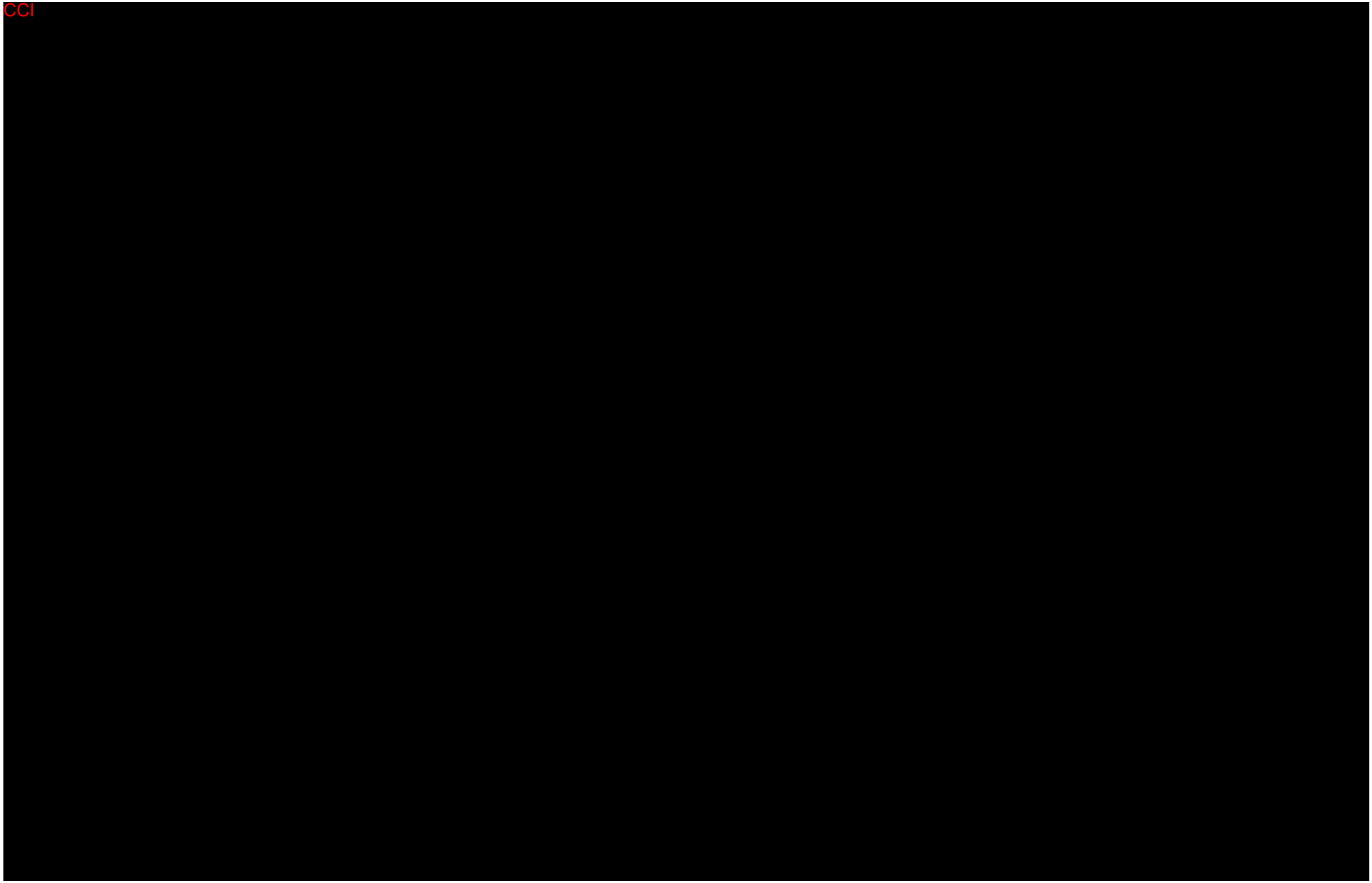
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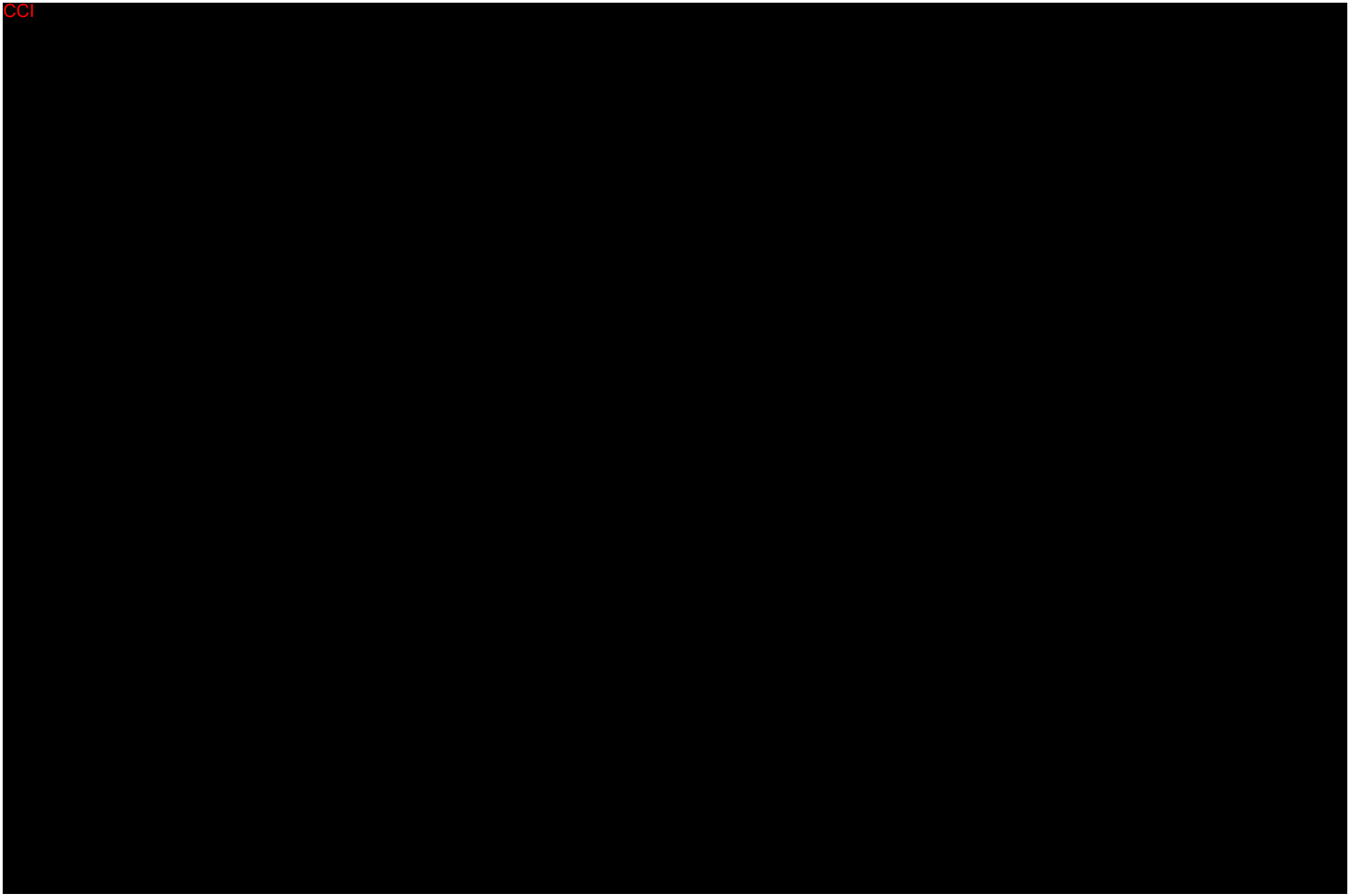

