Statistical Analysis Plan

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Official Title of Study: Triple thErapy in paTients With COPD Under Real lIve Setting (the TETRIS Study)

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Statistical Analysis Plan (SAP)

Study Title/Acronym:	TETRIS – Triple thErapy in paTients with COPD under Real llve Setting		
Sponsor:	GlaxoSmithKline group of companies (GSK)		
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	0.2	15.04.2021	Completion of list of tables; implementation of comments from first GSK review
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	1.0	05.07.2022	Final version
	1.1	20.08.2024	Renaming of Institut Dr. Schauerte Signature Page: Update Changes made for imputation of COPD therapy start / stop date (chapter 6.3) Additional definitions of derived variables (chapter 6.6) Updated Stratifications lists and definitions (chapter 8), Added additional analyses (chapter 8.3)
	2.0	25.10.2024	Finalisation of V1.1 after approval by GSK

Signature and Approval

Author

PPD

I agree to the contents of this document.

PPD

Biostatistician
Real World Evidence Germany GmbH

25/Oct/2024 02:48 PM CEST

Date

Reviewer/Approver

PPD

I agree to the contents of this document.

PPD

Senior Data Manager
Real World Evidence Germany GmbH

25/Oct/2024 01:56 PM CEST

Date

Sponsor Representatives

PPD

I agree to the contents of this document.

PPD

GSK – Medical Affairs Lead
GlaxoSmithKline GmbH & Co. KG

25/Oct/2024 01:11 PM CEST

Date

PPD

I agree to the contents of this document.

PPD

Principle Statistician
GlaxoSmithKline GmbH & Co. KG

25/Oct/2024 01:36 PM CEST

Date

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1. Definitions/Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ARR	Absolute risk reduction
BMI	Body Mass Index
CAT	COPD Assessment Test
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CSR	Clinical Study Report
CT	Computed Tomography
DD	Drug dictionary
DLCO	Diffusing capacity of lung for carbon monoxide
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	Eosinophil
EQ-5D	European Quality of Life 5 Dimensions
EW	Early Withdrawal
FeNO	Fractional exhaled nitric oxide
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General Practitioner
HRQoL	Health-related Quality of Life
hsCRP	High-sensitivity C-reactive protein
ICF	Informed Consent Form
ICS	Inhaled Corticosteroid
ICU	Intensive Care Unit
LABA	Long-Acting Beta 2 Agonist
LAMA	Long-Acting Muscarinic Antagonist
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Multiple Inhaler Triple Therapy
NIS	Non-interventional Study
NNH	Number needed to harm
NNT	Number needed to treat
OCS	Oral Corticosteroids
PPS	Per-protocol Set
PROs	Patient-Reported Outcomes

QoL	Quality of Life
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDV	Source Data Verification
SE	Standard error
SITT	Single Inhaler Triple Therapy
SOP	Standard Operating Procedure
VAS	Visual Analogue Scale
VRR	Validity Review Report
WBC	White Blood Cell
WHO	World Health Organization

2. Introduction

2.1 Background

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), chronic obstructive pulmonary disease (COPD) is a disabling respiratory disease characterised by airflow obstruction and associated symptoms, including breathing difficulties caused by shortness of breath and wheezing, airway hyperactivity, chronic cough, sputum production, exercise intolerance, and poor quality of life. The main risk factor for COPD is tobacco smoking but other environmental exposures such as biomass fuel exposure and air pollution may contribute. Besides exposures, host factors predispose individuals to develop COPD. These include genetic abnormalities, abnormal lung development and accelerated aging.

At least 50% of patients with COPD fails to achieve adequate control of symptoms or exacerbation risk reduction while receiving only a single long-acting bronchodilator, such as a LAMA or LABA. Escalation to multiple bronchodilators with or without an inhaled corticosteroid (ICS) will depend on the patient's symptom burden (including dyspnoea, cough, sputum production as assessed by the COPD assessment test or modified Medical Research Council breathlessness scores) and risk of exacerbations. Fixed-dose LAMA/LABA is relatively new to the market. Current treatment guidelines recommend the use of triple therapy with an ICS/LAMA/LABA for patients currently on bronchodilators with persistent symptoms and/or at risk for future exacerbations. In addition to multiple inhaler triple therapy (MITT) with multiple inhalers, single inhaler triple therapy (SITT) is currently available.

In accordance with the GOLD recommendations, it is important to assess the characteristics and treatment patterns of patients prior to triple therapy initiation, in order to determine adherence to these guidelines and understand how patients progress to triple therapy. Despite a clearly defined guidance from GOLD treatment recommendations for the initiation and maintenance of triple therapy, treatment changes in Germany, including de-escalation, are often seen in treatment reality. The TETRIS study is intended to provide information on how many COPD patients remain continuously on triple therapy in Germany. The reasons for treatment changes are hardly known, as are possible clinical consequences. Therefore, this observational study will also retrospectively capture the reasons in Germany to put the patients on MITT or SITT considering existing treatment recommendations. When evaluating all information that is collected about the therapy and patient environment, SITTs and MITTs will be looked at both separately and combined.

TETRIS will observe patients with COPD with or without comorbid asthma who are on an existing combined treatment of LAMA, LABA and ICS. The study is intended to gain a better understanding of what influences the treatment decision of German physicians in primary and secondary care under real life conditions. TETRIS is also designed to elicit the reasons for treatment changes and to describe long-term outcomes with patients initiated on triple therapy over a period of two years. Another goal is to describe the temporal dynamics of treatment pattern and to unravel potentially complex patient journeys in different German regions. Research investigating the patient journey is required to better understand the individualized treatment regime of a patient over time with COPD in Germany and to address the limitations faced by health care professionals when aiming to optimise treatment according to current GOLD COPD recommendations.

A further aim of TETRIS is to identify and follow-up a variety of 'treatable traits' in COPD patients, which - when modified - may lead to improved health outcomes. Therefore, COPD patients with signs of asthma or an asthma history will also be included to gain a better understanding of this phenotype. Recognition of certain patient characteristics may already be directly or indirectly linked to treatment decisions and therefore are of particular interest to be further explored in clinical practice.

In order to be able to map treatment reality in Germany as comprehensively as possible, the TETRIS study will collect all relevant data. The results may guide the medical community to provide a more targeted medical education approach of the unmet medical need in COPD. The data will enable the medical community to ensure that patients receive optimised therapy for their COPD by driving better informed treatment decisions. In addition, analysis comparing patient characteristics in the event of maintenance or interruption of triple therapy could provide further valuable insights that contribute to an understanding of the treatment reality in Germany.

2.2 Protocol Version and Amendments

The conduct of this study is based on the TETRIS Non-Interventional Study Protocol, version 2.0 from February 14th, 2022.

3. Project Objectives

The primary objective is to describe the percentage of participants with diagnosed COPD with or without comorbid asthma who continuously receive triple therapy for 6, 12 and 24 months after study enrolment. SITTs and MITTs will be looked at both separately and combined.

For all secondary objectives, SITTs and MITTs will also be looked at both separately and combined:

- Describe profiles of COPD patients who initiated or are on triple therapy (LAMA/LABA/ICS) in Germany, for example patient and disease characteristics when initiating triple therapy
- Describe the distribution and frequency of combined treatable traits in COPD patients
- Describe the percentage of participants with at least one switch from triple therapy to LAMA/LABA or to ICS/LABA after 6, 12 and 24 months
- Describe COPD treatment decisions of German physicians who have either initiated patients on triple or decided to change actual therapy, for example distribution and frequency of prespecified reasons to initiate or change triple therapy
- Describe clinical outcomes in COPD patients initiated on triple therapy, for example annual rate of moderate and/or severe exacerbations
- Describe the patient journey of COPD patients initiated on triple therapy, for example annual rate of COPD related primary and secondary care contacts
- Describe safety with focus on pneumonia and cardiovascular events

4. Project Design

This study is a multi-centre, prospective observational cohort study. Participants with COPD have already been treated with triple therapy for at least 2 but not longer than 48 weeks will be enrolled into one of the following two cohorts:

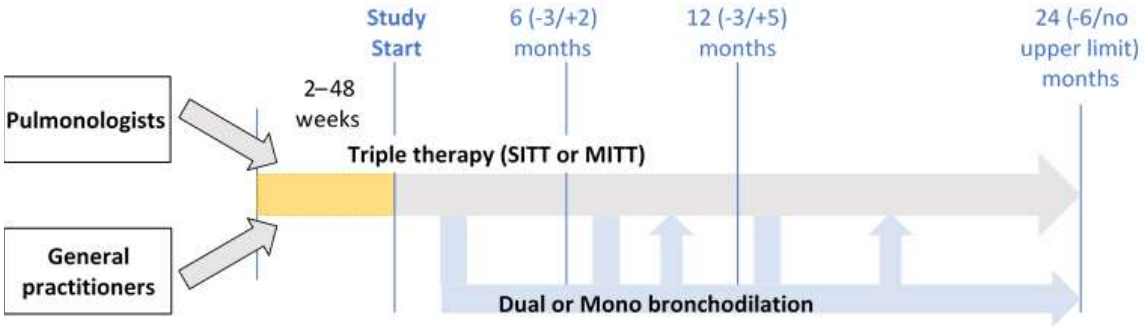
- Cohort A: treatment by settled general practitioners ("GPs", primary care, practitioner / registered doctor)
- Cohort B: treatment by settled pulmonologists ("specialists", primary or secondary care)

The data collection in the study includes two parts:

- Part 1 involves the cross-sectional phenotyping of participating COPD patients at study enrolment (referred to as "visit 1")
- Part 2 involves a two-year longitudinal follow-up period to monitor / document all visits of the study participants during the 24-months observation period. The study assumes that most COPD patients see their doctor every 3 months (at least to get a new prescription). Further data should therefore be provided in the clinical routine after approximately
  - 6 (-3/+2) months (referred to as "visit 2"),
  - 12 (-3/+5) months (referred to as "visit 3")
  - and for the last visit after approximately 24 (-6/no upper limit) months (referred to as "visit 4").

  There should be a minimum interval of 3 months between each of these visits, otherwise the visit is counted as an interim visit.

For each additional patient visit to the treatment centre between study visits 1 and 4, safety data, exacerbations, hospital stays as well as treatment changes and reasons for this are recorded. Patients will participate in the study for approximately two years from enrolment to the last study contact (visit 4).



