Integrated Analysis Plan

Study Number:	MS700568_0157
Clinical Study Protocol Title:	A 2-year extension study to evaluate long-term effectiveness of Mavenclad® in participants who have completed Trial MS700568_0022 (MAGNIFY MS)
Study Phase:	IV
Merck Compound:	Mavenclad®
Protocol Version:	20 August 2020 / Version 1.0
Integrated Analysis Plan Author:	**Coordinating Author** PPD PPD
Integrated Analysis Plan Date and Version:	05 October 2023 / Version 2.0 (Final)
Integrated Analysis Plan Reviewers:	**Function** **Name** PPD

Approval Page

Integrated Analysis Plan: MS700568_0157

A 2-year extension study to evaluate long-term effectiveness of Mavenclad® in participants who have completed Trial MS700568_0022 (MAGNIFY MS)

Approval of the IAP by all Merck Data Analysis Responsible has to be documented within EDMS via eSignature. With the approval, the Merck responsible for each of the analysis also takes responsibility that all reviewers' comments are addressed adequately.

By using eSignature, the signature will appear at the end of the document.

1 Table of Contents

2 List of Abbreviations and Definition of Terms

CCI [redacted]	[redacted]
AE	Adverse Event
CCI [redacted]	[redacted]
ATC	Anatomical Therapeutic Chemical classification
CCI [redacted]	[redacted]
CDISC	Clinical Data Interchange Standards Consortium
CDP	Confirmed Disability Progression
CI	Confidence Interval
(e)CRF	(electronic) Case Report Form
CAR	Censoring at Random
CNAR	Censoring not at Random
CCI [redacted]	[redacted]
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CCI [redacted]	[redacted]
CV	Coefficient of Variation
CCI [redacted]	[redacted]
DMD	Disease Modifying Drug
DTS	Data Transfer Specification
EAIR	Exposure Adjusted Incidence Rate
EDMS	Electronic Document Management System
EDSS	Expanded Disability Status Scale
ES	Enrolled Set
EW	Early Withdrawal
FAS	Full Analysis Set
CCI [redacted]	[redacted]
HRA	High-relapse Activity
IA	Interim Analysis
IAP	Integrated Analysis Plan
ICH	International Conference on Harmonization

CCI	[redacted]
[redacted]	[redacted]
IPD	Important Protocol Deviation
KM	Kaplan-Meier
LLOQ	Lower Limit of Quantification
LS	Least Square
M	Month
MAR	Missing At Random
MCF	Mean Cumulative Function
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects Linear Model with Repeated Measure
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
CCI	[redacted]
NA	Not Applicable
NE	Not Evaluable
NEDA	No Evidence of Disease Activity
CCI	[redacted]
[redacted]	[redacted]
CCI	[redacted]
PD	Protocol Deviation
CCI	[redacted]
PT	Preferred Term
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAF	Safety Analysis Population
SD	Standard Deviation
CCI	[redacted]
SDTM	Study Data Tabulation Model
SE	Standard Error
SMC	Safety Monitoring Committee
CCI	[redacted]

SOC	System Organ Class
T1 Gd+	T1 gadolinium-enhancing
CCI	[redacted]
TCS	Treatment Completer Set
TLF	Tables, Listings, and Figures
WHO-DD	World Health Organization Drug Dictionary
CCI	[redacted]

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	17 Aug 2022	PPD	New Document
2.0	05 Oct 2023	PPD	• Author and reviewers list updated • Editorial changes to harmonize terminology • References to parent study IAP added where applicable • Section 4: Explanation added regarding use of parent study data • CCI [redacted] • Section 6.1, Interim Analysis: NEDA-3 analysis to be performed on subgroups (subset analyses removed) • Section 6.1, Interim Analysis: Relapse Report analysis added • Section 6.1, Interim Analysis: Artefact to analyze "Annex 2" in Interim Analysis to be removed • Section 7: Explanation added regarding use of "new" vs. "all" T1-Gd+ lesions in Extension Study Period • Section 8.1: Previous and concomitant medications to be summarized on the FAS • Section 8.2: Definition of subset analyses updated • Section 9: Definition of percentage calculation for by visit summaries updated • Section 9.7: Missing data imputation rules corrected • Section 9.9: Reference to section 10.2 added • Section 9.10: Clarification added • Section 9.11: Link corrected • Section 10.1: Duration of gap period to be presented separately • Sections 10.1, 11.1, 11.2, 12: Summaries updated consistent to CLARIFY MS Extension study • Section 11.2: Summary for medical history in parent study added • Sections 14.1.1, 14.2.1, 14.2.2, CCI : The start date for the time to event analyses during the Extension Study Period will be Visit end date of M24 Visit + 1, instead of the NEDA-3 assessment date at M24 Visit + 1. • Section 14.1.1: Detailed definitions for NEDA components added • Sections 14.1.2, 14.2.2: Log-rank test and resulting p-values removed for subgroup analyses by "Previous treatment with DMDs"

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
			• Section 14.1.2, 14.2.1: Summary for crude percentages of NEDA components added • Section 14.2.1: Definition of event date corrected • Section 14.2.2: Percentile summary added • Section 14.2.3: Clarification for definition of recurrent qualifying relapses added • CCI [redacted] • CCI [redacted] • Section 14.3.2: Summary for "Level of Education" CCI [redacted] • Section 15.1.1: Summaries for AEs and study treatment related AEs leading to discontinuation added consistent to CLARIFY MS Extension study (MS700568_0158) • Section 15.2.3: Summaries for "AEs associated to Lymphopenia" added • Section 16.1: minor wording update • Section 18.1: Updated list of DMDs in Appendix 1 • Section 18.3: List of terms for Lymphopenia added as Appendix 3

4 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP) is to document technical and detailed specifications for the analysis of data collected for protocol MS700568_0157. Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR). Additionally,

the planned analyses identified in this IAP may be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

The IAP is based upon Section 9 (Statistical considerations) of the study protocol and protocol amendments and is prepared in compliance with ICH E9. CCI [redacted]

The analyses described in this IAP will also include data from the MAGNIFY MS trial (MAGNIFY MS study MS700568_0022, referred to as the parent study in the current document). Therefore, the study protocol and protocol amendments of the MAGNIFY MS trial, as well as the MAGNIFY MS IAP version 3.0, will also be referenced, where applicable. When analysis datasets from parent study will be utilized, no separate removal of data, not specifically required for the analysis of the MAGNIFY MS Extension Study, will be done.

The wording used in this IAP is chosen to best match the respective wording in the study protocol template, the CSR template, CDISC requirements and special requirements for table layouts. Therefore, the following approach is used:

Generally, the term ‘participant’ will be used instead of ‘subject’ or ‘patient’. However, in tables and listings the term ‘subject’ will be used to match CDISC requirements, except for in-text tables where ‘participant’ will be used to match the CSR and protocol templates. Similarly, the term ‘study intervention’ will be used in this document instead of ‘treatment’ to match protocol and CSR templates, however, tables and listings will use ‘treatment’ for brevity reasons. Exceptions from this rule are commonly used terms like “on-treatment”, “treatment-emergent”, “treatment policy”, “subject-years”, “by-subject”, or names of eCRF pages like “Treatment Termination” page.

5 Objectives and Endpoints

Objectives	Endpoints	IAP section
Primary		
To evaluate the long-term disease activity during Year 3 and 4 after initial dose of cladribine tablets	• Proportion of participants with No Evidence of Disease Activity (three parameter [NEDA-3]) during Year 3 Visit and Year 4 Visit Period after the initial dose of cladribine tablets	14.1
Secondary		

To further explore the long-term treatment effect of cladribine tablets	• Proportion of participants with NEDA-3 during Year 3 Visit Period after the initial dose of cladribine tablets
	• Proportion of participants with NEDA-3 during Year 4 Visit Period after the initial dose of cladribine tablets
	• Proportion of participants with NEDA-3 after start of study medication during the parent study until the end of Year 3 Visit after the initial dose of cladribine tablets
	• Proportion of participants with NEDA-3 after start of study medication during the parent study until the end of Year 4 Visit after the initial dose of cladribine tablets
	• Proportion of participants remaining NEDA-3 during Year 3 Visit Period or Year 4 Visit Period after the initial dose of cladribine tablets among those with NEDA-3 during Course 1 Treatment Period or Course 2 Treatment Period in the parent study
	• Time to first disease activity, defined as the time to first occurrence of either qualifying relapse, or confirmed disability progression (CDP), or new or enlarging T2-hyperintense lesions, or new T1 gadolinium-enhancing (Gd+) lesions, during Year 3 Visit and Year 4 Visit Period after initial dose of cladribine tablets
	• Time to first disease activity, defined as the time to first occurrence of either qualifying relapse, or CDP, or new or enlarging T2-hyperintense lesions, or new T1 Gd+ lesions, during the parent study until the end of Year 4 Visit after the initial dose of cladribine tablets (i.e., between initial dose and end of the extension study)
	• Time from the initial dose of cladribine tablets to
	  • first new or enlarging T2 lesion
	  • first new T1 Gd+ lesion
	  • first CDP, as measured by Expanded Disability Status Scale (EDSS)
	  • first qualifying relapse
	  • recurrent qualifying relapses
	• Time from M24 Visit in the parent study to
	  • first new or enlarging T2 lesion
	  • first new T1 Gd+ lesion
	  • first CDP, as measured by EDSS
	  • first qualifying relapse
	  • recurrent qualifying relapses
	  • treatment start with other DMDs
		14.2