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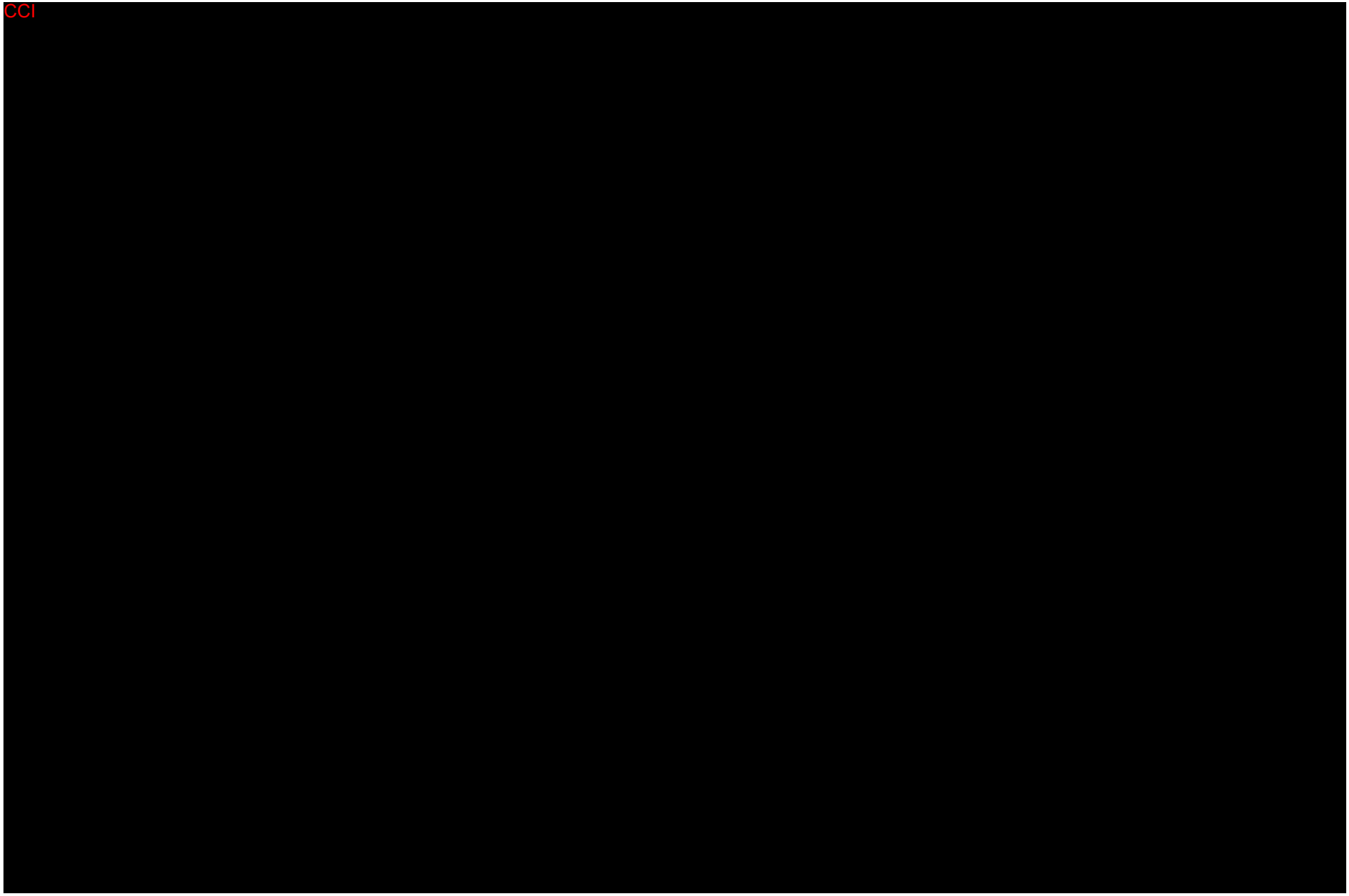

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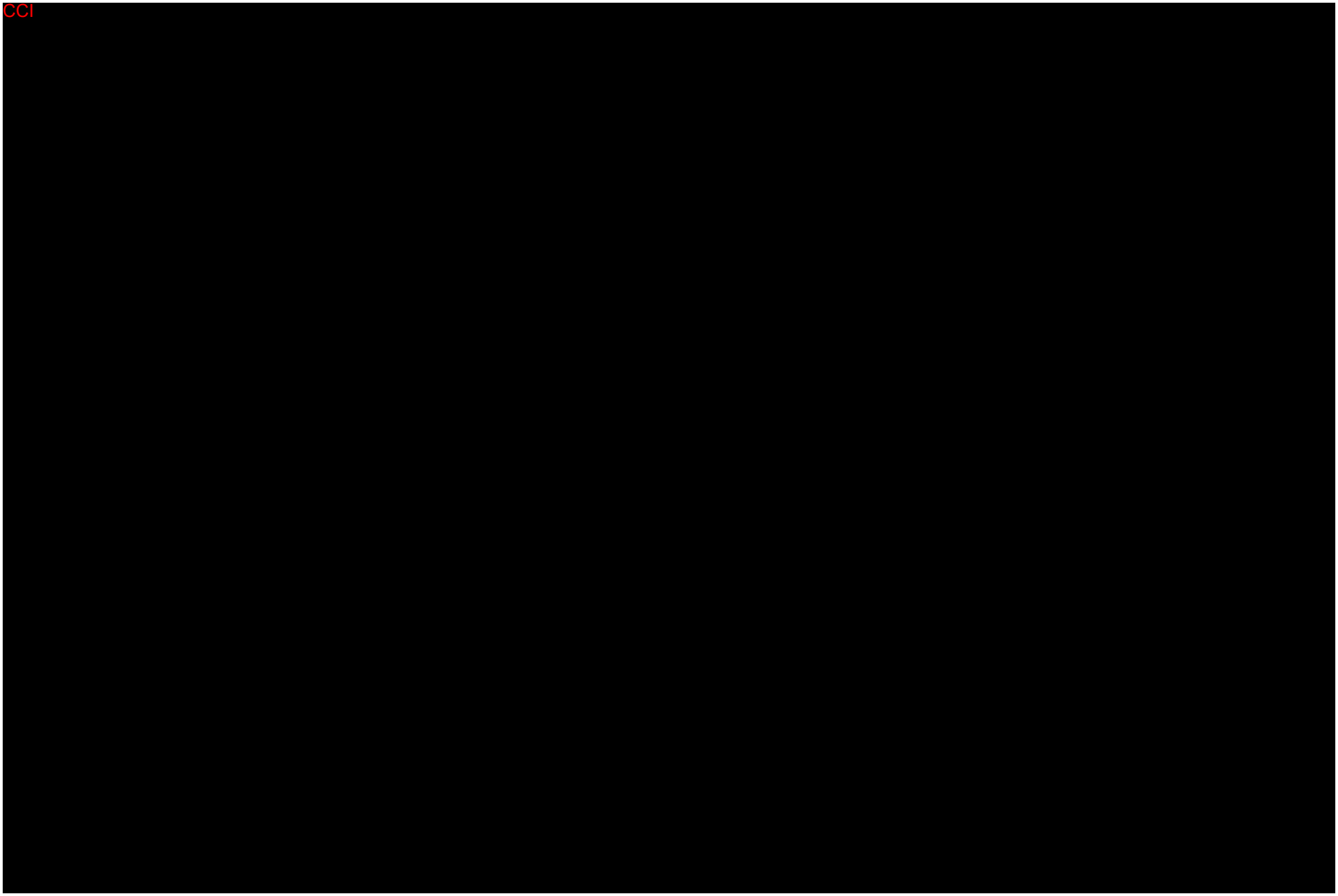