5. SOPs/Manuals/further Working Instructions

5.1 Relevant SOPs/Manuals/Working Instructions

Document No.	Document Title	Version	Date
STAT-01	Statistical Analyses	8	30-JUN-2021
STAT-02	Quality Assurance Validation of Statistical Analyses	2	30-JUN-2021

5.2 SOP Deviations

N/A

6. General Statistical Considerations

All issues concerning data cleaning, permissible data clarifications, and medical coding will be described in detail in the data management plan. All statistical issues including calculated variables are detailed in this plan. Determination of sample size was detailed in the study protocol.

6.1 General Principles

The statistical evaluation will be performed by using the software package SAS release 9.4.

Descriptive analysis of the data will be performed using summary statistics for categorical and quantitative (continuous) data. Continuous data will be described by the number of non-missing values, median, mean, standard deviation, minimum, and maximum as well as lower and upper quartiles. Frequency tables will be generated for categorical data. Selected continuous variables will be categorized in a clinically meaningful way (see Table 1).

Table 1: Categories for Continuous Variables

Variable	Categories
Age group [years]	18-39 / 40-64 / ≥65
EOS group 1 [cells/µl]	<100 / 100 - <200 / 200 - <300 / ≥300
EOS group 2 [cells/µl]	<300 / ≥300
FEV_1/FVC ratio group	<0.7 / ≥0.7
CAT sum score group	≤10 / 11-19 / ≥20
Exacerbation history group	0 / 1 / ≥2 exacerbations
Peripheral blood eosinophil count group at baseline [cells/µl]	<100 / 100 - <300 / ≥300
Time on triple therapy before study start (months)	<3 / 3 - <6 / ≥6

6.2 Handling of Loss to Follow-up and Premature Discontinuation

Participants may be withdrawn from the study if they become pregnant or enrol in another study with treatment intervention. Furthermore, patients may discontinue study participation – with or without formal withdrawal of their informed consent and with or without giving reasons – at any time during the study.

It is essential for the study objectives to obtain as complete follow-up of patients as is possible in a non-interventional study. An example in the patient journey where a patient may get lost to follow-up could be: Patients may move to another outpatient care physician for personal reasons.

A supporting concept with mitigation measures will be provided to avoid loss of patients at the risk points above. The concept provides that physicians as well as patients can refer to a change of doctor via a central homepage. The new supervising physician has the opportunity to also participate in the study. With these measures we expect to be able to reduce the dropout rate to 5-10%.

Patients discontinuing are asked to consent to a final data collection ("early withdrawal observation"). Patients are also asked to consent to the further use of their data collected until study discontinuation, and this decision is documented. If patients do not consent to the further use of their data, these data will be deleted or used only in anonymized form conforming to data protection regulations (General Data Protection Regulation of the European Union and related German law on data protection).

The number of dropouts will be analysed descriptively and their impact on the primary endpoint will be investigated.

6.3 Handling of Missing Data

Analyses will be based on available data. Missing data will not be imputed and will be displayed as a separate category.

If a variable is completely or systematically missing, it is excluded from the analyses. If a variable is missing for only some of the patients or arbitrarily missing, a missing data category will be added and used in the analyses. However, in case of a considerable amount of missing data (1/3 or more) for one variable, the impact of this missing data will be investigated by conducting the analysis without the corresponding variable – as a sensitivity analysis. If a variable is missing but equivalent information can be inferred using available variables, the corresponding information will be used instead.

6.4 Interim Analysis and Data Monitoring

Two interim analyses are planned:

- The first interim analysis is intended to collect and analyse cross-sectional data / baseline characteristics and is planned after at least 825 patients (~75%) of the total study population have been recruited; in this analysis, only baseline characteristics and safety results will be presented.
- The second interim analysis is intended to include 6 and 12 months data for a subset of the study population and is planned after full recruitment or after 2 years from study start, whatever occurs earlier.

The final analysis will be performed after a 24-month follow-up from study enrolment for all patients.

6.5 Data Rules

Concerning time-windows for month 6, month 12 and month 24, a check is implemented within the EDC system. Relevant data for all other time points in between can be documented in the section for cross-visit information of the EDC system.

Adverse events / drug reactions are coded on a regular basis using the current version of MedDRA.

Current COPD triple therapy is coded on a regular basis using the current version of WHO drug dictionary (only tradenames).

No coding is necessary for the parameters "other COPD pre-treatment" and "respiratory concomitant medication, other substance classes".

6.6 Definition of Derived Variables

Variable	Definition
Duration of participation in a DMP [months]	Round ((Date of visit 1 – Date of start of participation) / (365 / 12))
Duration since diagnosis of COPD [months]	Round ((Date of visit 1 – Date of diagnosis of COPD) / (365 / 12))
EQ-5D-5L total score	See Appendix "EQ-5D_German Value Set"
Usage of ICS for COPD therapy	If last pretreatment before start of triple therapy = ICS/LABA then usage of ICS for COPD therapy = yes
Duration of previous triple therapy [days]	Stop date of previous therapy – Start date of previous therapy
Eosinophil (value in unit "/nl")	If unit = "/µl" then (value = value / 1000 and unit = "/nl")
Leucocytes (value in unit "/nl")	If unit = "/µl" then (value = value / 1000 and unit = "/nl")
Time between initial visit and follow-up visits [days]	Date of follow-up visit – Date of initial visit
Number of changes of COPD therapy	Every start or stop date of a COPD therapy after initial visit is counted as change
Duration until changes of COPD therapy	Start date of current therapy – Start date of previous therapy
FEV_1/FVC ratio	FEV_1 [l] / FVC [l]
Average number of hospitalizations per year during previous triple therapy	Sum of numbers of hospitalizations / number of documented years

Variable	Definition
Triple therapy once daily vs. twice daily	Manually derived from WHO-DD-Coding of therapy
SITT vs. MITT	Manually derived from WHO-DD-Coding of therapy
Site location north Germany	Bremen, Hamburg, Mecklenburg-Vorpommern, Niedersachsen, Schleswig-Holstein
Site location south Germany	Bayern. Baden Württemberg
Site location east Germany	Brandenburg, Berlin, Sachsen, Sachsen-Anhalt, Thüringen
Site location west Germany	Nordrhein-Westfalen, Hessen, Rheinland-Pfalz, Saarland
Number of hospitalizations due to exacerbation	Only "yes" is counted, "unknown" is treated as "no"
Annual rates	(Number of events / days of observation)*365
Clinically important deterioration	Deterioration, if at least one of the following conditions exists at any point of time during the observational period: ▪ Decrease (≥100 mL) of FEV_1 from baseline (missings are treated as no decrease) ▪ Increase (>2 units) of CAT from baseline (missings are treated as no increase) ▪ Any documented exacerbation ▪ All cause mortality
Stop date of previous COPD therapy (current COPD therapy) = start date of subsequent COPD therapy (current COPD therapy)	Set stop date of previous COPD therapy = stop date – 1
Stop date of previous COPD therapy (first use of triple COPD therapy) = date of visit 1 and date of first current triple COPD therapy = date of visit 1 + 1	Consider start date of first current triple COPD therapy within a 5 days range as triple therapy at baseline
Incomplete date of exacerbation (missing day), but month and year indicates date after V1	Set day = 1
Exacerbation was indicated as "Exacerbation since start of current triple therapy", but date of exacerbation is before V1	Set source as exacerbation during the last 3 years before start of current triple therapy
Incomplete end date of fatal adverse event (missing day)	Set day = day of date of discontinuation if month and year of end date of fatal adverse event = month and year of date of discontinuation

Calculation of number needed to treat (NNT) / number needed to harm (NNH):

Both parameters are calculated for the data of the individual first 365 days of observation per patient. For this calculation the first occurrence of exacerbation, pneumonia and cardiovascular events are taken into account.

Five patient groups are analysed:

- SITT versus not SITT – a patient is classified as SITT, if the treatment is SITT continuously for the first 365 days of observation
- MITT versus not MITT – a patient is classified as MITT, if the treatment is MITT continuously for the first 365 days of observation
- De-escalation versus no de-escalation – a patient is classified as de-escalation, if there is at least one change from triple therapy to a therapy with just two components within the first 365 days of observation
- Switch versus no switch – a patient is classified as switch, if there is no de-escalation of therapy, but at least one switch between SITT and MITT within the first 365 days of observation
- Triple therapies interrupted by ICS and/or LAMA "off/on" periods vs other within the first 365 days of observation

The calculation of NNT and NNH is based on Kaplan-Meier analyses: for each of the five groups a survival analysis is performed. For four time points (3, 6, 9 and 12 months after individual start of observation), the estimated survival probabilities S_a (active treatment group) and S_c (control treatment group) are calculated. The absolute risk reduction (ARR) is defined as $S_a - S_c$. Then, NNT /NNH can be derived as $1/(S_a - S_c)$.

For this estimation, a 95% confidence interval can be calculated: The standard error (SE) of the ARR is $\sqrt{[S_a^2(1-S_a)/n_a + S_c^2(1-S_c)/n_c]}$. Based on this, the confidence interval is ARR +/- 1.96*SE(ARR). From the lower and upper bound (A_l and A_u) of the interval, the confidence interval of NNT/NNH can be derived as $1/ A_l$ to $1/ A_u$.

7. Analysis Sets

This study plans to recruit a population of approximately 1.100 patients with moderate to severe COPD with or without comorbid asthma who have been on triple therapy for at least 2 and for a maximum of 48 weeks.

Participants are only eligible to be included in the TETRIS study if all of the following inclusion criteria apply:

- Male or female participant is at least 18 years of age at the time of signing the informed consent
- Participant is on a single or multiple inhaler triple therapy (SITT or MITT) for treatment of an obstructive respiratory disease for a period of 2 to 48 weeks prior enrolment with a combination of inhaled LAMA, LABA and ICS either on a triple maintenance treatment or an intermediate triple therapy regime (ICS "on/off" or LAMA "on/off")
- Participants are treated according to a physician's diagnosis of COPD (Cohort A) / have a confirmed physician's diagnosis (based on spirometry or body plethysmography) of COPD (Cohort B)
- Participants need to give and be capable of giving signed informed consent (ICF) which includes compliance with the requirements and restrictions listed in the ICF and in this protocol

Participants are ineligible to be included in the study if any of the following criteria apply:

- Participant has a diagnosis of pure asthma, without clinical features of COPD
- Participant has a current diagnosis of lung cancer or lung metastasis
- Participant has a current primary diagnosis of diffuse pan-bronchiolitis, or a primary diagnosis of bronchiectasis or pulmonary fibrosis or cystic fibrosis or other significant respiratory disorders
- Participant is currently enrolled or has participated in a study within the last 90 days before signing of consent involving investigational study treatment intervention. If, while enrolled in the present study, the participant enrols in another study involving investigational study treatment intervention, he/she will be withdrawn from the present study
- Recent (≤3 months) major cardiac or pulmonary event (e.g. myocardial infarction, pulmonary embolism)

7.1 Assignment of Analysis Sets

Final decisions regarding the assignment of patients to analysis sets will be made during the validity review meeting and documented in the validity review report.