To evaluate long-term safety of cladribine tablets	• Occurrences of adverse events (AEs) and serious adverse events (SAEs) during Year 3 Visit and Year 4 Visit Period after the initial dose of cladribine tablets	15

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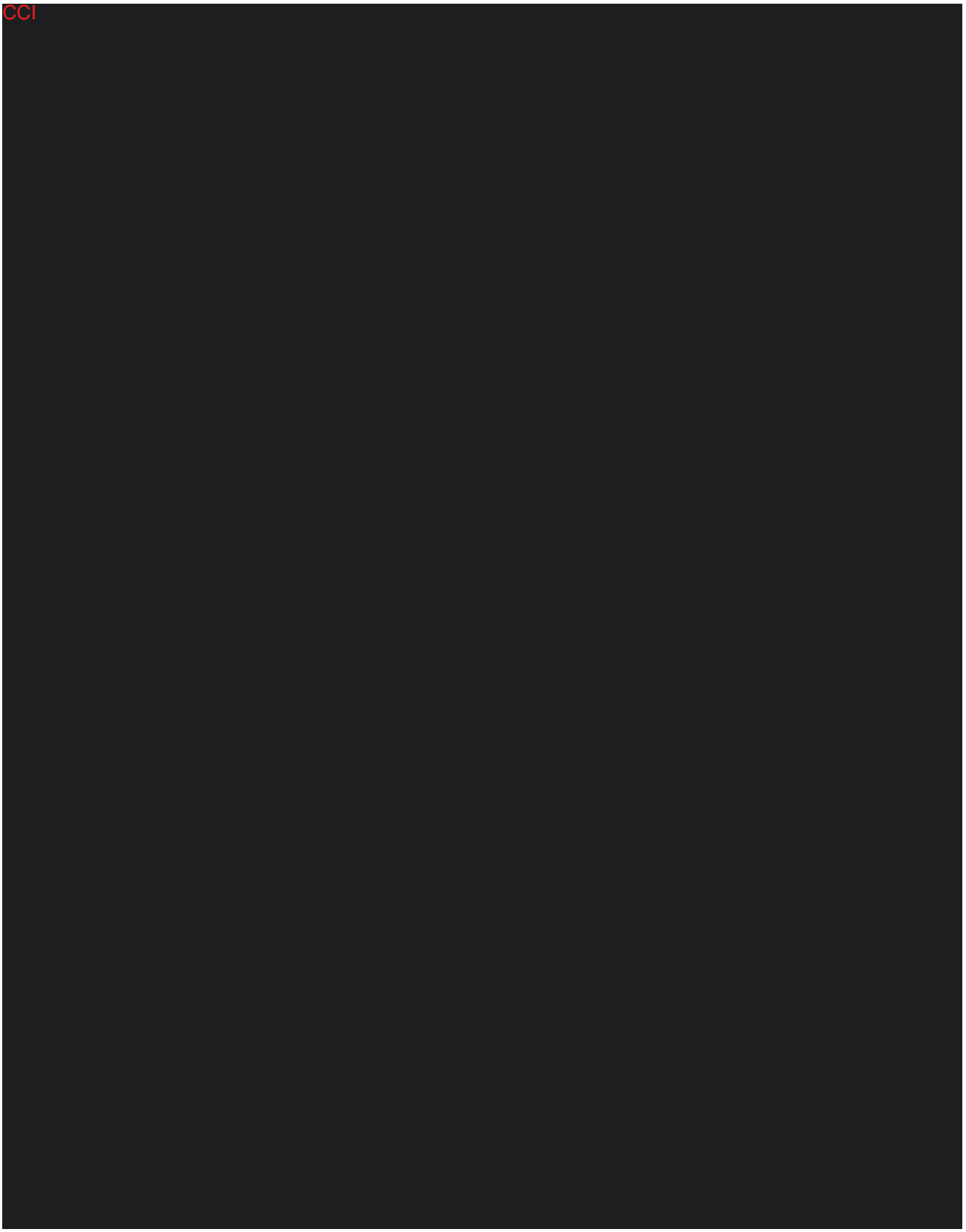

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6 Overview of Planned Analyses

The following analyses are planned for the study:

- Interim analysis (IA) at the end of Year 3 Visit (i.e., Visit 1 of the MAGNIFY MS Extension Study) after the initial dose of cladribine tablets (i.e., after all participants have completed the Year 3 Visit assessment).
- Final analysis at the end of the MAGNIFY MS Extension Study.

The following bioinformatic analyses of the main study are described in the Clinical Study Protocol (CSP), version 1.0:

CCI

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The analyses for the protocol endpoint "Explore the association between genetic variants, clinical efficacy, CCI and MRI endpoints" (see Section 5) will be specified in these Annexes.

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6.1 Interim Analysis

The IA will be exploratory in nature. There will be no stopping criteria or any other planned adaptations to the study associated with this IA. Due to the exploratory nature of the study, no alpha spending was planned to control for overall type-I-error inflation.

The IA will be performed when all participants have completed Visit 1 or have discontinued from the study prior to Visit 1.

The IA will describe the following characteristics of the study population (overall and by "Previous treatment with DMDs" subgroup as defined in Section 8.2):

- Disposition of participants and discontinuations including and up to the cut-off point (Section 10.1)
- Demographics, Medical History, and Other Baseline Characteristics including MS Disease Characteristics, MRI Baseline Characteristics and Vital Signs (Section 11)
- Previous or concomitant medications including and up to the cut-off point (Section 12)

and will include analyses of the following secondary, CCI and safety endpoints as described in the respective referenced sections up to Visit 1 or the cut-off point:

- NEDA-3 (Section 14.2.1 including subgroup analyses)
    - Proportion of participants with NEDA-3 during Year 3 Visit Period after the initial dose of cladribine tablets
    - Proportion of participants with NEDA-3 after the start of study medication during the parent study until the end of Year 3 Visit after the initial dose of cladribine tablets

- Time from M24 Visit to treatment start with other DMDs (Section 14.2.3 including subgroup analysis)

CCI [redacted]

- Relapse Report: The number of participants with (qualifying) relapses, the number of (qualifying) relapses, CCI [redacted] CCI will be presented for the Extension Study Period and the Parent and Extension Study Period. Also, the number of participants with relapses and number of relapses which were treated with steroids or leading to hospitalization will be presented separately.

- CCI [redacted]

[redacted]

- CCI [redacted]

CCI [redacted]

- Occurrences of AEs and SAEs during Year 3 Visit Period after initial dose of cladribine tablets, overall and by "Previous treatment with DMDs" subgroup as defined in Section 8.2, including and up to the cut-off point of IA (Section 15)

The following table lists all assessments which will be included in the IA.

Assessments	MAGNIFY MS Screening	MAGNIFY MS Baseline	MAGNIFY MS M24 Visit[$]	MAGNIFY Extension Baseline	MAGNIFY Extension Visit 1 +/- 30 days
Informed Consent				X	
Inclusion/exclusion criteria				X	
Demography	X			X	
Vital Sign	X	X			
Concomitant medications and procedures				X*	X
MRI					
MRI	X	X	X		X
Disability					
EDSS	X	X	X	X*	X
CCI					
CCI					
Relapse reporting		X	X	X*	X
Safety Assessments					
Adverse event reporting	X	X	X	X*	X
Medical history				X**	
CCI					

$All Visits (up to the M24 Visit) where the assessment is available in MAGNIFY MS trial will be included if checked.
*Baseline data will be collected retrospectively from the gap period between MAGNIFY MS Final Visit (M24) and MAGNIFY MS Extension Baseline.
** Ongoing SAEs and events of lymphopenia (also if not serious) with an onset date prior to the parent study exit date will be recorded as medical history in the extension study.

6.1.1 Cut-off Date

Only data up to and including Visit 1 of each participant will be analyzed in the IA. Therefore, the cut-off date is defined as the maximum Visit 1 date (i.e., date of the last assessment for Visit 1). For participants with a missing Visit 1, the cut-off date will be 1 year (360 days) after end date of M24 Visit in the MAGNIFY MS trial. This includes participants of the MAGNIFY MS Extension Study who discontinued before Visit 1.

Cut-off date (Visit 1 done) = Visit 1 end date (i.e., Maximum Visit 1 date)

Cut-off date (Visit 1 not done) = 1 year (360 days) after end date of M24 Visit in the MAGNIFY MS trial

Any assessments from later than Visit 1 will not be included in the IA, however, any events or concomitant medications reported during these visits that have an onset/start date before or at the cut-off date will be included.