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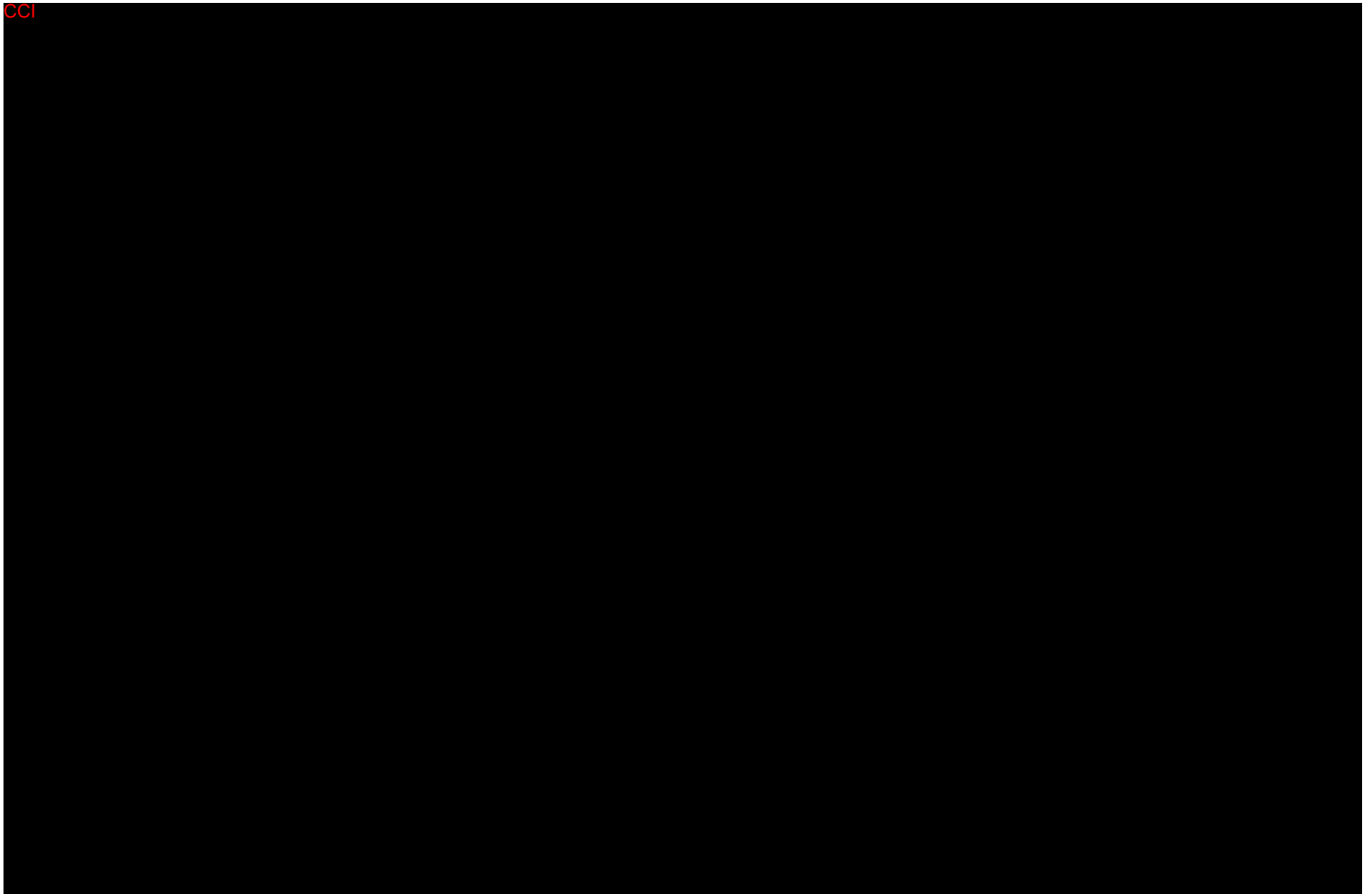