The population enrolled in the data analysis will include all participants who sign the ICF and who complete both, inclusion and exclusion criteria and visit 1. This population will be the primary analysis population for all endpoints, including safety data. Therefore, there is no difference between the safety analysis set and the full analysis set.

8. Statistical Methodology

This is a descriptive study which is designed to estimate the primary endpoint with a specific precision. The study is not powered to detect differences and no formal statistical hypothesis testing will be performed for any of the endpoints. Endpoints with continuous measures will be analysed by the number of non-missing values, mean, standard deviation [SD], median, minimum, maximum, as well as lower and upper quartiles and two-sided 95% confidence intervals, discrete and categorical endpoints by frequencies and percentages, and event/survival-endpoints counts will be analysed by providing event rates per participant-year and Kaplan-Meier estimates.

In order to get a more detailed idea of how therapy and outcome parameters develop during the 24-month observation period, the following subgroups will be investigated separately for all analyses concerning the primary and secondary endpoints (see also section 7 of the appendix "TETRIS_SAP_list of planned tables_2024-10-25_Final"):

(1) triple therapy once daily vs. twice daily (sequence during follow-up observation)

(2) SITT vs. MITT (sequence during follow-up observation, based on baseline therapy, population consists only of patients with constant and identical triple therapy during the whole observational period (no change of therapy documented after baseline)

(3) SITT vs. SITT (based on WHO-DD-Coding; sequence during follow-up observation, sequence starting with baseline, sequence consists only of different kinds of SITT)

(4) continuous vs. interrupted triple therapy (follow-up data) ("interrupted" means that at any time there is a double therapy, single therapy or even a break in the therapy data)

(5) physician cohorts (sequence during follow-up observation) (based on baseline status, only two groups "Hausarzt" and "Pneumologe" ("Allgemeinarzt" is classified as "Hausarzt"))

(6) COPD vs. COPD with asthma (baseline data)

Further exploratory subgroups:

(7) by smoking status at baseline (non- vs. current vs. ex-smoker)

(8) by gender

(9) by site location (north/south/east/west Germany, based on baseline status)

(10) by season (based on calendar time, applicable for a few tables, only for patients with exacerbations and hospitalisations)

(11) by MITT vs. 5 specific SITT (Trimbow DPI, Trimbow MDI, Trelegy, Trixeo, Elebrato;
sequence during follow-up observation, sequence starting with baseline, population consists only of patients who are treated continuously with MITT or any kind of SITT (changes between these treatments are allowed))
(12) by SITT DPI (Trimbow DPI, Trelegy, Elebrato) versus SITT MDI (Trimbow MDI, Trixeo);
sequence during follow-up observation, sequence starting with baseline, population consists only of patients who are continuously on (any kind of, changes are allowed) SITT therapy

(13) by GOLD severity at baseline, only GOLD 1-4 (not GOLD A-D)

(14) by DMP or non-DMP at baseline

If a subgroup of one of these strata consists of less than 5% of the total number of patients, this subgroup will not be presented in the statistical analyses.

According to the descriptive study design all endpoints will be analysed descriptively.

8.1 Primary Outcome Variables

Objective	Endpoints
Evaluate the percentage of patients who continuously receive triple therapy	• Patients who continuously receive triple therapy for 6, 12 and 24 months (including stratification by SITT vs. MITT), or more detailed: 1. Patients with continuously received triple therapy during the study of (at least) 24 month 2. Patients with continuously received triple therapy during the study of (at least) 12 month 3. Patients with continuously received triple therapy during the study of (at least) 6 month • Time to stop triple therapy

8.2 Secondary Outcome Variables

Objective	Endpoints
Describe profiles of COPD patients who initiated or are on triple therapy (LAMA/LABA/ICS) in Germany	Patient and disease characteristics when initiating triple therapy: • Percentage of COPD patients with diagnosis of asthma at the age of <40 years • Percentage of patients with peripheral blood EOS of <100 cells/µl, 100-200 cells/µl, 200-300 cells/µl and > 300 cells/µl • Percentage of participants with a physician's diagnosis of COPD by site localization and physician´s group • Percentage of participants with different symptom and risk classes (GOLD) • Medications received by COPD patients (including OCS), split by physician group and site localization • Time on triple therapy before study start (<3 months / 3 - <6 months / >=6 months)
Describe the distribution and frequency of combined treatable traits in COPD patients	• Percentage of patients presenting with a smoking history (when initiating triple therapy and at different time points during a 24-month observation period) • Percentage of patients with a non-smoking history when initiating triple therapy • Percentage of patients with a FEV1/FVC ratio <0.7 at study enrolment and at a 6, 12 and 24 months documentation • Percentage of patients with any moderate/severe exacerbation in the 24 months prior to study enrolment or 3 months prior to

	each subsequent on-study visit during a 24-month observation period • Percentage of patients with a CAT score ≤10 / 11-19 / ≥20 at baseline and at a 6, 12 and 24 months documentation • Percentage of patients with peripheral blood eosinophil (EOS) count ≥100 cells/µl at baseline and at a 6, 12 and 24 months documentation • Percentage of patients with chronic bronchitis phenotype
Describe the percentage of participants with at least one switch from triple therapy to LAMA/LABA or to ICS/LABA after 6, 12 and 24 months	• Patients with at least one switch from triple therapy to LAMA/LABA after 6, 12 and 24 months • Patients with at least one switch from triple therapy to ICS/LABA after 6, 12 and 24 months
Describe COPD treatment decisions of German physicians who have initiated patients on triple therapy	• Distribution (by physician group) and frequency of prespecified reasons to initiate triple therapy (either MITT or SITT) • Percentage of patients changing from triple to dual therapy and back to triple therapy (re-escalation) during a 24-month observation period after study enrolment (split by SITT and MITT and split by LAMA/LABA and ICS/LABA) • Percentage of patients with at least one re-escalation from LAMA/LABA or ICS/LABA or LAMA to triple therapy during the 24-month observation period • Percentage of patients with at least one change from MITT to SITT or SITT to MITT during a 24-month observation period • Percentage of patients with at least one change from SITT to SITT or MITT to MITT during a 24-month observation period • Percentage of patients changing from once daily to twice daily medication or vice versa or between different inhaler types • Percentage of patients changing between different inhaler types • Distribution (by physician group) and frequency of prespecified reasons to change a triple therapy (either MITT or SITT) • Distribution and frequency of prespecified reasons to change triple therapy to another triple therapy • Distribution and frequency of prespecified reasons to change triple therapy to therapy de-escalation • Distribution and frequency of prespecified reasons to change de-escalated therapy back to triple therapy (re-escalation)
Describe clinical outcomes in COPD patients initiated on triple therapy	• Mean annual rate of moderate and/or severe exacerbations over a 24-month observation period (including subgroup analysis by peripheral blood eosinophil count, smoking status and asthma history) • Mean annual rate of hospitalizations due to severe exacerbations • Change of lung function parameters during a 24-month observation period (including subgroup analysis by peripheral blood eosinophil count, smoking status and asthma history)

	• Change of COPD symptoms during a 24-month observation period • Change in HRQoL during a 24-month observation period • Percentage of COPD patients experiencing a clinically important deterioration during a 24-month observation period • Time to first moderate or severe exacerbation during a 24-month observation period • Time to first hospitalization during a 24-month observation period • Time to death during a 24-months observation period
Describe safety with triple therapy	• Safety with focus on pneumonia and cardiovascular events • Benefit-harm profiles for single-inhaler triple therapies (SITTs, including Trelegy, Trimbow and Breztri) • Benefit-harm profiles for major multiple inhaler triple therapy (MITT) combinations • Benefit-harm profiles for triple therapies interrupted by ICS and/or LAMA "off/on" periods • Benefit-harm profiles for triple therapies switching between SITT and MITT

8.3 Additional Analysis

The following additional analyses will be performed:

Composite endpoint 1a:

- Number and proportion of patients after 12/24 months on Trelegy and Elebrato, who meet the following criteria:
    - Are exacerbation free for at least 12/24 consecutive months
    - Are OCS free for at least 12/24 consecutive months
    - CAT ≤ 20 for at least 12/24 consecutive months
    - Change from baseline in FEV1 ≥ 0mL for at least 12/24 consecutive months

a. Analyze them as individual components (ie with an OR between each) and as a set (ie with AND between each = composite).

b. Sensitivity of the above with 6 months data, and 6 consecutive months.

- Comprehensive review of the patient characteristics at baseline and at each of 6-12-24 months, by the response category of the composite, ~~subdivided by brand~~
    - Include also the following: mean CAT/EQ5D score, time meeting composite measure
    - Test of correlation between CAT/EQ5D and the response category at 12 months and 24 months

- Durability: the proportion of patients who meet the composite at 12 months and who go on to meet it also at 24 months
    - Sensitivity – redo the above with patients who meet it at 6 months who go on to meet it at 12 months and also 24 months.

Characteristics of these patients, including CAT/EQ5D scores, exacerbation history, age, sex, etc.

Composite endpoint 1b:
This composite includes the same parameters as composite 1 but excluding OCS free. The same analyses will be performed as for composite 1a.

Composite endpoint 2:

The below individual components and a composite of them have to be investigated:

- No decline in Trough FEV1

No decline is defined as a change from baseline in trough FEV1 of >=0mL. Decline is defined as a change from baseline in trough FEV1 of <0mL or a missing trough FEV1 with no subsequent non-missing on-treatment trough FEV1 assessments. Subjects will not have a decline status derived if baseline trough FEV1 is missing. Subjects will not have a decline status derived at a particular visit where the trough FEV1 value is missing but subsequent on-treatment trough FEV1 assessments are present.

- No decline in CAT

No decline is defined as a change from baseline in CAT score of <=0 units. Decline is defined as a change from baseline in CAT score >0 units or a missing CAT score with no subsequent on-treatment scores. Subjects will not have a decline status derived if baseline CAT score is missing. Subjects will not have a decline status derived at a particular visit where the CAT score is missing but subsequent on-treatment CAT scores are present.