All data included in the IA will undergo a data cleaning process, however, as no decisions on further study conduct are based on this IA, it is not required to have all data 100% cleaned.

Details and level of data cleaning will be documented in data management plans. The quality of the data will be reviewed during the Data Review Meeting.

6.1.2 Data Handling after Cut-off Date

Data not included in the IA do not undergo the cleaning process.

Data other than the date of death obtained after the cut-off will not be displayed in any listings or used for summary statistics. If the stop date for an AE is after the date of cut-off, the AE will be considered as ongoing during the IA.

6.2 Final Analysis

The final analysis will be performed at the end of study, i.e., when all participants have completed Visit 2 or have discontinued from the study prior to Visit 2 and will include all described analyses of this IAP. The final analysis will be based on all data available in the database at the time of the final database lock.

7 Changes to the Planned Analyses in the Clinical Study Protocol

Below changes are made in the IAP compared to the planned analyses in the CSP.

- Visits (Year 3 Visit [Visit 1] and Year 4 Visit [Visit 2]) in the Extension Study were not scheduled in calendar years from initial dose of cladribine tablets in parent study. Instead, these visits were scheduled relative to the final visit (M24 Visit) of parent study (see Section 9.5). Since there was potentially substantial delay in parent study visit schedule (could be more than 6 months), Year 3 Visit (or Year 4 Visit) would not reflect Year 3 (or Year 4) after initial dose of cladribine tablets. Therefore, the below text replacement for protocol endpoints is implemented in the IAP Section 5 for clarification.
    - "during Year 3 / Year 4 / Year 3 and 4 after initial dose of cladribine tablets" is replaced with "during Year 3 Visit Period / Year 4 Visit Period / Year 3 Visit and Year 4 Visit Period after initial dose of cladribine tablets", respectively.
    - "at the end of Year 3 / Year 4 after initial dose of cladribine tablets" is replaced with "at the end of Year 3 Visit / Year 4 Visit after initial dose of cladribine tablets", respectively.
    - "over the 2-year extension study period (Year 3 and 4 after initial dose of cladribine tablets" and "during the first and second year of extension study (Year 3 and 4 after the initial dose of cladribine tablets)" are replaced with "over the extension study period".
    - "over the 4-year study period of the parent and extension study (Year 1 to 4 after initial dose of cladribine tablets)" is replaced with "over the study period of the parent and extension study".
- It was described in the CSP that "In addition, interim analysis at extension study Baseline or at the end of Year 3 after the initial dose of cladribine tablets may be performed". Due

to the same reason as above, it is decided during IAP development that the IA will be performed at the end of Year 3 Visit (Visit 1). See detailed description in Section 6.1.

- The protocol endpoint "Proportion of participants remaining NEDA-3 during Year 3 Visit Period or Year 4 Visit Period after the initial dose of cladribine tablets among those with NEDA-3 during Year 1 or 2 after initial dose of cladribine tablets" is replaced with "Proportion of participants remaining NEDA-3 … among those with NEDA-3 during Course 1 Treatment Period or Course 2 Treatment Period in the parent study", as Study Periods in parent study were not defined in calendar years relative to initial dose of cladribine tablets.

- The text "the onset of action of cladribine treatment" in protocol endpoints is replaced with "start of study medication", as these refer to the same day (Day 1 as defined in Section 9.5) and the latter is chosen to keep consistent with parent study Day 1 definition.

- The protocol endpoint "Time from the initial dose of cladribine tablets to treatment start with other DMDs" is removed. This is because in the parent study, a participant receiving any rescue medication with any other DMD would not participate further in any trial assessments and should instead complete the early termination visit for final assessment. Such participants would not have EDSS or MRI assessment at M24 Visit and therefore would not be included in the Extension Study as per inclusion criteria. Hence, the Extension Study population have excluded potentially a subgroup of participants who started DMDs earlier during the parent study. The analysis of "time from initial dose of cladribine to treatment start with other DMDs" conducted on the Extension Study population would be biased and, therefore, would not be performed.

- The protocol endpoints "time from extension study baseline to …" are replaced with "Time from M24 Visit in the parent study to …". This is because the Extension Study baseline is planned to coincide with the parent study last visit (M24 Visit), while in practice it can occur after the parent study last visit and before Visit 1, resulting in incomparable starting dates across participants for the planned time-to-event analyses in protocol. These time-to-event analyses will be more meaningful to start from the intended Extension Study baseline, i.e., M24 Visit in the parent study.

- The protocol endpoints, "time from … to second qualifying relapse" are replaced with "time from … to recurrent qualifying relapses". Correspondingly, a recurrent event analysis will be implemented as specified in Section 14.2.3.

CCI [redacted]

- CCI [redacted]

CCI [redacted]

- 6-months confirmed disability progression (6MCDP), is used in the IAP to keep consistent with the parent study IAP, although 3 months confirmed disability progression, 3MCDP, is defined in the CSP.

- As data provided from MRI vendor only contains absolute values for (all) T1-Gd+ lesions per assessment (no new T1-Gd+ lesions), in consequence (all) T1-Gd+ lesions per assessment will be used for definition of disease activity and for calculation of Combined Unique Active (CUA) lesions during MAGNIFY MS Extension Study. However, as MAGNIFY MS Extension Study only has yearly MRI assessments the number of "new" and "all" T1-Gd+ lesions can be considered identical (see also explanation in Section 9.8).

CCI [redacted]

8 Analysis Sets and Subgroups

8.1 Definition of Analysis Sets

Enrolled Set (ES)

All participants who provided informed consent.

Full Analysis Set (FAS)

The FAS will include all enrolled, eligible participants.

Safety Analysis Population (SAF)

All participants treated with at least one dose of cladribine tablets during the parent study.

Treatment Completer Set (TCS)

All participants from the FAS who completed the full treatment course of the first and second year in the parent study (i.e., participants who were in TCS-2 as defined in MAGNIFY MS IAP version 3.0).

Analyses per Analysis Set

Unless otherwise specified, all efficacy analyses will be performed on the FAS and all safety analyses will be performed on the SAF. The primary analysis will also be repeated on the TCS as a sensitivity analysis.

If not stated otherwise, disposition of participants will be summarized on the ES, previous and concomitant medications will be summarized on the FAS, and the analyses on demographics and other baseline characteristics will be based on the FAS.

8.2 Subgroup Definition and Parameterization

Subgroup analyses will be performed on subgroups as defined below.

- Previous (prior to parent study Baseline) treatment with DMDs:
    - DMD pre-treated: Participants will be categorized as DMD pre-treated if they have taken DMDs any time before start of study medication.
    - Pre-treatment naïve: all participants not classified as DMD pre-treated.

Details of the definition of DMDs used for subgroups classification are specified in MAGNIFY MS IAP version 3.0. The updated list of DMDs (Appendix 18.1) will be used to identify DMD in concomitant medications in the Extension Study.

All descriptive statistical analyses will be presented separately for the DMD subgroups. The primary analysis, secondary analyses and selected exploratory analyses will also be repeated for this subgroup.

Subset analyses will be performed on the subsets defined as follows:

- Participants with NEDA-3 during Course 1 Treatment Period
- Participants with NEDA-3 during Course 2 Treatment Period

Secondary analyses of NEDA-3 during Year 3 Visit Period and during Year 4 Visit Period (see Section 14.2.1) will be repeated on these subsets. Definition of NEDA-3 during Course 1 Treatment Period and Course 2 Treatment Period is described in Section 14.2.1.

9 General Specifications for Data Analyses

Unless otherwise specified, continuous variables will be summarized using descriptive statistics, i.e., the number of participants with non-missing values (n), mean, standard deviation, median, 25th percentile (Q1) and 75th percentile (Q3), minimum, and maximum.

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise stated the calculation of proportions will be based on the number of participants of the analysis set of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

Descriptive statistics by nominal visit or time point will include only data from scheduled visits. Unscheduled visits will be included in the derivation of baseline or worst on-treatment values.

All statistical tests mentioned in this IAP are to be regarded as descriptive and exploratory, and differences with a p-value of 0.05 or less will be considered nominally statistically significant. No correction for multiple testing will be applied for any of the analyses. If confidence intervals (CI) are to be calculated, these will be two-sided with a confidence probability of 95%, unless otherwise specified in this IAP.

Study data will be integrated with study data from the MAGNIFY MS trial as required to perform the statistical analyses, i.e., study data up to M24 visit is integrated from the MAGNIFY MS trial.

If not specified otherwise, all listings will only include data collected in the Extension Study, including the gap period between the MAGNIFY MS trial and MAGNIFY MS Extension Study. Listings regarding demographic and other Baseline characteristics will include data from MAGNIFY MS Baseline.

If data from parent study are used, all rules from parent study IAP still apply for the analysis of these data, except alternative rules are explicitly specified in this IAP.