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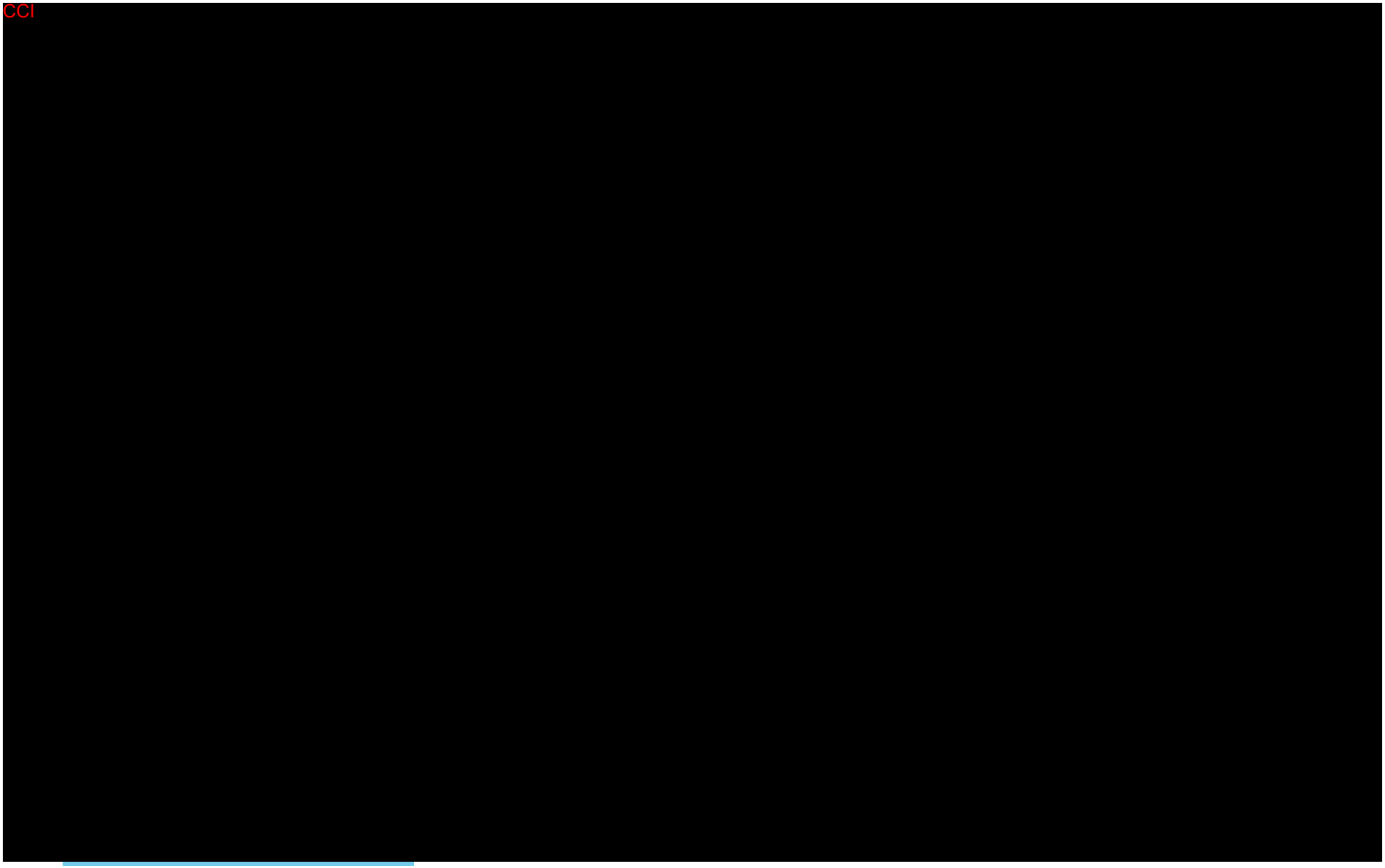

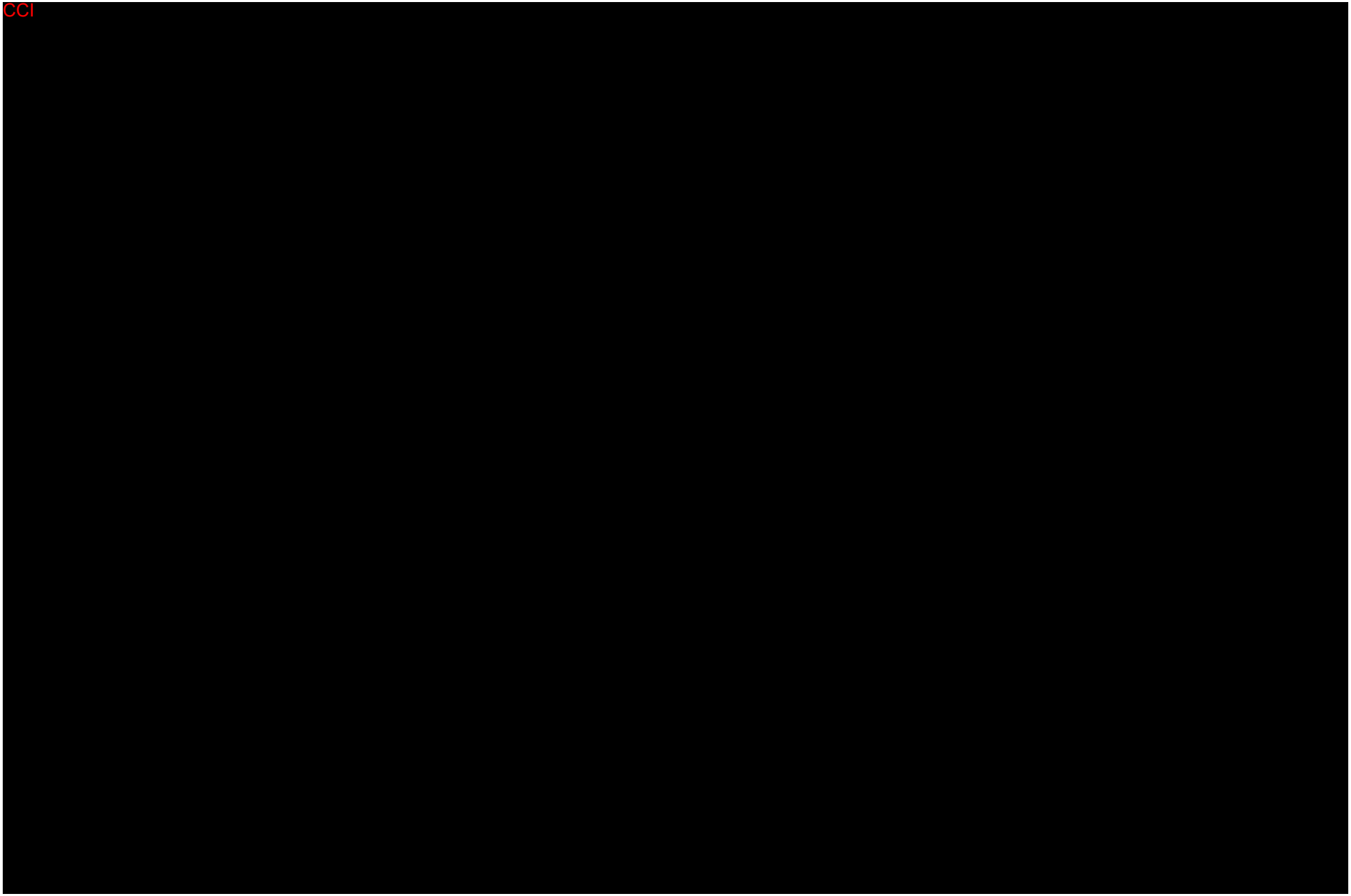
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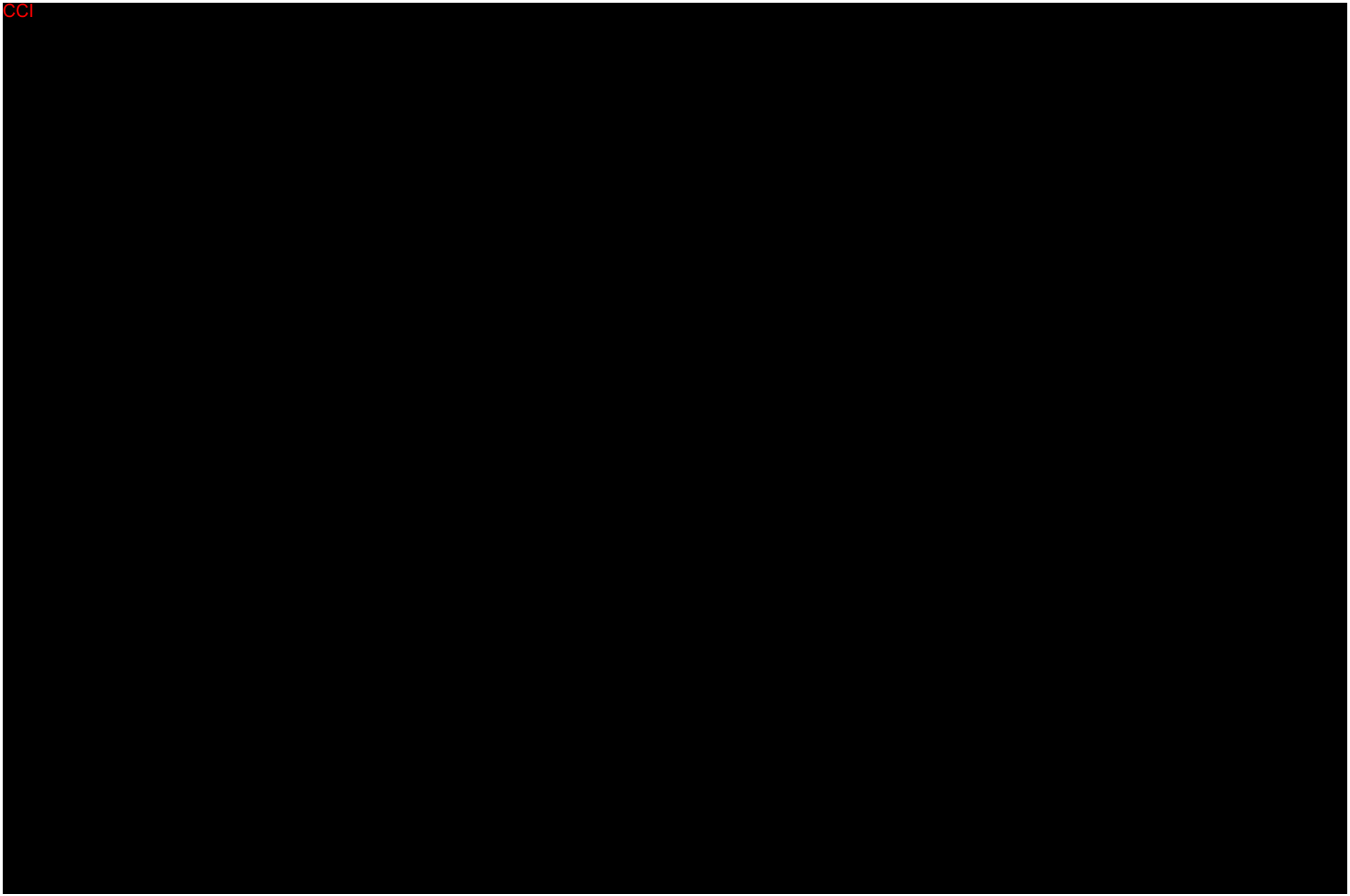