- No moderate/severe Exacerbation up until the timepoint of interest

For the composite - No decline is defined as a no decline in Trough FEV1, no decline in CAT Score, and no moderate/severe exacerbation up to visit of interest. Decline is defined as a decline in at least one of the components. Otherwise the decline status is missing.

CAT Responder by visit (6 month, 12 month, 24 month)

A CAT responder is a subject with a change in Cats core ≤-2.
A CAT non-Responder is a subject with a change in CAT score >-2.
Subjects will not have a response status derived, if baseline CAT score is missing. Subjects will not have a response status derived at a particular visit where the CAT score is missing, but subsequent on-treatment CAT scores are present.

Responder analysis will be performed for all FAS patients.

8.4 Safety Analysis

Safety analysis is part of the secondary outcomes, see above.

8.5 Confounder or bias adjusted Analyses

N/A

8.6 Analysis of Representativeness

N/A

8.7 Additional Analyses planned to be reported outside the Study Report

N/A

9. Appendices

Appendix	Document
List of planned tables	TETRIS_SAP_list of planned tables_2024-10-25_Final
Analysis instruction for EQ-5D questionnaire	EQ-5D_German Value Set
Publication "Calculating the number needed to treat for trials where the outcome is time to an event"	Altmann BMJ 1999; 319 NNT for time to event

1. Inclusion and exclusion criteria

Table Inclusion and exclusion criteria (all documented patients)

Table COPD with or without asthma

2. Baseline data

2.1 Demographics

Table Age [years]

Table Gender

Table Height [cm]

Table Weight [kg]

Table Smoking status

Table Duration of smoking [years] (only current smokers)

Table Number of cigarettes per day (only current smokers)

Table Package years (only current smokers)

Table Package years (only previous smokers)

Table Educational level

Table Living situation

Table Health insurance (multiple answers possible)

Table Participation in a DMP

Table Kind of DMP (listing, only patients with participation)

Table Duration of participation [months] (only patients with participation)

Table Only treating pneumologist

Table Number of further treating physicians (only patients with further treating physicians)

Table Kind of other specialists (multiple answers possible, only patients with further treating physicians)

2.2 Medical history

Table Medical history (multiple answers possible)

Table Medical history treated with systemic/oral corticosteroid (multiple answers possible)

Table Medical history considered for decision for triple therapy (multiple answers possible)

Table Chronic bronchitis currently diagnosed

Table Treatment-requiring asthma at any time before inclusion in study (only patients without current asthma)

2.3 COPD anamnesis

Table Duration since diagnosis of COPD [months]

Table ICD-10 classification of COPD

2.4 COPD status

Table Symptom and risk class (GOLD A-D)

Table Symptom and risk class (GOLD 1-4)

Table CAT done (yes/no)

Table CAT sum score

Table EQ-5D-5L/VAS done (yes/no)

Table EQ-5D-5L mobility

Table EQ-5D-5L self-care

Table EQ-5D-5L usual activities

Table EQ-5D-5L pain/discomfort

Table EQ-5D-5L anxiety/depression

Table EQ-5D-5L total score

Table EQ-5D-VAS

2.5 Exacerbations

Table Number of exacerbations in the last 3 years before start of current triple therapy

Table Number of hospitalizations due to exacerbation in the last 3 years before start of current triple therapy

Table Number of exacerbations since start of current triple therapy

Table Number of hospitalizations due to exacerbation since start of current triple therapy

2.6 COPD pretreatment

Table Last pretreatment before start of triple therapy (LAMA / ICS/LABA / LABA/LAMA / other)

Table One or two inhalers (only patients with ICS/LABA combination)

Table Kind of inhalers (only patients with ICS/LABA combination)

Table One or two inhalers (only patients with LABA/LAMA combination)

Table Kind of inhalers (only patients with LABA/LAMA combination)

Table Kind of other therapy (only patients with other therapy)

Table Usage of ICS for COPD therapy before start of triple therapy

2.7 Current COPD triple therapy

Table Reasons for start of COPD triple therapy (multiple answers possible) -overall and by physician group)

Table Reasons – source for worsening of quality of life and/or lung function (multiple answers possible, only patients with worsening)

Table Reasons – number of exacerbations (only patients with exacerbations)

Table Reasons – number of months with exacerbations (only patients with exacerbations)

Table Reasons – specification of other

Table Current COPD triple therapy (combination of trade names)

Table Dosage form (single inhalator / combination, therapy-based analysis)

Table Dosage form (powder / aerosol, therapy-based analysis)

Table First usage of triple therapy

Table Duration of previous triple therapy [days] (only patients with previous triple therapy)

Table Type of previous triple therapy (SITT / MITT, only patients with previous triple therapy)

2.8 Concomitant respiratory medication

Table Concomitant respiratory medication (no/yes)

Table Substance class of concomitant respiratory medication (multiple answers possible, only patients with concomitant respiratory medication)

Table Oral glucocorticosteroids – reason (multiple answers possible, only patients with oral glucocorticosteroids)

Table Oral glucocorticosteroids because of exacerbations – specification (only patients with oral glucocorticosteroids because of exacerbations)

Table Respiratory antibiotics – reason (multiple answers possible, only patients with respiratory antibiotics)

Table Respiratory antibiotics because of exacerbations – specification (only patients with respiratory antibiotics because of exacerbations)

Table Other cardiac or respiratory substances – specification (substance-based analysis)

2.9 Hospitalizations

Table Number of hospitalizations per patient since start of current triple therapy
Table Duration of hospitalizations (based on total hospitalizations) Strata: (2)
Table Reasons for hospitalizations (multiple answers possible, based on total hospitalizations)
Table Switch of COPD therapy due to hospitalization (based on total hospitalizations)
Table Previous triple therapy (no/yes/unknown)
Table Hospitalizations during previous triple therapy (no/yes/unknown, only patients with previous triple therapy)
Table Average number of hospitalizations per year during previous triple therapy

2.10 Diagnostic measures

Table Diagnostic measures (multiple answers possible)
Table Lung functional parameters – BD (only patients with lung functional parameters)
Table Lung functional parameters – FEV_1 [l / %] (only patients with lung functional parameters)
Table Lung functional parameters – FVC [l / %] (only patients with lung functional parameters)
Table Thorax CT – results (multiple answers possible, only patients with lung functional parameters)
Table DLCO [mmol/min/kPa / %] (only patients with DLCO)
Table hsCRP [mg/l] (only patients with hsCRP)
Table Blood count – eosinophil [% / /nl] (only patients with blood count)
Table Blood count – leucocytes [/nl] (only patients with blood count)
Table FeNO [ppb] (only patients with FeNO)

3. Follow-up visits

Table Kind of visit (on-site vs. remote) (all visits)
Table Time between initial visit and follow-up visits [days]
Table Number of visits between current documentation and last documented visit (visit 2-4)

3.1 Demographics

Table Weight [kg] per visit and change since initial visit (all visits)
Table Change of smoking status (no/yes, visit 2-4)
Table New smoking status (visit 2-4, only patients with change of smoking status)
Table Duration of smoking [years] (visit 2-4, only patients with change to current smoker)
Table Number of cigarettes per day (visit 2-4, only patients with change to current smoker)
Table Package years (visit 2-4, only patients with change to current smoker)
Table Package years (visit 2-4, only patients with change to previous smoker)

3.2 COPD status

Table Change in symptoms since last visit (visit 2-4)
Table Change in symptom and risk class (yes/no/not assessed, visit 2-4)
Table New symptom and risk class vs. previous symptom and risk class (GOLD A-D, separate cross table for visit 2-4, only patients with change in symptom and risk class)
Table New symptom and risk class vs. previous symptom and risk class (GOLD 1-4, separate cross table for visit 2-4, only patients with change in symptom and risk class)
Table Change in CAT (yes/no/not assessed)

Table CAT sum score per visit and change since initial visit (visit 2-4, only patients with change in CAT)
Table EQ-5D-5L/VAS done (yes/no, visit 2-4)
Table EQ-5D-VAS per visit and change since initial visit (visit 2-4, only patients with new EQ-5D-VAS)
Table EQ-5D-5L mobility (visit 3)
Table EQ-5D-5L mobility (visit 4)
Table EQ-5D-5L self-care (visit 3)
Table EQ-5D-5L self-care (visit 4)
Table EQ-5D-5L usual activities (visit 3)
Table EQ-5D-5L usual activities (visit 4)
Table EQ-5D-5L pain/discomfort (visit 3)
Table EQ-5D-5L pain/discomfort (visit 4)
Table EQ-5D-5L anxiety/depression (visit 3)
Table EQ-5D-5L anxiety/depression (visit 4)
Table EQ-5D-5L total score at visit 3 and change since initial visit (only patients with EQ-5D-5L at visit 3)
Table EQ-5D-5L total score at visit 4 and change since initial visit (only patients with EQ-5D-5L at visit 4)

3.3 Current COPD therapy

Table Change of COPD therapy (visit 2-4)
Table Reasons for change of COPD therapy (visit 2-4, only patients with change of COPD therapy, no tabulation of documented number of exacerbations)
Table Frequency of pre-specified reasons to change a triple therapy (either MITT or SITT) overall and by physician group

3.4 Exacerbations

Table Number of exacerbations since last visit (visit 2-4)
Table Number of hospitalizations due to exacerbation since last visit (visit 2-4)

3.5 Hospitalizations

Table Number of hospitalizations per patient since last visit (visit 2-4)
Table Duration of hospitalizations since last visit (based on total hospitalizations)
Table Reasons for hospitalizations since last visit (multiple answers possible, based on total hospitalizations)
Table Switch of COPD therapy due to hospitalization since last visit (based on total hospitalizations)

3.6 Diagnostic measures

Table Diagnostic measures (multiple answers possible, visit 2-4)
Table Lung functional parameters – BD (only patients with lung functional parameters, visit 2-4)
Table Lung functional parameters – FEV_1 [l / %] (only patients with lung functional parameters, visit 2-4)
Table Lung functional parameters – FVC [l / %] (only patients with lung functional parameters, visit 2-4)
Table Thorax CT – results (multiple answers possible, only patients with lung functional parameters, visit 2-4)
Table DLCO [mmol/min/kPa / %] (only patients with DLCO, visit 2-4)
Table hsCRP [mg/l] (only patients with hsCRP, visit 2-4)

Table Blood count – eosinophil [% / /nl] (only patients with blood count, visit 2-4)