All analyses will be performed using SAS® Software version 9.4 or higher or R (http://www.r-project.org/), Version 3.6.3 or higher as applicable.

9.1 Definition of Baseline and Change from Baseline

The Baseline is defined as the MAGNIFY MS Baseline (parent study Baseline) that is specified in Section 9 of MAGNIFY MS IAP version 3.0, unless otherwise specified.

Absolute and percent changes from baseline are defined as:

- Absolute change = Visit value – Baseline value
- Percent change = 100 * (Visit value – Baseline value) / Baseline value

The Percentage Change from Baseline will be set to missing for participants with a zero at Baseline.

All changes that are defined as comparing to prior initial dose of cladribine tablets will use the MAGNIFY MS Baseline as reference.

9.2 Definition of Visit Dates

The visit start date is the date of the first assessment which belongs to the corresponding visit.

The visit end date is the date of the last assessment which belongs to the corresponding visit.

9.3 Definition of Duration

Durations in days will be calculated by the difference of start and stop date + 1 if not otherwise specified.

9.4 Conversion Factors

The following conversion factors will be used to convert days into months or years for all observations except Visit related dates:

- 1 month = 30.4375 days,
- 1 year = 365.25 days.

9.5 Time Window

- Day 1 is the day of start of study medication at MAGNIFY MS Baseline Visit, the day before is Day -1 (no Day 0 is defined).
- Study day is defined relative to Day 1.

The visit schedule in the Extension Study is defined as follows:

- 1 month = 30 days,
- 1 year = 360 days,

relative to the M24 Visit in the parent study.

- MAGNIFY Extension Baseline Visit: The visit is planned to coincide with or be as near to M24 as possible to minimize the transition gap period, it may also be the same visit as M24.
- Visit 1: 1 year ((360 days) after M24 Visit (± 30 days)
- Visit 2: 2 years (720 days) after M24 Visit (± 30 days)

Visit 1 and Visit 2 will also be referred to as the M36 Visit and the M48 Visit, respectively, in the following sections of this IAP as well as in the Tables, Listings, and Figures (TLF) outputs, for consistent presentation of analyses and results over time. Footnotes will be added in the TLF outputs to clarify that these Visits are to be understood as nominal Visits.

In each analysis, should an assessment be delayed, participants' assessment data will be treated as though it occurred at the nominal time point specified (i.e., data collected out of visit windows will not be excluded or adjusted in any analysis) and inferences will be conducted accordingly. Thus, further time windows will not be specified. The MRI assessment will be the only exception to this rule. Handling of out-of-window MRI assessments is discussed in Section 9.8.

All observations from unscheduled visits will be included only in the analyses of visit independent summaries (e.g., counts of AEs, concomitant medications and procedures, relapse reporting and EDSS) unless for the last assessment available. In this case the missing Early Withdrawal (EW) visit will be imputed by the unscheduled visit.

The assessments of the EW visit will be mapped to the nearest planned post-baseline visit with a missing assessment before or after the EW visit of the individual assessment for all statistical analyses and descriptive summaries. As not all assessments of the EW are performed at each visit, the different assessments of the EW can be assigned to different visits. If the duration (in days) between the EW visits and two missing planned visits are equal, then the assessment will be assigned to the later visit.

9.6 Study Period

Study Periods

The following study periods are defined:

Treatment Period (i.e., **Parent Study Period**): see MAGNIFY MS IAP version 3.0 for definition.

Course 1 Treatment Period: see MAGNIFY MS IAP version 3.0 for definition.

Course 2 Treatment Period: see MAGNIFY MS IAP version 3.0 for definition.

Gap Period:
- Start = Visit end date of M24 Visit + 1
- End = Extension Study Baseline Visit start date

Year 3 Visit Period:
- Start = Visit end date of M24 Visit + 1
- End = Visit end date of M36 Visit

Year 4 Visit Period:
- Start = Visit end date of M36 Visit + 1
- End = Visit end date of M48 Visit

Year 3 Visit and Year 4 Visit Period (i.e., **Extension Study Period**):
- Start = Visit end date of M24 Visit + 1
- End = Visit end date of M48 Visit

After start of study medication until end of Year 3 Visit Period:
- Start = Start of study medication (see MAGNIFY MS IAP version 3.0 for definition)
- End = Visit end date of M36 Visit

After start of study medication until end of Year 4 Visit Period (i.e., **Parent and Extension Study Period**):
- Start = Start of study medication (see MAGNIFY MS IAP version 3.0 for definition)
- End = Visit end date of M48 Visit

In case of missing M48 Visit or early discontinuation before an End of Period defined above, the Visit end date of EW Visit will be used to replace the corresponding End date, or the study discontinuation date will be used if the EW visit was not performed.

In case of missing M36 Visit, the Visit end date of M36 Visit in the above definitions (including Start and End) will be replaced by MAGNIFY MS M24 Visit date + 480 days (which is obtained by 360 (12 months) + 90 (3 months delay allowed for FAS) + 30 (Visit window)), or the Visit end date of EW Visit if earlier, or date of discontinuation if earlier and the EW Visit was not performed.

Study Periods for MRI Assessments

The MRI scans in the parent study were reconciled during central MRI review process. Therefore, MRIs were considered as Baseline MRIs if assigned to the Baseline Visit by the central imaging review.

The following study periods for MRI assessments are defined as per MAGNIFY MS IAP version 3.0 with extension to Month 36 Visit and Month 48 Visit MRI scans:

Baseline Period (p_0): The Baseline Period is defined as the Period between the Screening and the Baseline MRI scan in MAGNIFY MS trial.

Post-Baseline Periods ($p_{post\text{-}Baseline}$):

Yearly Periods:

Period 12.1 ($p_{12.1}$) is defined as the Period between Baseline to Month 12 MRI scans,

Period 12.2 ($p_{12.2}$) is defined as the Period between Month 12 to Month 24 MRI scans,

Period 12.3 ($p_{12.3}$) is defined as the Period between Month 24 to Month 36 MRI scans,

Period 12.4 ($p_{12.4}$) is defined as the Period between Month 36 to Month 48 MRI scans.

2-Year Period:

Period 24.1 ($p_{24.1}$) is defined as the Period between Baseline to Month 24 MRI scans.

3-Year Period:

Period 36.1 ($p_{36.1}$) is defined as the Period between Baseline to Month 36 MRI scans.

4-Year Period:

Period 48.1 ($p_{48.1}$) is defined as the Period between Baseline to Month 48 MRI scans.

Sequential Visit Periods:

For $p_{100.0}$, $p_{100.1}$, $p_{100.2}$, $p_{100.3}$, $p_{100.6}$, $p_{100.12}$, $p_{100.15}$, $p_{100.18}$, $p_{100.24}$, see Section 9 of MAGNIFY MS IAP version 3.0.

Period 100.36 ($p_{100.36}$) is defined as the Period between Month 24 to Month 36 (equivalent to $p_{12.3}$) MRI scans.

Period 100.48 ($p_{100.48}$) is defined as the Period between Month 36 to Month 48 (equivalent to $p_{12.4}$) MRI scans.

9.7 Imputation of Missing Data

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

In all participant data listings, imputed values will be presented, and imputed information will be flagged.

Missing statistics, e.g., when they cannot be calculated, should be presented as "nd". For example, if n=1, the measure of variability (SD) cannot be computed and should be presented as "nd".

Where tables are presented over time, the total number of participants with missing and non-missing observations at each time point should reflect the complete population.

Incomplete or missing start dates of DMDs reported during the Extension Study Period will be imputed as follows:

- In cases where the start date is completely missing the start date will be replaced by M24 Visit + 1
- if start date is partially missing but the start month and year, or the start year are equal to the M24 Visit date then the onset date will be replaced by M24 Visit + 1.
- In all other cases the missing onset day or missing onset month will be replaced by 1st day of the known month or 1st day of the known year.

Incomplete or missing onset dates of relapses reported at Extension Study Baseline Visit (i.e., relapses experienced during gap period) will be imputed as follows:

- In cases where the onset date is completely missing the onset date will be replaced by M24 Visit + 1
- if onset date is partially missing but the onset month and year, or the onset year are equal to the M24 Visit date then the onset date will be replaced by M24 Visit + 1.
- In all other cases the missing onset day or missing onset month will be replaced by 1st day of the known month or 1st day of the known year.

Incomplete or missing onset dates of relapses reported after Extension Study Baseline Visit will be imputed as follows:

- In cases where the onset date is completely missing the onset date will be replaced by the Extension Study Baseline Visit date + 1.
- if onset date is partially missing but the onset month and year, or the onset year are equal to the Extension Study Baseline Visit, then the onset date will be replaced by the Extension Study Baseline Visit date + 1.

- In all other cases the missing onset day or missing onset month will be replaced by 1st day of the known month or 1st day of the known year.