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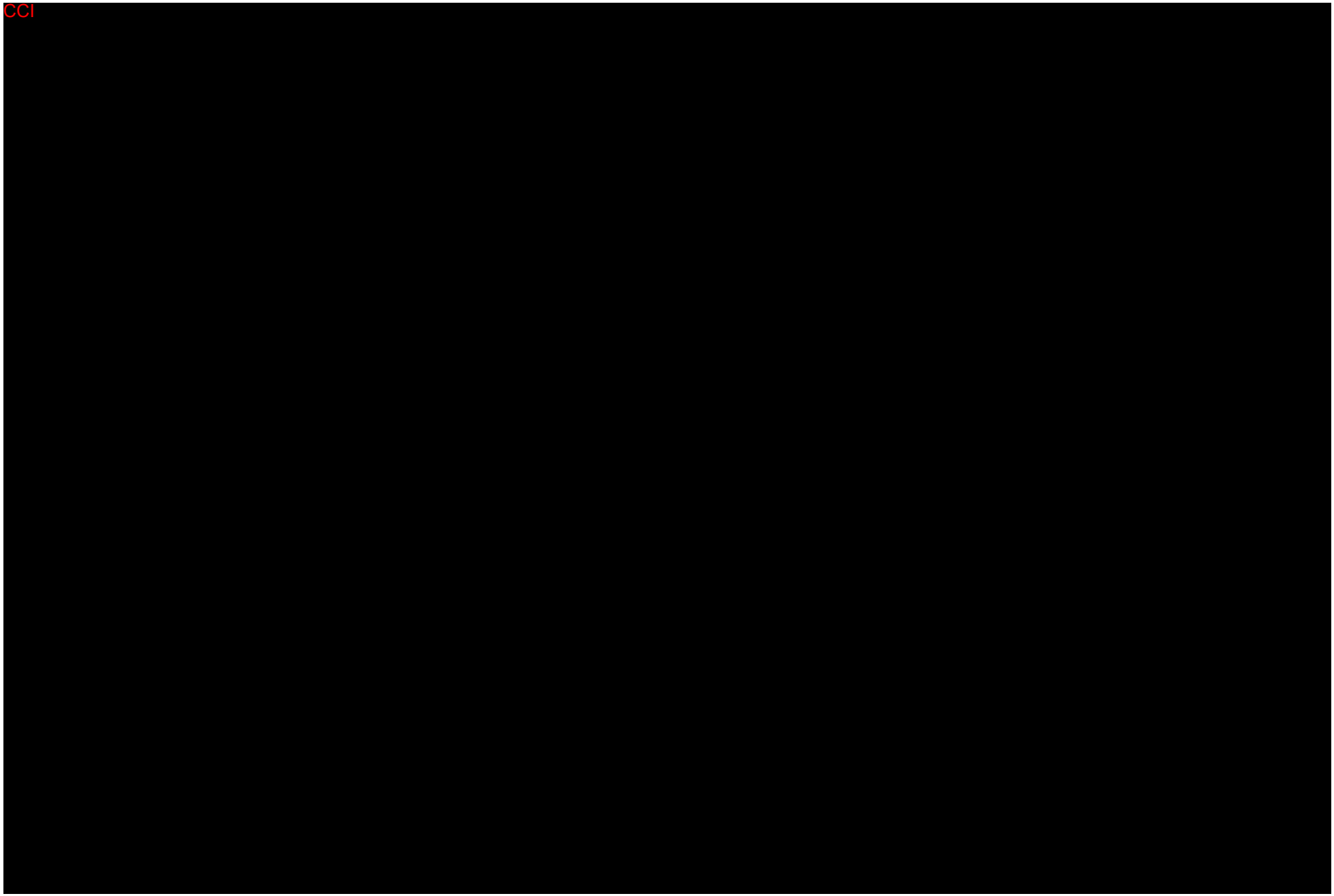