Table Blood count – leucocytes [/nl] (only patients with blood count, visit 2-4)

Table FeNO [ppb] (only patients with FeNO, visit 2-4)

4. Cross visit data

4.1 Current COPD therapy

Table Number of changes of COPD therapy

Table Duration until changes of COPD therapy

Table New COPD therapy after 1st, 2nd, 3rd … change (combination of trade names)

Table Dosage form after 1st, 2nd, 3rd … change (single inhalator / combination, therapy-based analysis)

Table Dosage form after 1st, 2nd, 3rd … change (powder / aerosol, therapy-based analysis)

4.2 Concomitant respiratory medication

Table Substance class of concomitant respiratory medication (multiple answers possible, only patients with any concomitant respiratory medication within their observational period)

Table Oral glucocorticosteroids – reason (multiple answers possible, only patients with any oral glucocorticosteroids within their observational period)

Table Oral glucocorticosteroids because of exacerbations – specification (only patients with any oral glucocorticosteroids because of exacerbations within their observational period)

Table Respiratory antibiotics – reason (multiple answers possible, only patients with any respiratory antibiotics within their observational period)

Table Respiratory antibiotics because of exacerbations – specification (only patients with any respiratory antibiotics because of exacerbations within their observational period)

Table Other cardiac or respiratory substances – specification

5. Premature discontinuation

Table Number of patients with premature discontinuation

Table Reasons for premature discontinuation (multiple answers possible, only patients with premature discontinuation)

Table Agreement with further use of data (only patients with withdrawal of informed consent)

Table Number of exacerbations since last visit (only patients with premature discontinuation)

Table Number of hospitalizations due to exacerbation since last visit (only patients with premature discontinuation)

Table Number of hospitalizations per patient since last visit (only patients with premature discontinuation)

Table Duration of hospitalizations since last visit (based on total hospitalizations, only patients with premature discontinuation)

Table Reasons for hospitalizations since last visit (multiple answers possible, based on total hospitalizations, only patients with premature discontinuation)

Table Switch of COPD therapy due to hospitalization since last visit (based on total hospitalizations, only patients with premature discontinuation)

6. Adverse drug reactions / serious adverse events

Table Number of AEs / ADRs / SAEs /SADRs (event based)

Table Number of patients with AEs / ADRs / SAEs /SADRs (patient based)

Table Characteristics of non-serious ADRs (relation to GSK product, relation to non-GSK product, outcome, action taken, discontinuation from the study, intensity / event-based analysis)

Table Non-serious ADRs (MedDRA SOC & PT)

Table Characteristics of SAEs without relation to study medication (reason for seriousness, possible cause in case of non-related SAEs, outcome, action taken, discontinuation from the study, intensity / event-based analysis)

Table SAEs without relation to study medication (MedDRA SOC & PT)

Table Characteristics of SADRs (reason for seriousness, relation to GSK product, relation to non-GSK product, outcome, action taken, discontinuation from the study, intensity / event-based analysis)

Table SADRs (MedDRA SOC & PT)

Table Listing of non-serious ADRs

Table Listing of SAEs without relation to study medication

Table Listing of SAEs with relation to study medication

7. Primary and secondary outcomes

7.1 Primary Outcomes

Table Continuous triple therapy for 6, 12 and 24 months

Table Time to stop of triple therapy (Kaplan-Maier analysis)

7.2 Secondary Outcomes

Table Diagnosis of asthma and age <40 years at time of initial visit

Table Peripheral blood EOS (group 1) at time of initial visit

Table Site localization of physician

Table Physician cohort

Table Symptom and risk class (GOLD)

Table Substance class of concomitant respiratory medication (multiple answers possible) by physician group and site localization

Table Time on triple therapy before study start

Table Change of smoking status (cross table, visit 1 versus visit 2-4)

Table FEV1/FVC ratio (group, visit 1-4)

Table Any moderate/severe exacerbation in the 24 months prior to study enrolment or 3 months prior to each subsequent on-study visit during a 24-month observation period

Table CAT sum score (group, visit 1-4)

Table Peripheral blood EOS (group 2, visit 1-4)

Table Chronic bronchitis phenotype

Table At least one switch from triple therapy to LAMA/LABA (visit 2-4)

Table At least one switch from triple therapy to ICS/LABA (visit 2-4)

Table At least one re-escalation (change from triple to dual therapy (LAMA/LABA or ICS/LABA), and back to triple therapy) split by LAMA/LABA and ICS/LABA

Table At least one re-escalation (change from triple (SITT, MITT) and back to triple therapy) split by SITT/MITT

Table At least one escalation beyond triple therapy with oral glucocorticosteroids

Table At least one escalation beyond triple therapy with LTRA

Table At least one escalation beyond triple therapy with intravenous systemic steroids

Table At least one escalation beyond triple therapy with oral betamimetica

Table At least one escalation beyond triple therapy with immune therapy

Table At least one escalation beyond triple therapy with respiratory antibiotics

Table At least one escalation beyond triple therapy with other cardiac or respiratory substances

Table At least one change from MITT to SITT or from SITT to MITT

Table At least one change from SITT to SITT or from MITT to MITT

Table	At least one change from once daily to twice daily or from twice daily to once daily or between different inhaler types
Table	At least one change between different inhaler types
Table	Reasons for change a triple therapy (either MITT or SITT)
Table	Reasons for change from triple therapy to another triple therapy
Table	Reasons for change from triple therapy to therapy de-escalation
Table	Reasons for change from de-escalated therapy back to triple therapy
Table	Mean annual rate of moderate and/or severe exacerbations over a 24-month observation period – overall and by peripheral blood eosinophil count, smoking status and asthma history
Table	Mean annual rate of hospitalizations due to severe exacerbations
Table	Change of FEV1 [l / %] (visit 1 versus visit 2-4) – overall and by peripheral blood eosinophil count, smoking status and asthma history
Table	Change of FVC [l / %] (visit 1 versus visit 2-4) -– overall and by peripheral blood eosinophil count, smoking status and asthma history
Table	Change of FEV1/FVC ratio (visit 1 versus visit 2-4) – overall and by peripheral blood eosinophil count, smoking status and asthma history
Table	Change of symptom and risk class (GOLD A-D, cross table, visit 1 versus visit 2-4)
Table	Change of symptom and risk class (GOLD 1-4, cross table, visit 1 versus visit 2-4)
Table	Change in CAT sum score (visit 1 versus visit 2-4)
Table	Change in EQ-5D-5L total score (visit 1 versus visit 3-4)
Table	Change in EQ-5D-VAS (visit 1 versus visit 2-4)
Table	Clinically important deterioration
Table	Time to first moderate or severe exacerbation (Kaplan-Maier analysis)
Table	Time to first hospitalization / hospitalization (Kaplan-Maier analysis)
Table	Time to death (SAE: date of death / Kaplan-Maier analysis)
Table	Safety with focus on pneumonia and cardiovascular events (MedDRA, number of events in observational period)
Table	Number needed to treat/harm (exacerbations, SITT versus not SITT)
Table	Number needed to treat/harm (pneumonia, SITT versus not SITT)
Table	Number needed to treat/harm (cardiovascular events, SITT versus not SITT)
Table	Number needed to treat/harm (exacerbations, MITT versus not MITT)
Table	Number needed to treat/harm (pneumonia, MITT versus not MITT)
Table	Number needed to treat/harm (cardiovascular events, MITT versus not MITT)
Table	Number needed to treat/harm (exacerbations, de-escalation versus no de-escalation)
Table	Number needed to treat/harm (pneumonia, de-escalation versus no de-escalation)
Table	Number needed to treat/harm (cardiovascular events, de-escalation versus no de-escalation)
Table	Number needed to treat/harm (exacerbations, switch versus no switch)
Table	Number needed to treat/harm (pneumonia, switch versus no switch)
Table	Number needed to treat/harm (cardiovascular events, switch versus no switch)
Table	Number needed to treat/harm (exacerbations, triple therapies interrupted by ICS and/or LAMA “off/on” periods vs other)
Table	Number needed to treat/harm (pneumonia, triple therapies interrupted by ICS and/or LAMA “off/on” periods vs other)
Table	Number needed to treat/harm (cardiovascular events, triple therapies interrupted by ICS and/or LAMA “off/on” periods vs other)

7.3 Additional analyses

7.3.1 Composite endpoint 1a - exacerbation free, OCS free, CAT<=20 , FEV1 change from baseline >=0 ml for at least 12 month

Table Number and proportion of patients exacerbation free, OCS free, CAT<=20, FEV1 change from baseline after 6, 9, 12 and 24 months

Table Number and proportion of patients reaching composite endpoint 1 (exacerbation free, OCS free, CAT<=20, FEV1 change from baseline - OR condition) after 12 months

Table Number and proportion of patients reaching composite endpoint 1 (exacerbation free, OCS free, CAT<=20, FEV1 change from baseline - AND condition) after 12 months

Table Number and proportion of patients reaching composite endpoint 1 (exacerbation free, OCS free, CAT<=20, FEV1 change from baseline - OR condition) after 24 months

Table Number and proportion of patients reaching composite endpoint 1 (exacerbation free, OCS free, CAT<=20, FEV1 change from baseline - AND condition) after 24 months

Table Number and proportion of patients reaching composite endpoint 1 (exacerbation free, OCS free, CAT<=20, FEV1 change from baseline - OR condition) after 6 months - sensitivity analysis

Table Number and proportion of patients reaching composite endpoint 1 (exacerbation free, OCS free, CAT<=20, FEV1 change from baseline - AND condition) after 6 months - sensitivity analysis

Table Patient characteristics at baseline, 6,12 and 24 months by response of composite endpoint 1 (OR condition) - 12 month data

Table Patient characteristics at baseline, 6,12 and 24 months by response of composite endpoint 1 (AND condition) - 12 month data

Table Patient characteristics at baseline, 6,12 and 24 months by response of composite endpoint 1 (OR condition) - 24 month data

Table Patient characteristics at baseline, 6,12 and 24 months by response of composite endpoint 1 (AND condition) - 24 month data

Table Correlation between OCS free, CAT<=20 and response category of composite endpoint 1 (exacerbation free, OCS free, CAT<=20, FEV1 change from baseline - OR condition) - 12 month data

Table Correlation between OCS free, CAT<=20 and response category of composite endpoint 1 (exacerbation free, OCS free, CAT<=20, FEV1 change from baseline - OR condition) - 24 month data