Incomplete or missing onset dates of AE-associated dates during the Extension Study Period will be imputed as follows:

- In case the onset date is missing completely or missing partially but the onset month and year, or the onset year are equal to the M24 Visit date then the onset date will be replaced by the M24 Visit + 1.
- In all other cases the missing onset day or missing onset month will be replaced by 1st day of the known month or 1st day of the known year.
- Incomplete stop dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of participant's death. In the latter case the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete stop date will not be imputed.

9.8 Data Handling for MRI data

MRI data will be integrated with MRI data from the MAGNIFY MS trial, which will be handled according to "Data Handling for MRI data – Data handling of Tertiary endpoints" in Section 9 of the MAGNIFY MS IAP version 3.0.

The MRIs will be evaluated by independent central review. The assignment of MRIs to the respective Visits in the parent study was ensured by the central reading process, while this process is not adopted in the Extension Study. Therefore, the statistical analysis will be based on the MRI Visit assignments as provided by central reading for parent study data and MRI Visit assignments as reported in the eCRF for Extension Study data. A 6-months window will be allowed for the Extension Study MRI data. An MRI assessment will be excluded from all analyses if the absolute value of (MRI assessment date – Visit date) > 185 days (which is obtained by 180 [6 months] + 5 [window allowed by protocol]).

All derived lesion counts (except for the Mean T1 Gd+ lesion count) as specified below will be classified as Not Evaluable (NE) if one of the components required for the calculation has been classified as NE by the central reading. The Mean T1 Gd+ lesion count will be set to NE only, if all T1 Gd+ lesion counts that correspond to the respective Period are classified as NE. In all other cases the mean will be calculated based on the available counts during the respective Period.

For definition of Period see Section 9.6 "Study Periods for MRI Assessments".

T1 Gd+ lesion count

- The T1 Gd+ are defined as follow: T1 Gd+ lesion count (by Visit) = T1 Gd+ lesions count from the MRI at the respective Visit.

- Mean T1 Gd+ lesion count (by Period) = sum of all T1 Gd+ lesion counts during the Period / # of scans belonging to the respective Period with non-missing T1 Gd+ lesion count.

All MRI scans belonging to a Period are MRI scans that have been performed during the Period including start and end Visits. For post-Baseline periods starting at Baseline, the Baseline Visit will not be included. For example, Period 48.1 will include all MRI scans during both MAGNIFY MS trial and Extension Study except Screening and Baseline Visit.

- New T1 Gd+ lesion count (by Period)
    - For Periods including up to Month 24 Visit, refer to "Data handling for MRI data: Data handling of Tertiary endpoints" in Section 9 of MAGNIFY MS IAP version 3.0
    - For other Periods ending at Month 36 / Month 48 Visit,
      New T1 Gd+ lesion count = T1 Gd+ lesions count from the MRI at Month 36 / Month 48 Visit due to longer periods

      For example: New T1 Gd+ lesion count of the Period between Month 24 and Month 36 (p12.3) is equal to T1 Gd+ lesion count from the MRI at Month 36 Visit.

Active T2 lesion count

As the active (i.e., the new or enlarging) T2 lesion count depends on the length of the Period, it will be presented as reported (non-standardized) and annualized (standardized to 1 years (365.25 days)):

- Period length (days) = MRI date at end of Period – MRI date at start of Period +1,
- Annualized active T2 lesion count (by Period) = Total number of active T2 lesions per Period * 365.25/ Period length.

The following types of T2 lesions are defined per Period (standardized and non-standardized):

- Total new T2 lesion count =
  Total number of new T2 lesions with T1 Gd+
  + Total number of new T2 lesions without T1 Gd+
- Total enlarging T2 lesion count =
  Total number of enlarging T2 lesions with T1 Gd+
  + Total number of enlarging T2 lesions without T1 Gd+
- Total active T2 lesion count =
  Total new T2 lesion count
  + Total enlarging T2 lesion count

Note: the number of new or enlarging T2 (with and without T1 Gd+) will be provided by central reading for each of the Periods including the Sequential Visit Periods.

9.9 Data Handling in Case of PDs

Protocol Deviations (PDs) in the Extension Study will not be considered in the planned statistical analyses (i.e., all data will be analyzed independent from any reported PD). Further details on a subset of protocol deviations are described in Section 10.2.

9.10 Covariates and Stratification Factors

The following covariates are defined:

Unless otherwise specified, these factors will be obtained from the baseline information of the **MAGNIFY MS Baseline**.

Age

See MAGNIFY MS IAP version 3.0.

EDSS at Baseline

see MAGNIFY MS IAP version 3.0.

Pooled centers

Some centers will have few eligible participants only. Therefore, the centers will be pooled together by country except for

- sites that have more than 12 participants in the FAS (i.e., these sites will not be pooled with any other site).

Some countries will have few eligible participants only. Therefore, countries will be pooled as follows:

  - Scandinavia = Finland and Sweden
  - Mediterranean = Italy and Spain
  - France-UK = France and UK
  - Austria-Hungary-Czech = Austria, Hungary, and Czech Republic
  - Australia-Canada = Australia and Canada

The following MRI specific covariate is defined:

Time between scans: in Years

Time between scans (in Years) is calculated as follows:

- Time between scans (in Years) = (MRI date of the Visit - MRI of the previous Visit + 1) /365.25, i.e.:
  - If (Visit= Month 36) then Time between scans (in Years) = (MRI date at Month 36 - MRI date at Month 24 + 1)/ 365.25
  - If (Visit= Month 48) then Time between scans (in Years) = (MRI date at Month 48 - MRI date at Month 36 + 1)/ 365.25

If the corresponding MRI is available and the time between scans is missing (due to preceding MRI being missing) it will be replaced by expected time as follows:

- Month 36 Visit = 1 year
- Month 48 Visit = 1 year

For calculations for Month 1, 2, 3, 6, 12, 15, 18, 24 Visits, see MAGNIFY MS IAP version 3.0 Section 9.

9.11 Definition of Start of COVID-19 Pandemic

The start of COVID-19 pandemic will be defined by country as the earliest date of either the date of the first death from COVID-19 occurred in each country according to the published data by

European Center for Disease Prevention and Control on 26th June 2020 (https:/www.ecdc.europa.eu/en/publications-data/download-todays-data-geographic-distribution-covid-19-cases-worldwide) or 11th March 2020 (when the WHO declared COVID-19 pandemic).

9.12 Visit timing with respect to COVID-19 pandemic

A visit is defined to be performed after the start of COVID-19 pandemic if the visit end date is greater than the start of COVID-19 pandemic date.

10 Study Participants

The subsections in this section include specifications for reporting participant disposition and study intervention/study discontinuations. Additionally, procedures for reporting PDs are provided.

10.1 Disposition of Participants and Discontinuations

This section describes participant disposition in the extension study.

Participant disposition in this Extension Study will be presented for the ES:

- Total number of participants enrolled in the MAGNIFY MS Extension Study (i.e., participants who gave informed consent for the Extension Study)
- Number of participants who discontinued in the Screening phase by the main reason:
  - Subject did not meet all eligibility criteria
  - Withdrawal by subject
  - Progressive Disease
  - Adverse Event
  - Lost to Follow-up
  - Death
  - Other
- Number of eligible participants in the Extension Study, overall and by the following categories:
  - Number and percentage of eligible participants enrolled before the start of COVID-19
  - Number and percentage of eligible participants ongoing at data cut-off (applicable to IAs only)
  - Number and percentage of eligible participants who completed the study
  - Number and percentage of eligible participants who discontinued the study, with the primary reason of discontinuation:
    - Withdrawal by subject

- Progressive disease
- Adverse event
- Lost to follow-up
- Death
- Protocol non-compliance
- Other

The duration of gap period between MAGNIFY MS Trial and MAGNIFY Extension Study Baseline will be summarized using the following classes:

- No gap (i.e., Month 24 Visit and Extension Baseline coincide)
- Duration of gap period < 1 month
- Duration of gap period ≥ 1 month and < 3 months
- Duration of gap period ≥ 3 months and < 6 months
- Duration of gap period ≥ 6 months and < 9 months
- Duration of gap period ≥ 9 months and ≤ 12 months
- Duration of gap period > 12 months

Additionally, duration of gap period will be summarized using descriptive statistics.

Percentages will be presented with respect to the number of eligible participants.

The number of participants in each analysis set will be provided overall, by region, by country within region and by site.

The following participant data listings will be provided:

- Listing of discontinued participants for the FAS,
- Listing of participants excluded from the Analysis Sets.

10.2 Protocol Deviations / Exclusion from Analysis Sets

10.2.1 Important Protocol Deviations

Important protocol deviations (IPDs) are a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being.

Important protocol deviations will be identified for all participants by either site monitoring, medical review processes or programming and confirmed prior to or at the Data Review Meeting at the latest.

Any IPD is documented in SDTM datasets whether identified through site monitoring, medical review or programming. The management of protocol deviations is outside of this IAP document.