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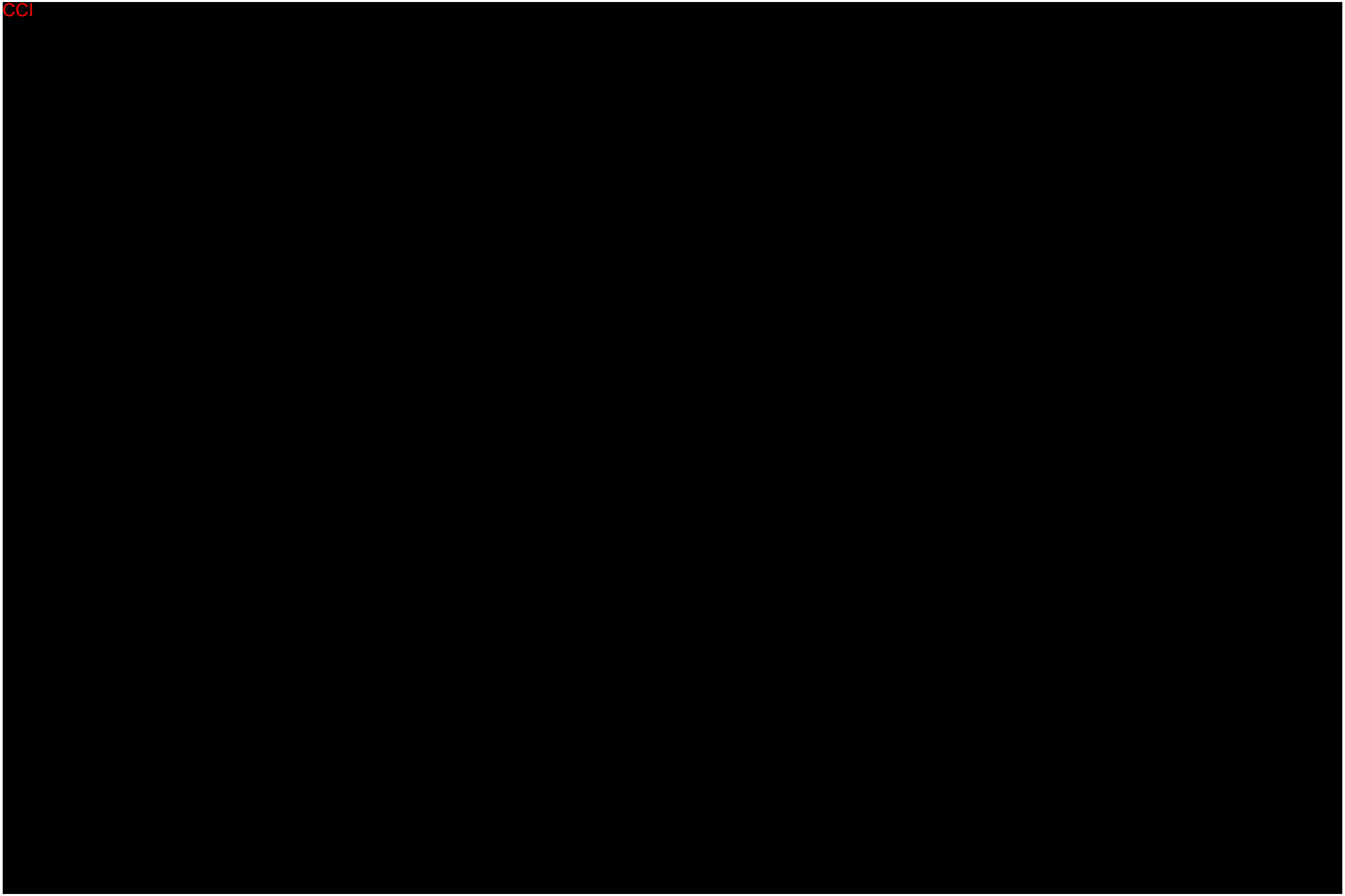
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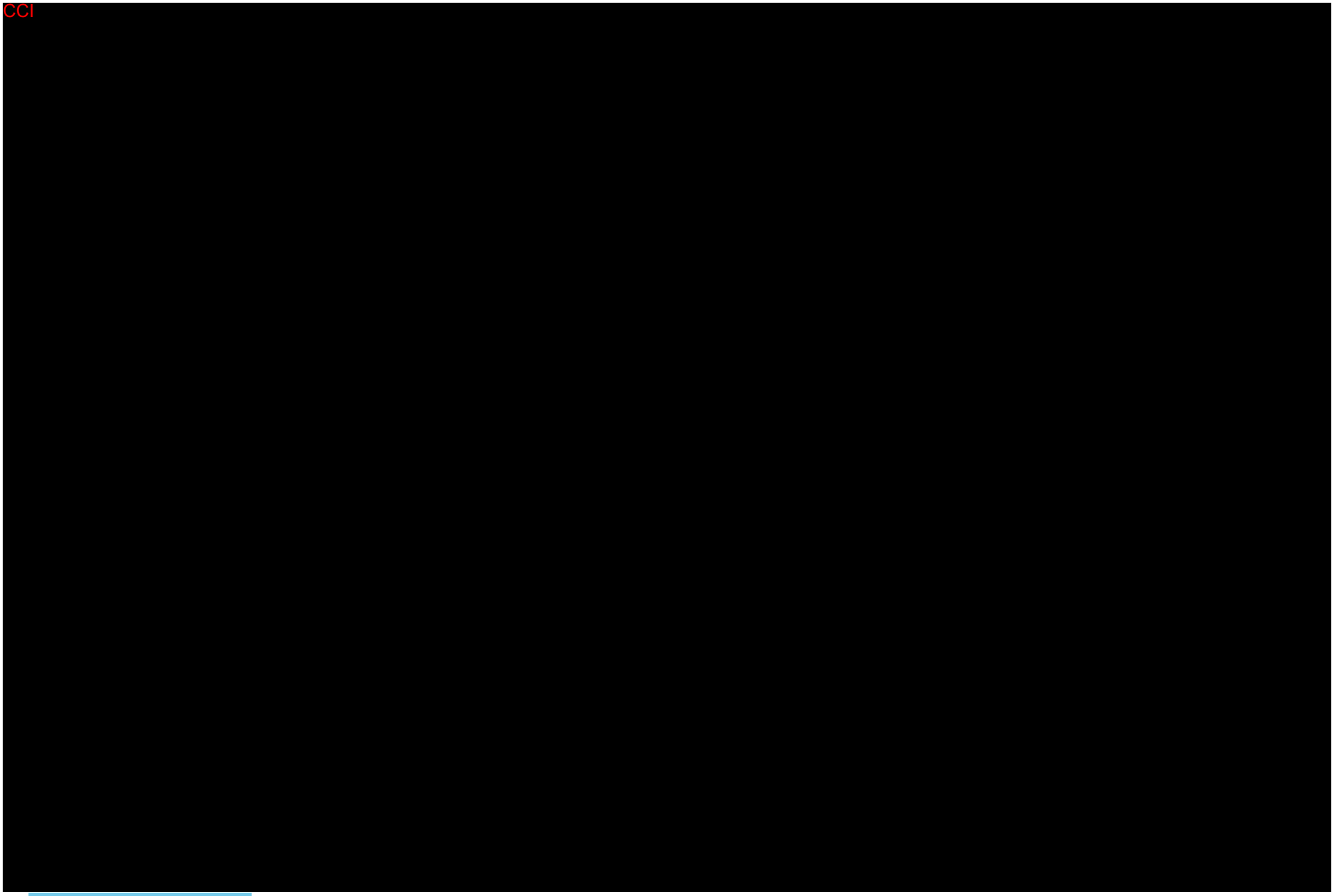