Table Correlation between OCS free, CAT<=20 and response category of composite endpoint 1 (exacerbation free, OCS free, CAT<=20, FEV1 change from baseline - AND condition) - 12 month data

Table Correlation between OCS free, CAT<=20 and response category of composite endpoint 1 (exacerbation free, OCS free, CAT<=20, FEV1 change from baseline - AND condition) - 24 month data

Table Number and proportion of patients who meet the composite endpoint 1 (OR Condition) at 12 months and 24 months

Table Number and proportion of patients who meet the composite endpoint 1 (AND Condition) at 12 months and 24 months

Table Number and proportion of patients who meet the composite endpoint 1 (OR Condition) at 6 month , at 12 months and 24 months - sensitivity analysis

Table Number and proportion of patients who meet the composite endpoint 1 (AND Condition) at 6 month , at 12 months and 24 months - sensitivity analysis

Table Patient characteristics at baseline, 6, 12 and 24 months for patients who meet the composite endpoint 1 (OR condition) at 12 and 24 months

Table Patient characteristics at baseline, 6, 12 and 24 months for patients who meet the composite endpoint 1 (AND condition) at 12 and 24 months

7.3.2 Composite endpoint 1b - exacerbation free, CAT<=20 , FEV1 change from baseline >=0 ml for at least 12 month

Table Number and proportion of patients exacerbation free, CAT<=20, FEV1 change from baseline after 6, 9, 12 and 24 months

Table Number and proportion of patients reaching composite endpoint 1 (exacerbation free, CAT<=20, FEV1 change from baseline - OR condition) after 12 month

Table Number and proportion of patients reaching composite endpoint 1 (exacerbation free, CAT<=20, FEV1 change from baseline - AND condition) after 12 month

Table Number and proportion of patients reaching composite endpoint 1 (exacerbation free, CAT<=20, FEV1 change from baseline - OR condition) after 24 month

Table Number and proportion of patients reaching composite endpoint 1 (exacerbation free, CAT<=20, FEV1 change from baseline - AND condition) after 24 month

Table Number and proportion of patients reaching composite endpoint 1 (exacerbation free, CAT<=20, FEV1 change from baseline - OR condition) after 6 months - sensitivity analysis

Table Number and proportion of patients reaching composite endpoint 1 (exacerbation free, CAT<=20, FEV1 change from baseline - AND condition) after 6 months - sensitivity analysis

Table Patient characteristics at baseline, 6,12 and 24 months by response of composite endpoint 1 (OR condition) - 12 month data

Table Patient characteristics at baseline, 6,12 and 24 months by response of composite endpoint 1 (AND condition) - 12 month data

Table Patient characteristics at baseline, 6,12 and 24 months by response of composite endpoint 1 (OR condition) - 24 month data

Table Patient characteristics at baseline, 6,12 and 24 months by response of composite endpoint 1 (AND condition) - 24 month data

Table Correlation between CAT<=20 and response category of composite endpoint 1 (exacerbation, CAT<=20, FEV1 change from baseline - OR condition) – 12 month data

Table Correlation between CAT<=20 and response category of composite endpoint 1 (exacerbation, CAT<=20, FEV1 change from baseline - OR condition) – 24 month data

Table Correlation between CAT<=20 and response category of composite endpoint 1 (exacerbation, CAT<=20, FEV1 change from baseline - AND condition) – 12 month data

Table Correlation between CAT<=20 and response category of composite endpoint 1 (exacerbation, CAT<=20, FEV1 change from baseline - AND condition) – 24 month data

Table Number and proportion of patients who meet the composite endpoint 1 (OR Condition) at 6, 12 and 24 months - sensitivity analysis

Table Number and proportion of patients who meet the composite endpoint 1 (AND Condition) at 6, 12 and 24 months - sensitivity analysis

Table Patient characteristics at baseline, 6, 12 and 24 months for patients who meet the composite endpoint 1 (OR condition) at 12 and 24 month

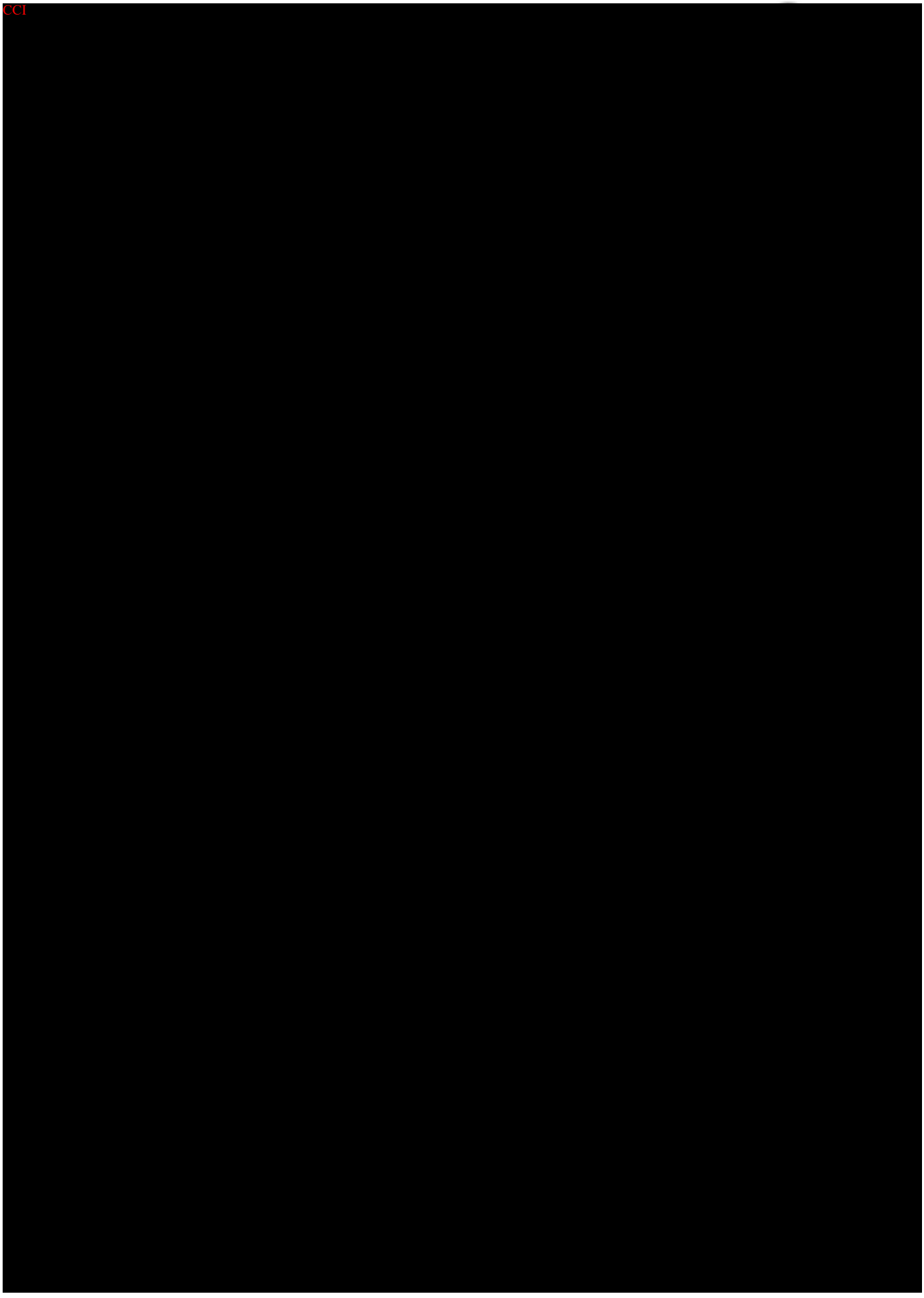
Table Patient characteristics at baseline, 6, 12 and 24 months for patients who meet the composite endpoint 1 (AND condition) at 12 and 24 month

7.3.3 Composite endpoint 2 - decline in FEV1, CAT score, exacerbations

Table Number of patients and proportions of response categories for composite endpoint 2 - overall and stratified by individual components

7.3.4 CAT response

Table Number and proportion of CAT responders (yes (<=-2)/no (>-2)) by visit (6 month, 12 month, 24 month)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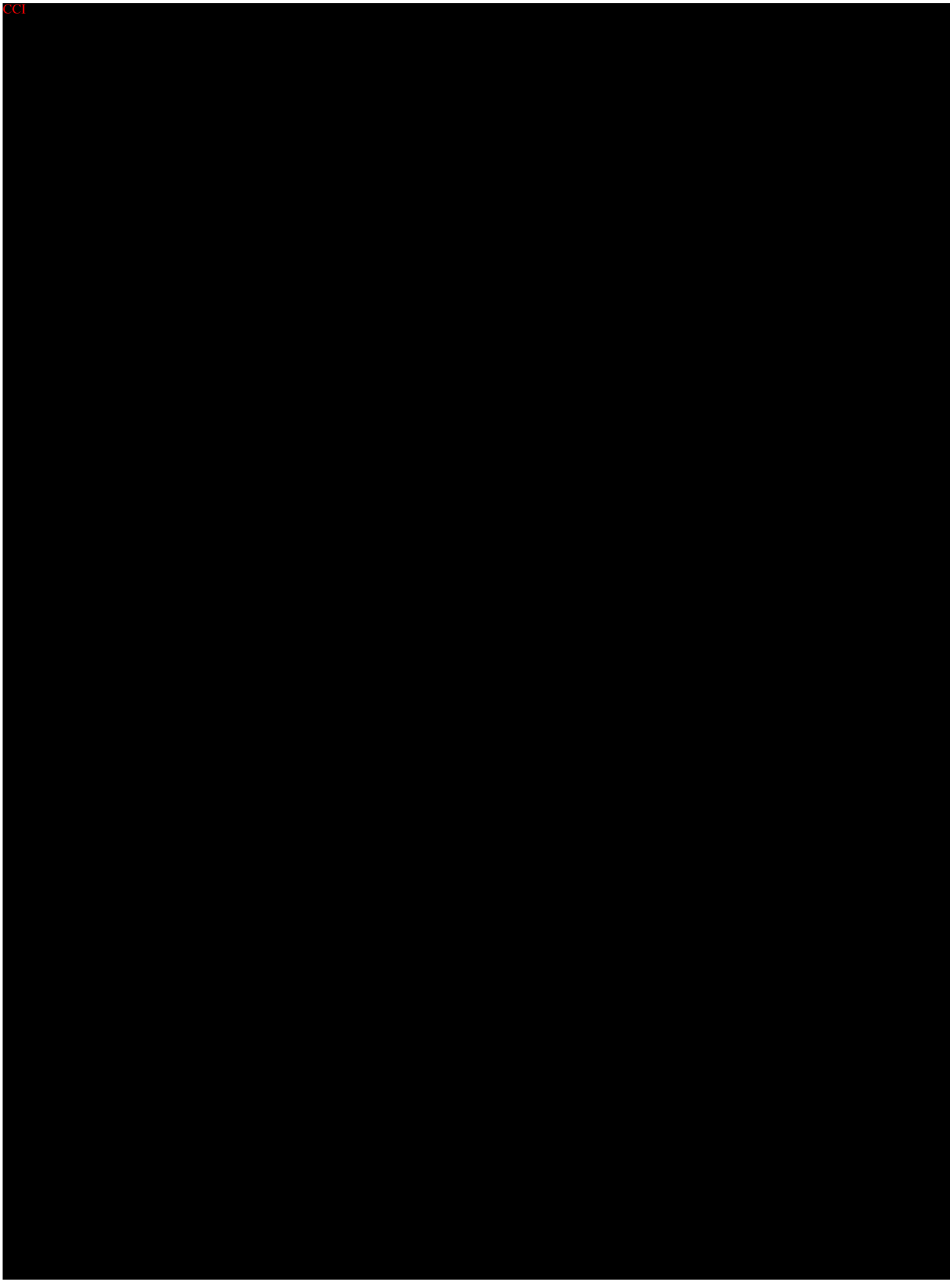