The following summary tables and listings of IPDs will be provided for the FAS:

- Number and proportion of participants with IPDs by classification of IPDs (overall and based on relationship to COVID-19 pandemic),
- Listing of IPDs (including information regarding relationship to COVID-19 pandemic).

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

A frequency table, as well as a listing, organized according to reasons for exclusion from the FAS and TCS, respectively, will be provided, if applicable.

Possible reasons for exclusion from the FAS include:

- Not fulfill any of the inclusion criteria
    - Participants of the MAGNIFY MS trial who received at least a single dose of cladribine tablets during the MAGNIFY MS trial
    - Data on MRI is available/acquired from at least parent study Month 18 or Month 24 visit
    - Data on EDSS and relapse is available/acquired from parent study Month 24 visit
    - Capable of giving signed informed consent
- Meet any of the exclusion criteria
    - Participant is considered by the Investigator, for any reason, to be an unsuitable candidate for the study
    - Participation in other studies/trials

Possible reasons for exclusion from the TCS include:

- Participants are not included in the FAS
- Participants did not complete the full treatment course of the first and second year in the parent study

11 Demographics and Other Baseline Characteristics

If not stated otherwise, the following analyses will be performed based on the FAS.

11.1 Demographics

Demographic characteristics will be summarized descriptively using the information from the Screening/Baseline Visit eCRF pages in the MAGNIFY MS trial. The data will be presented in a summary table as well as a listing as specified in MAGNIFY MS IAP version 3.0. In addition, age at time of informed consent as collected from the "Demographics" eCRF page in the MAGNIFY MS Extension Study will be added in both the summary table and the listing.

11.2 Medical History

The medical history will be summarized from the "Medical History" eCRF page of the MAGNIFY MS Extension Baseline, using the most recent Medical Dictionary for Regulatory Activities (MedDRA) version at time of database lock, preferred term (PT) as event category and system organ class (SOC) body term as Body System category. Each participant will be counted only once within each PT or SOC.

Additionally, also the medical history from the "Medical History" eCRF page of the MAGNIFY MS Baseline, using the MedDRA version that has been applied for coding of Medical History in the parent study, will be summarized as well.

Medical history will be displayed in terms of frequency tables: ordered by primary SOC and PT in alphabetical order.

11.3 Other Baseline Characteristics

Other baseline characteristics at MAGNIFY MS Baseline, including MS Disease Characteristics, MRI Baseline Characteristics and Vital Signs, will be presented as specified in MAGNIFY MS IAP version 3.0.

EDSS assessment at Extension Baseline Visit was performed for almost all participants, regardless of whether they had a gap period, and will be listed only. The EDSS scores of participants who had a gap period will still be considered for determining disease progression, as planned in the CSP.

12 Previous or Concomitant Therapies/Procedures

Relevant previous medications at MAGNIFY MS Baseline will be summarized as specified in MAGNIFY MS IAP version 3.0.

Concomitant medications are medications, other than study medications, which are taken by participants after the initial dose of cladribine tablets (including the study period of the MAGNIFY MS trial and the Extension Study which is including the gap period between the MAGNIFY MS trial and MAGNIFY MS Extension Study).

Concomitant medications will be summarized separately for the study period of the MAGNIFY MS trial and the Extension Study Period.

Data will be used from the "Concomitant medication" eCRF page of the MAGNIFY MS trial and the Extension Study. All medications entered into the "Concomitant medication" eCRF page will be assumed to be "concomitant" irrespective of the actual start and end dates.

Anatomical Therapeutic Chemical classification (ATC)-1st level and PT will be tabulated as given from the World Health Organization Drug Dictionary (WHO-DD) dictionary. In case multiple ATCs are assigned to a drug, all ATC-1st level will be used for reporting.

The most current WHO-DD dictionary version at time of MAGNIFY Extension Study analysis data base lock will be used only for MAGNIFY MS Extension Study. For MAGNIFY MS parent study, the version of that has been used for coding of concomitant medications will apply. The WHO-DD dictionary used for coding will be listed as a footnote of corresponding table or listing.

Additionally, all DMDs which have been reported for the study period of the MAGNIFY MS trial and the MAGNIFY MS Extension Study will be presented together by PT. The updated list of DMDs (see Appendix 18.1) will be used to identify DMD in concomitant medications in MAGNIFY MS Extension Study instead of the parent study DMD list (see MAGNIFY MS IAP version 3.0). List could further be updated before database lock.

Concomitant procedures which were undertaken any time during the Extension Study Period will be listed by participant for the SAF.

13 Study Intervention: Compliance and Exposure

As no treatment is provided in the Extension Study, participants' compliance and exposure in the MAGNIFY MS trial will be presented for the Extension Study SAF as defined in MAGNIFY MS IAP version 3.0.

14 Efficacy Analyses

The following analyses will be performed based on the FAS except when otherwise stated.

For the detailed definition of covariates and stratification factors that are used in the statistical models see Section 9.10. Details about the derived MRI endpoints and general handling of MRI data is described in Section 9.8.

Descriptive summary statistics will be presented for the absolute values and the changes from Baseline as applicable by Visit [Protocol Scheduled Visits except for Baseline (defined in Section 9.1)] for all efficacy endpoints (and the components, where applicable) for the FAS and respective subgroups for which the variables are analyzed. Details about the presentation of continuous and categorical variables are given in Section 9.

Wherever possible, all estimated results from the statistical models will be calculated with the same observed margin which reflects the population of the whole corresponding analysis set, regardless of missing data (as described in MAGNIFY MS IAP version 3.0).

14.1 Primary Endpoint: Proportion of participants with No Evidence of Disease Activity (three parameter [NEDA-3]) during Year 3 Visit and Year 4 Visit Period after the initial dose of cladribine tablets

The primary endpoint for the Extension Study is defined as the proportion of participants with NEDA-3 during Year 3 Visit and Year 4 Visit Period after the initial dose of cladribine tablets, i.e., NEDA-3 during the following period will be evaluated:

- Year 3 Visit and Year 4 Visit Period (i.e., Extension Study Period)

For the detailed definition of Periods, see Section 9.6.

14.1.1 Primary Objective: Derivation and analysis of the primary endpoint

No Evidence of Disease activity (NEDA), also referred to as freedom from disease activity, is a new goal that is emerging in MS treatment. NEDA is a composite measure of disease activity, including relapses, cognition and disability progression, and MRI activity.

NEDA-3 during the Extension Study Period is defined as absence of the following three events during the Period:

- Qualifying Relapses
- 6-months Confirmed Disability Progression (6MCDP, see definition below)
- MRI Activity (i.e., presence of T1 Gd+ lesions and/or active T2 lesions)

NEDA-3 will be analyzed with the Kaplan-Meier (KM) time-to-event method to reduce the impact of unknown/missing information.

The start date will be the end date of M24 Visit + 1.

The event date will be defined as the minimum of

- the onset date of the first qualifying relapses during the Extension Study Period
- the start date of the first 6MCDP during the Extension Study Period (see definition below)
- the scan date of the first MRI during the Extension Study Period where at least one T1 Gd+ lesion or at least one active T2 lesion (see Section 9.8 for definition) is identified.

Imputation of partial onset dates of relapses is described in Section 9.7. Since full dates of MRI scan and EDSS assessment are mandatory, partial dates of 6MCDP, or MRI Activity are not expected.

If the participant did not experience any of the three events described above during the Extension Study Period, the minimum of the scan date of the last available MRI, the assessment date of the last available EDSS, and the Extension Study completion/discontinuation date will be used as the censoring date.

The time to disease activity (in months) will be calculated as [event date or censoring date as applicable – start date + 1]/30.4375. The number of participants at risk, failed, and survival rate (i.e., the proportion of participants with NEDA-3) along with the 95% CI will be estimated as per the KM method and reported at 6-months intervals. The KM survival curve will be plotted as well.

A descriptive summary of number and proportion of participants with event (overall and by type of event, i.e., qualifying relapse, 6MCDP, or MRI activity as the earliest event) and censored will be also presented.

6MCDP

The 6MCDP during Extension Study Period is defined as sustained increase in EDSS score that started during the Period. A Sustained Increase in EDSS score is defined by an increase of:

- at least 1.5 points if the Baseline EDSS score was 0, or
- at least 1 point if Baseline EDSS score was between 0.5 and 4.5 inclusively, or
- at least 0.5 point if the Baseline EDSS score was at least 5,

that occurs over a 6-months' time-period.

The increase will be defined as sustained when it occurs on two post-Baseline Visits during the Extension Study Period that are at least 166 days apart (to be consistent with the parent study minimum visit gap) and no observations at any other visits (including unscheduled visits) in between are less than the defined increase. The assessment date of the earlier of the two EDSS assessments with the defined increase will be defined as the start date of 6MCDP.

For descriptive summaries the following rules will be defined:

Qualifying Relapse

- Yes: any qualifying relapse reported during the Extension Study Period,
- No: Extension study period completed, and no qualifying relapse reported during the Extension Study Period,
- Unknown: otherwise.