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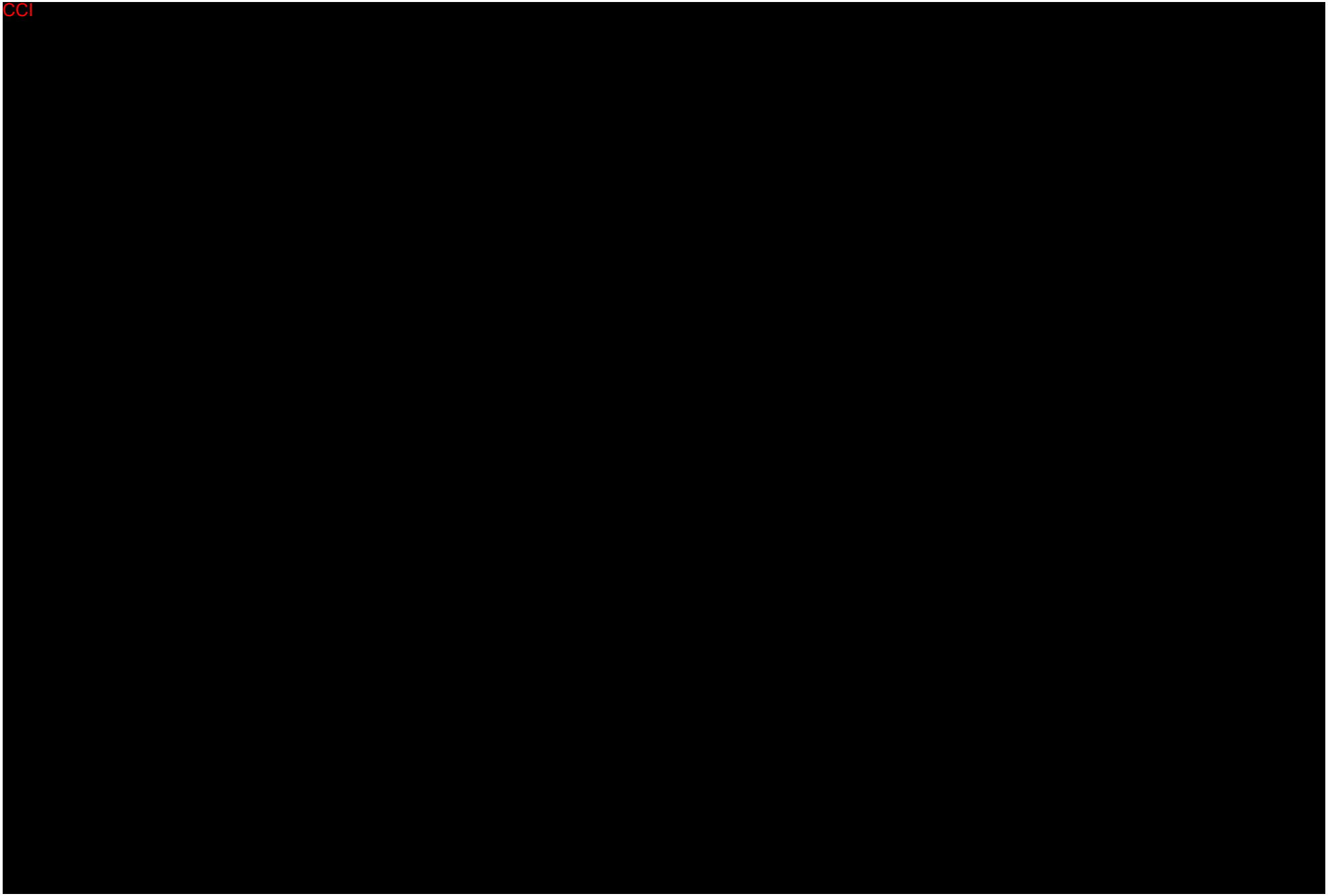