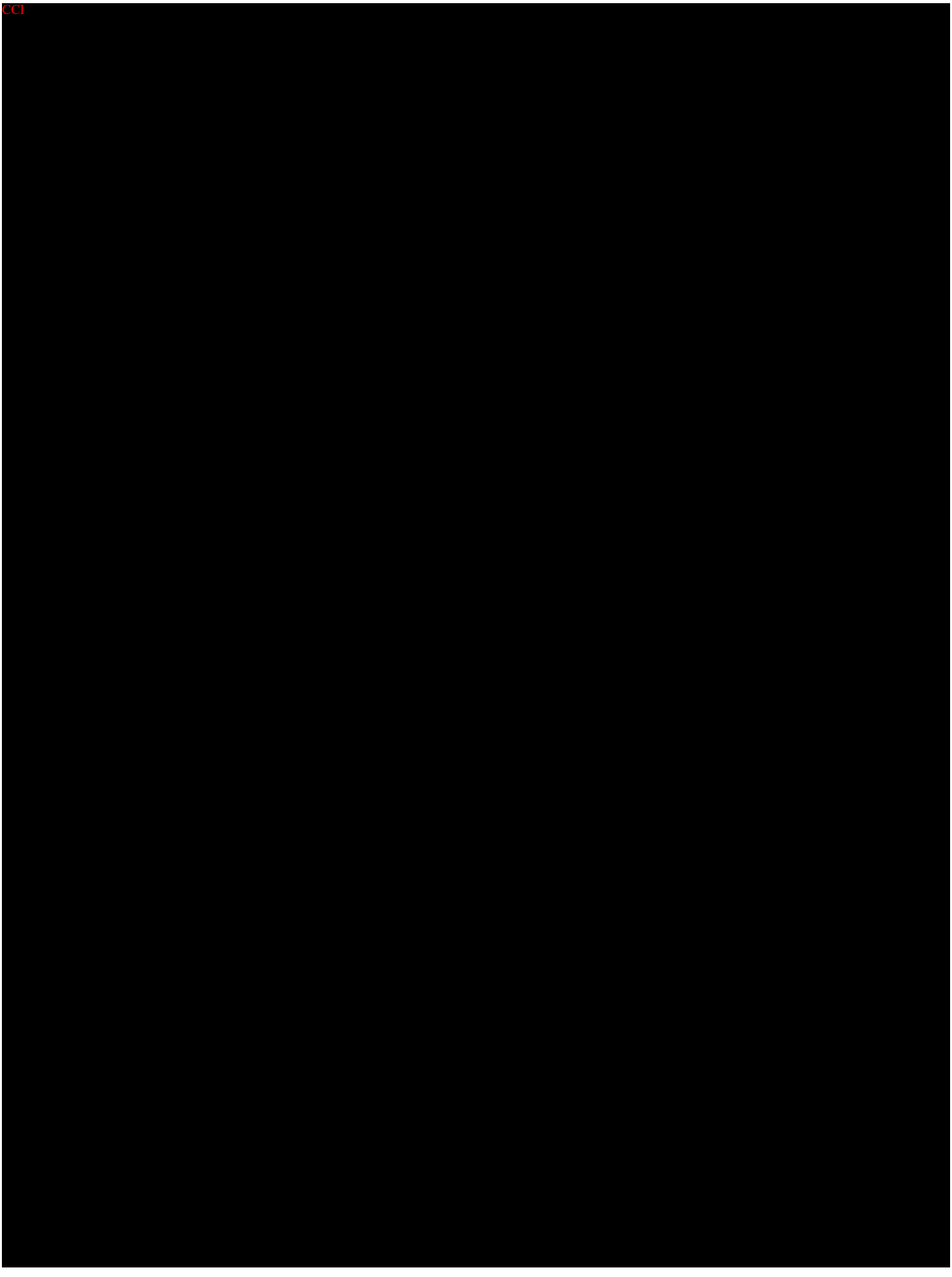
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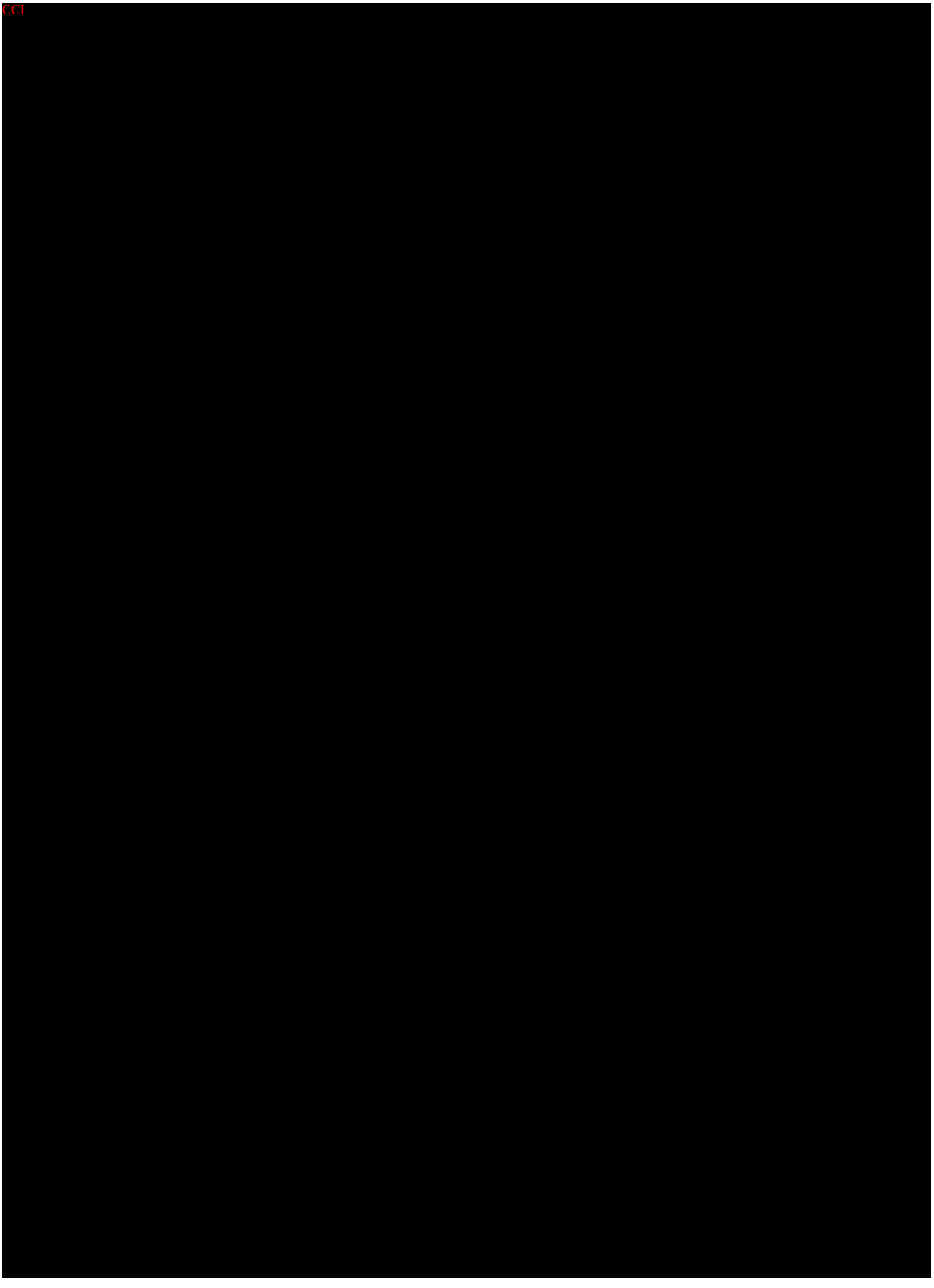
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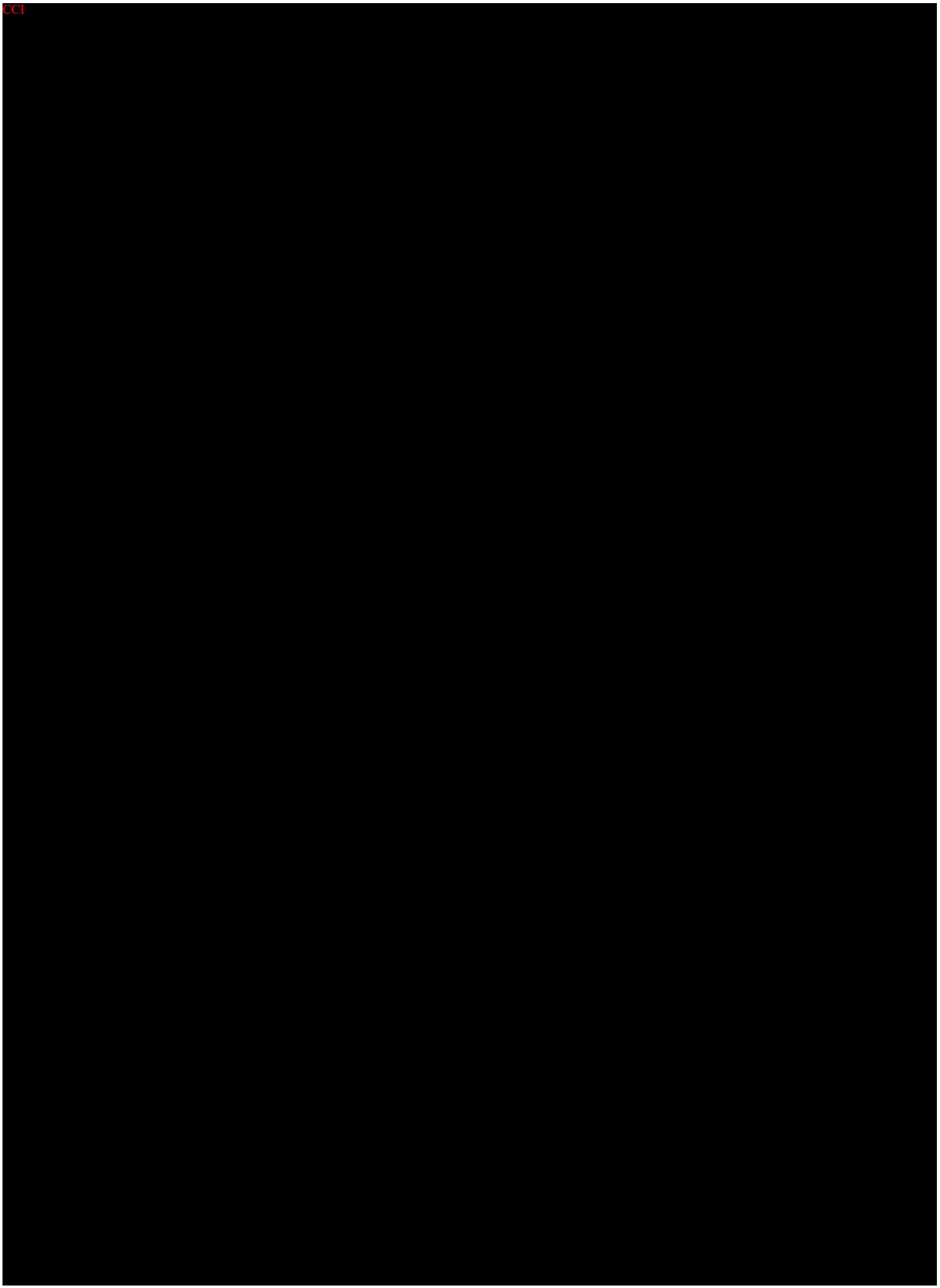