6MCDP

- Yes: sustained increase in EDSS score that started during the Extension Study Period,

- No: at least 2 post-Baseline EDSS assessments that are 166 (or more) apart and no sustained EDSS progression that started during the Extension Study Period,
- Unknown: Otherwise.

MRI activity

- Yes: any T1-Gd+ or active T2 observed during the Extension Study Period,
- No: at least one post-Baseline MRI and no T1-Gd+ or active T2 observed during the Extension Study Period,
- Unknown: otherwise.

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Primary endpoint: Proportion of participants with NEDA-3 during Year 3 Visit and Year 4 Visit Period after the initial dose of cladribine tablets			
Primary (FAS)	Time to event: [event date or censoring date as applicable – start date + 1]/30.4375	KM time-to-event: The number of participants at risk, failed, and survival rate (i.e., the proportion of participants with NEDA-3) along with the 95% CI will be estimated as per the KM method and reported at 6-months intervals. The KM survival curve will be plotted as well.	Imputation for partial dates is described in Section 9.7. Participants experienced no event will be censored as defined above (minimum of the scan date of the last available MRI scan, the assessment date of the last available EDSS, and the study completion/discontinuation date).

14.1.2 Primary Objective: Sensitivity Analyses of the Primary Endpoints

The robustness of the results of the primary analysis will be evaluated by the following:

- The primary analysis will be repeated on the TCS
- The primary analysis will be repeated by subgroup “Previous treatment with DMDs” on the FAS.

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Primary endpoint: Proportion of participants with NEDA-3 during Year 3 Visit and Year 4 Visit Period after the initial dose of cladribine tablets			
Sensitivity (TCS)	Same as in the Primary Analysis (see Section 14.1.1)	Same as in the Primary Analysis (see Section 14.1.1)	Same as in the Primary Analysis (see Section 14.1.1)
Sensitivity (FAS by subgroup "Previous treatment with DMDs")	Same as in the Primary Analysis (see Section 14.1.1)	Same as in the Primary Analysis (see Section 14.1.1) with KM estimates reported by subgroup.	Same as in the Primary Analysis (see Section 14.1.1)
Sensitivity (FAS)	Crude percentages and time to event with descriptive summaries for qualifying relapse, 6MCDP, or MRI activity and NEDA	A descriptive summary of number and proportion of participants with event A descriptive summary of time to earliest event (overall and by type of event, i.e., qualifying relapse, 6MCDP, or MRI activity).	Missings will be presented in a separate category

14.2 Secondary Endpoints

14.2.1 No Evidence of Disease Activity

As a secondary analysis, NEDA-3 during the following Periods (see definition in Section 9.6) will be analyzed similarly as in the primary analysis using the KM method:

Year 3 Visit Period

- Start date: end date of M24 Visit (see definition in Section 14.1.1) + 1
- Event date: same as in Section 14.1.1 accounting for events started during Year 3 Visit Period only
- Censoring date: the minimum of the scan date of the last available MRI during Year 3 Visit Period, the assessment date of the last available EDSS during Year 3 Visit Period, and the end date of Year 3 Visit Period (see definition in Section 9.6)

Year 4 Visit Period

- Start date: end date of M36 Visit + 1
- Event date: same as in Section 14.1.1 accounting for events started during Year 4 Visit Period only

- Censoring date: the minimum of the scan date of the last available MRI during Year 4 Visit Period, the assessment date of the last available EDSS during Year 4 Visit Period, and the Extension Study completion/discontinuation date

After start of study medication until end of Year 3 Visit Period

- Start date: date of Day 1 as defined in Section 9.5
- Event date: The event date will be defined as the minimum of
    - the onset date of the first qualifying relapses during the Parent and Extension Study Period
    - the start date of the first 6MCDP during the Parent and Extension Study Period
    - the scan date of the first MRI during the Parent and Extension Study Period where at least one T1 Gd+ lesion or at least one active T2 lesion (see Section 9.8 for definition) is identified,

  accounting for events started during "After start of study medication until end of Year 3 Visit Period" only.
- Censoring date: the minimum of the scan date of the last available MRI during "After start of study medication until end of Year 3 Visit Period", the assessment date of the last available EDSS during "After start of study medication until end of Year 3 Visit Period", and the end date of "After start of study medication until end of Year 3 Visit Period" (see definition in Section 9.6)

After start of study medication until end of Year 4 Visit Period (i.e. Parent and Extension Study Period)

- Start date: date of Day 1 as defined in Section 9.5
- Event date: same as for "After start of study medication until end of Year 3 Visit Period" accounting for events started during "After start of study medication until end of Year 4 Visit Period"
- Censoring date: the minimum of the scan date of the last available MRI during "After start of study medication until end of Year 4 Visit Period", the assessment date of the last available EDSS during "After start of study medication until end of Year 4 Visit Period", and the Extension Study completion/discontinuation date

Year 3 Visit Period (or Year 4 Visit Period) among participants with NEDA-3 during Course 1 Treatment Period (or Course 2 Treatment Period)

Analysis of NEDA-3 during the Year 3 Visit Period and analysis of NEDA-3 during the Year 4 Visit Period as defined above will be repeated, respectively, on the subset of participants with

NEDA-3 during Course 1 Treatment Period and on the subset of participants with NEDA-3 during Course 2 Treatment Period.

NEDA-3 during Course 1 Treatment Period is defined similarly as in Section 14.3.12 of MAGNIFY MS IAP version 3.0 with just Treatment Period replaced by Course 1 Treatment Period and the following definition for MRI activity:

- Yes: At least one T1 Gd+ at any scan assigned to Month 6, Month 12 Visit, or at least one active T2 during any of the following Periods: Baseline - Month 6, Month 6 - Month 12.
- No: T1 Gd+ = 0 at all scans assigned to Month 6, Month 12 Visit that have a value and at least one T1 Gd+ value from Month 6 or Month 12 Visit is available, and all active T2 = 0 during any of the following Periods: Baseline - Month 6, Month 6 - Month 12 that have a value and at least one active T2 value from Periods Baseline – Month 6 or Month 6 – Month 12 is available.
- Unknown: Otherwise.

NEDA-3 during Course 2 Treatment Period is defined similarly as in Section 14.3.12 of MAGNIFY MS IAP version 3.0 with just Treatment Period replaced by Course 2 Treatment Period and the following definition for MRI activity:

- Yes: At least one T1 Gd+ at any scan assigned to Month 18, Month 24 Visit, or at least one active T2 during any of the following Periods: Month 12 - Month 18, Month 18 - Month 24.
- No: T1 Gd+ = 0 at all scans assigned to Month 18, Month 24 Visit that have a value and at least one T1 Gd+ value from Month 18 or Month 24 Visit is available, and all active T2 = 0 during any of the following Periods: Month 12 - Month 18, Month 18 - Month 24 that have a value and at least one active T2 value from Periods Month 12 - Month 18, Month 18 - Month 24 is available.
- Unknown: Otherwise.

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Secondary endpoint: Proportion of participants with NEDA-3 during Year 3 Visit Period			
Secondary (FAS)	Time to event: [event date or censoring date as applicable – start date + 1]/30.4375 for NEDA-3 events started during the Year 3 Visit Period	Same as in the primary analysis (see Section 14.1.1 and for subgroup analysis see Section 14.1.2)	Same as in the primary analysis (see Section 14.1.1)
Secondary (FAS by subgroup "Previous treatment with DMDs")			

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Secondary (FAS for subset "participants with NEDA-3 during Course 1 Treatment Period")			
Secondary (FAS for subset "participants with NEDA-3 during Course 2 Treatment Period")			
Secondary endpoint: Proportion of participants with NEDA-3 during Year 4 Visit Period			
Secondary (FAS)	Time to event: [event date or censoring date as applicable – start date + 1]/30.4375 for NEDA-3 events started during the Year 4 Visit Period	Same as in the primary analysis (see Section 14.1.1 and for subgroup analysis see Section 14.1.2)	Same as in the primary analysis (see Section 14.1.1)
Secondary (FAS by subgroup "Previous treatment with DMDs")			
Secondary (FAS for subset "participants with NEDA-3 during Course 1 Treatment Period")			
Secondary (FAS for subset "participants with NEDA-3 during Course 2 Treatment Period")			
Secondary endpoint: Proportion of participants with NEDA-3 during "After start of study medication until end of Year 3 Visit Period"			
Secondary (FAS)			Same as in the primary analysis (see Section 14.1.1)