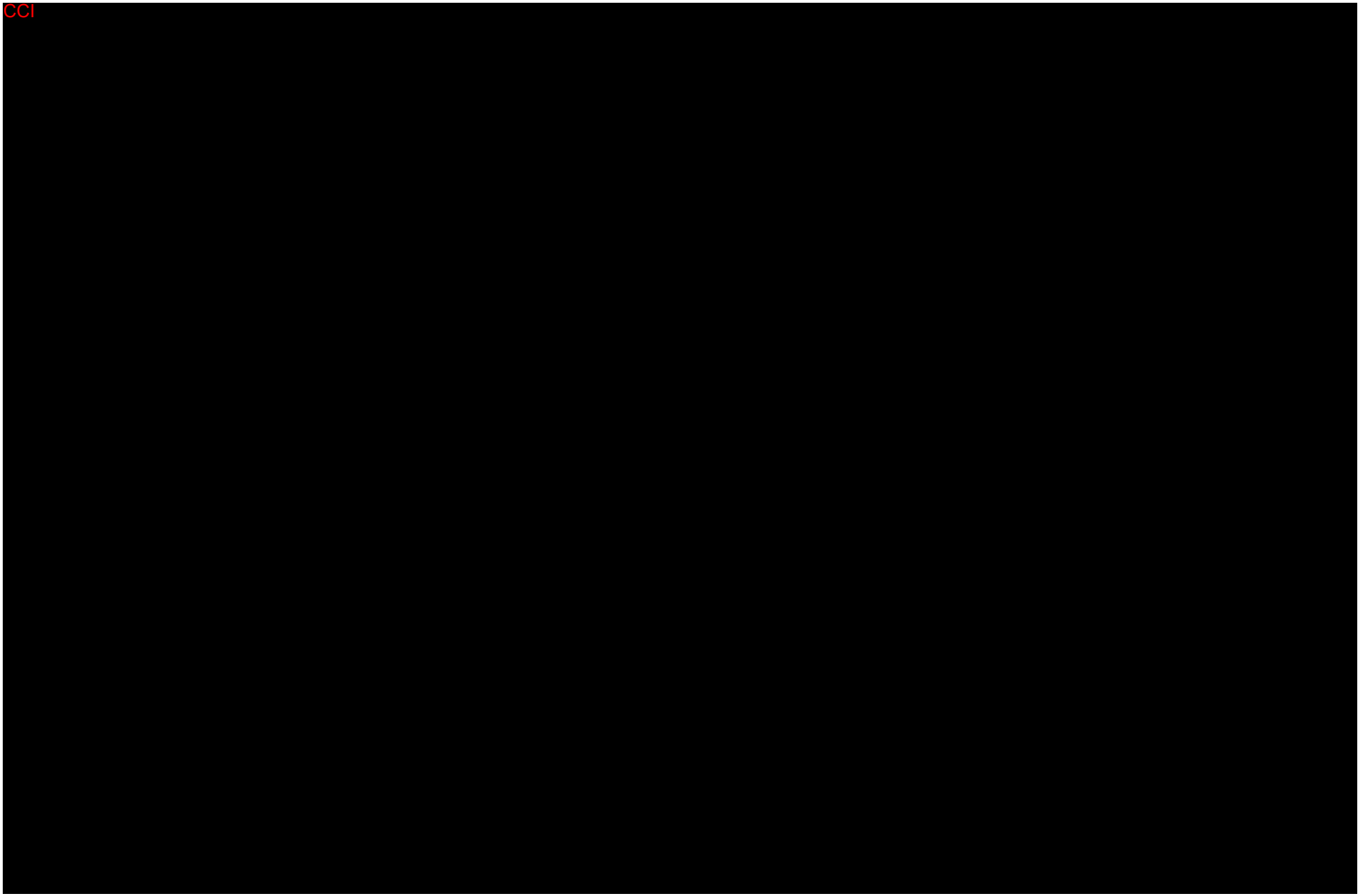
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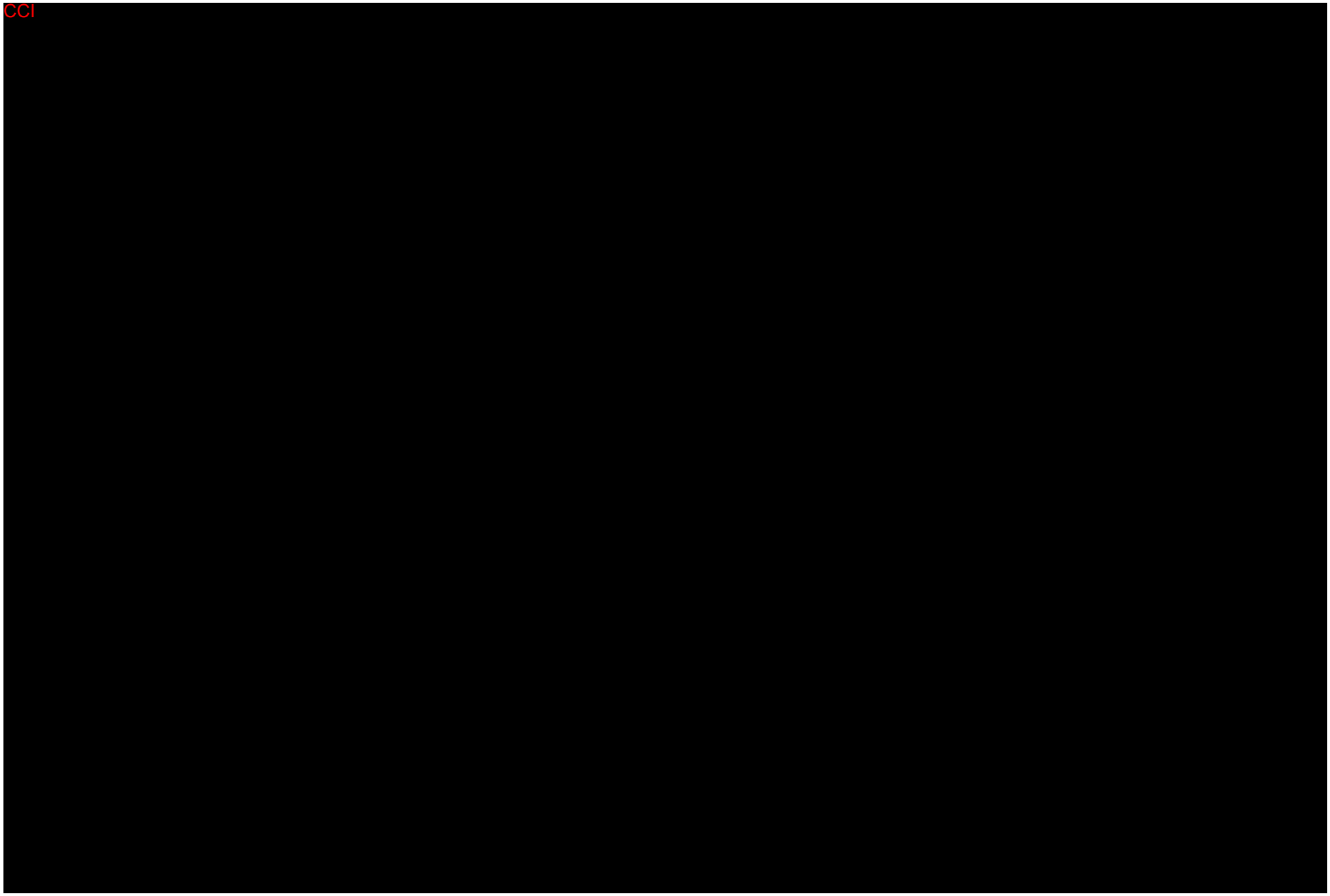

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SIGNATURE PAGE

STUDY TITLE:	Post-authorisation Safety Study (PASS): Observational Cohort Study of PAH Patients Newly Treated with either Uptravi® (selexipag) or Any Other PAH-specific Therapy, in Clinical Practice; and retrospective medical chart review of patients with PAH newly treated with either Uptravi® (selexipag) or any Other PAH-specific therapy
REPORT CONTRIBUTORS:	PPD, Irina Konourina, PPD

SPONSOR'S RESPONSIBLE PARTY:

NAME:	PPD
TITLE:	PPD

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

SIGNATURE:	eSignature has been applied on the next page.
DATE:	

SPONSOR'S RESPONSIBLE MEDICAL OFFICER:

NAME:	Irina Konourina, MD
INSTITUTION:	Actelion Pharmaceuticals Ltd. (a Janssen Pharmaceuticals Company of Johnson and Johnson)

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

SIGNATURE:	eSignature has been applied on the next page.
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Signature

User	Date	Reason
Konourina Irina 155007229	07-Mar-2024 14:00:20 (GMT)	Document Approval
PPD		