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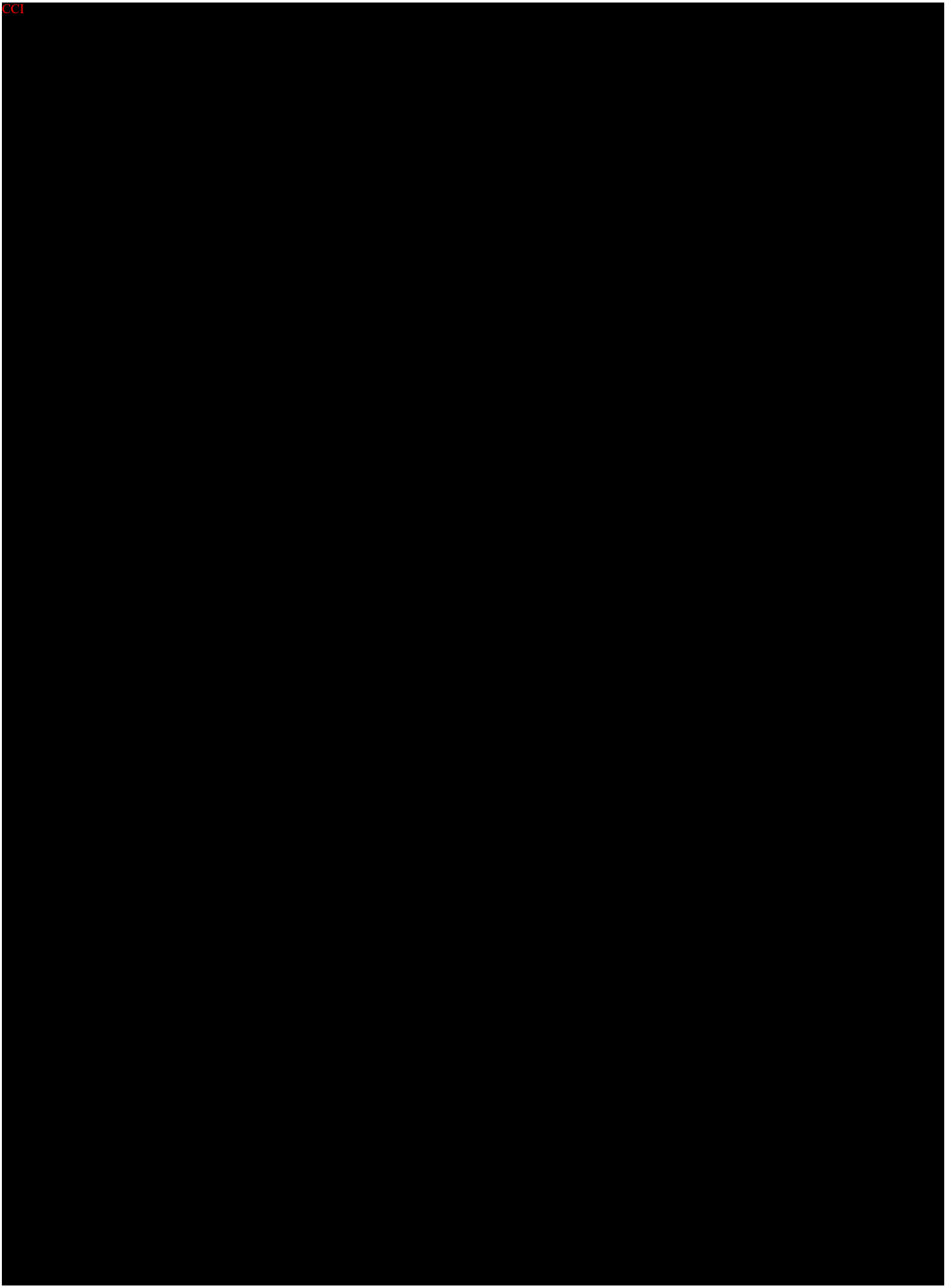
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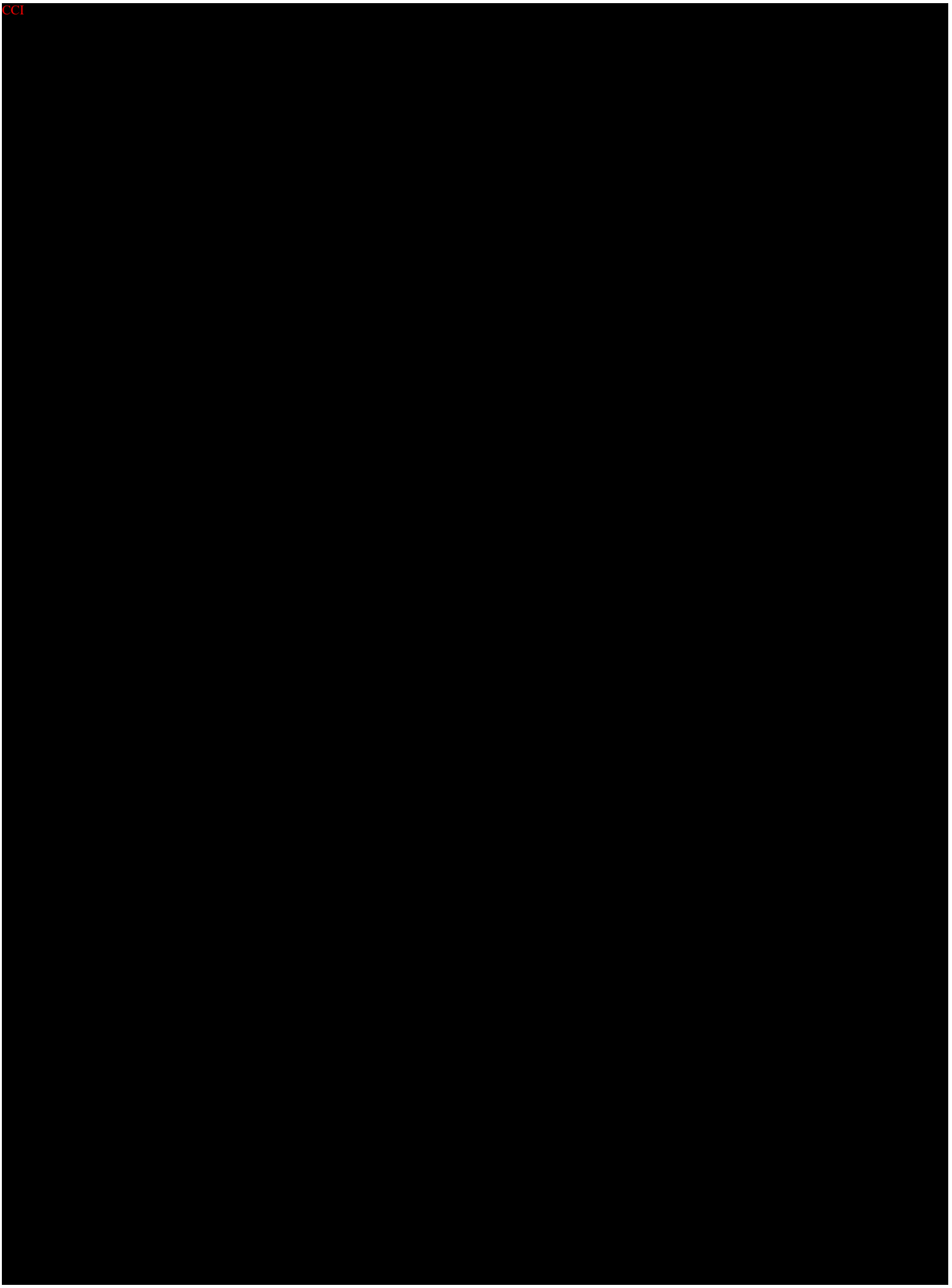
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