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Secondary (FAS by subgroup "Previous treatment with DMDs")	Time to event: [event date or censoring date as applicable – start date + 1]/30.4375 for NEDA-3 events started during the "After start of study medication until end of Year 3 Visit Period"	Same as in the primary analysis (see Section 14.1.1 and for subgroup analysis see Section 14.1.2)	
Secondary (FAS)	Crude percentages and time to event with descriptive summaries for qualifying relapse, 6MCDP, or MRI activity and NEDA	A descriptive summary of number and proportion of participants with event A descriptive summary of time to earliest event (overall and by type of event, i.e., qualifying relapse, 6MCDP, or MRI activity).	Missings will be presented in a separate category
Secondary endpoint: Proportion of participants with NEDA-3 during "After start of study medication until end of Year 4 Visit Period"			
Secondary (FAS) Secondary (FAS by subgroup "Previous treatment with DMDs")	Time to event: [event date or censoring date as applicable – start date + 1]/30.4375 for NEDA-3 events started during the "After start of study medication until end of Year 4 Visit Period"	Same as in the primary analysis (see Section 14.1.1 and for subgroup analysis see Section 14.1.2)	Same as in the primary analysis (see Section 14.1.1)
Secondary (FAS)	Crude percentages and time to event with descriptive summaries for qualifying relapse, 6MCDP, or MRI activity and NEDA	A descriptive summary of number and proportion of participants with event A descriptive summary of time to earliest event (overall and by type of event, i.e., qualifying relapse, 6MCDP, or MRI activity).	Missings will be presented in a separate category

14.2.2 Time to First Disease Activity

Time to first disease activity is defined as the time to first occurrence of either qualifying relapse, or 6MCDP, or new or enlarging T2-hyperintense lesions (active T2 lesions), or new T1 Gd+ lesions. This will be evaluated for the following Periods with corresponding start dates defined below:

- Extension Study Period
    - Start date for time to first disease activity: end date of M24 Visit + 1 (as defined in Section 14.1.1)
- Parent and Extension Study Period

- Start date for time to first disease activity: date of Day 1 (as defined in Section 9.5)

Since events described above are the same events as in NEDA-3 definition, the event date will be defined the same as in Sections 14.1.1 or 14.2.1, accounting for only events started during the above Periods, respectively. If the participant did not experience any disease event during a Period, the minimum of the scan date of the last available MRI during this Period, the assessment date of the last available EDSS during this Period, and the Extension Study completion/discontinuation date will be used as the censoring date.

Time to first disease activity (in months) will be calculated as [event date or censoring date as applicable – start date of the Period + 1]/30.4375 and the 5%, 10%, 15%, 25% percentile and median time to first disease activity will be estimated using the KM method along with the 95% CI.

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Secondary endpoint: Time from M24 Visit to first disease activity			
Secondary (FAS)	Time to event: [event date or censoring date as applicable – start date + 1]/30.4375 for disease activities started during Extension Study Period	KM time-to-event: 5%, 10%, 15%, 25% percentiles and Median time to disease activity will be estimated as per the KM method and reported along with the corresponding 95% CI.	Same as Section 14.1.1
Secondary (FAS by subgroup "Previous treatment with DMDs")	Same as above	Same as above with KM estimates reported by subgroup.	Same as Section 14.1.1
Secondary endpoint: Time from initial dose of cladribine tablets to first disease activity			
Secondary (FAS)	Time to event: [event date or censoring date as applicable – start date + 1]/30.4375 for disease activities started during Parent and Extension Study Period	Same as above.	Same as above.
Secondary (FAS by subgroup "Previous treatment with DMDs")			

14.2.3 Time to MRI Activities, 6MCDP, Qualifying Relapse and Treatment Start with Other DMDs

Time (in months) from the initial dose of cladribine tablets (i.e. start date = date of Day 1 as defined in Section 9.5) to the following events will be calculated as [event date or censoring date as applicable – start date + 1]/30.4375, and analyzed similarly as in Section 14.2.2 using the KM method.

- first new or enlarging T2 lesion
    - Event date: the scan date of the first MRI during the Parent and Extension Study Period where at least one active T2 lesion (see Section 9.8 for definition) is identified
    - Censoring date: participants with no active T2 lesion identified at any scans during the Parent and Extension Study Period will be censored at the scan date of the last available MRI during this Period
- first new T1 Gd+ lesion
    - Event date: the scan date of the first MRI during the Parent and Extension Study Period where at least one new T1 Gd+ lesion (see Section 9.8 for definition) is identified
    - Censoring date: participants with no new T1 Gd+ lesion identified at any scans during the Parent and Extension Study Period will be censored at the scan date of the last available MRI during this Period
- first 6MCDP, as measured by EDSS
    - Event date: the start date of the first 6MCDP during the Parent and Extension Study Period

      6MCDP during the Parent and Extension Study Period will be defined similarly as in Section 14.1.1 with just Extension Study Period replaced by Parent and Extension Study Period.
    - Censoring date: participants with no 6MCDP started during the Parent and Extension Study Period will be censored at the assessment date of the last available EDSS during this Period
- first qualifying relapse
    - Event date: the onset date of the first qualifying relapse during the Parent and Extension Study Period

- Censoring date: participants with no qualifying relapse reported during the Parent and Extension Study Period will be censored at the Extension Study completion/discontinuation date

Time (in months) from M24 Visit (i.e. start date = end date of M24 Visit + 1) to the following events will be calculated as (event date or censoring date as applicable – start date + 1)/30.4375, and analyzed similarly as in Section 14.2.2 using the KM method.

- first new or enlarging T2 lesion
  - Event date: the scan date of the first MRI during the Extension Study Period where at least one active T2 lesion (see Section 9.8 for definition) is identified
  - Censoring date: participants with no active T2 lesion identified at any scans during the Extension Study Period will be censored at the scan date of the last available MRI during this Period
- first new T1 Gd+ lesion
  - Event date: the scan date of the first MRI during the Extension Study Period where at least one new T1 Gd+ lesion (see Section 9.8 for definition) is identified
  - Censoring date: participants with no new T1 Gd+ lesion identified at any scans during the Extension Study Period will be censored at the scan date of the last available MRI during this Period
- first 6MCDP, as measured by EDSS
  - Event date: the start date of the first 6MCDP during the Extension Study Period (see definition in Section 14.1.1)
  - Censoring date: participants with no 6MCDP started during the Extension Study Period will be censored at the assessment date of the last available EDSS during this Period
- first qualifying relapse
  - Event date: the onset date of the first qualifying relapse during the Extension Study Period
  - Censoring date: participants with no qualifying relapse reported during the Extension Study Period will be censored at the Extension Study completion/discontinuation date
- treatment start with other DMDs

- Event date: the start date of the first other DMDs used during the Extension Study Period

- Censoring date: participants who did not use any other DMDs during the Extension Study Period will be censored at the Extension Study completion/discontinuation date

A recurrent event analysis will be performed on all qualifying relapses using the Mean Cumulative Function (MCF) method, where MCF(t) represents the mean cumulative number of relapses up to time t. The MCF estimate for recurrent events will be calculated and plotted for all qualifying relapses. The MCF Nelson estimates will be presented for every month along with their 95% CIs. The increase in MCF in each month, defined as MCF(t) - MCF(t-1) will also be displayed.

Time (in months) from the initial dose of cladribine tablets (i.e. start date = date of Day 1 as defined in Section 9.5) to each event and to censoring (as defined below) will be calculated as [event date or censoring date – start date + 1]/30.4375, and analyzed using the MCF method.

- recurrent qualifying relapse

    - Event date: the onset date of each qualifying relapse during the Parent and Extension Study Period

    - Censoring date: all participants with no qualifying relapse reported during the Parent and Extension Study Period will be censored at the Extension Study completion/discontinuation date

Time (in months) from M24 Visit (i.e. start date = end date of M24 Visit + 1) to each event and to censoring (as defined below) will be calculated as [event date or censoring date – start date + 1]/30.4375, and analyzed using the MCF method.

- recurrent qualifying relapse

    - Event date: the onset date of each qualifying relapse during the Extension Study Period

    - Censoring date: all participants with no qualifying relapse reported during the Extension Study Period will be censored at the Extension Study completion/discontinuation date

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Secondary endpoint: Time from the initial dose of cladribine tablets to MRI activities, 6MCDP, and qualifying relapse			
Secondary (FAS)		Same as in Section 14.2.2	Same as in Section 14.2.2

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Secondary (FAS by subgroup "Previous treatment with DMDs")	Time to event: [event date or censoring date as applicable – start date + 1]/30.4375 for first active T2 lesion identified during the Parent and Extension Study Period		
Secondary (FAS)	Time to event: [event date or censoring date as applicable – start date + 1]/30.4375 for first T1 Gd+ lesion identified during the Parent and Extension Study Period		
Secondary (FAS by subgroup "Previous treatment with DMDs")			
Secondary (FAS)	Time to event: [event date or censoring date as applicable – start date + 1]/30.4375 for first 6MCDP started during the Parent and Extension Study Period		
Secondary (FAS by subgroup "Previous treatment with DMDs")			
Secondary (FAS)	Time to event: [event date or censoring date as applicable – start date + 1]/30.4375 for first qualifying relapse reported during the Parent and Extension Study Period		
Secondary (FAS by subgroup "Previous treatment with DMDs")			
Secondary (FAS)			Same as Section 14.2.2

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Secondary (FAS by subgroup "Previous treatment with DMDs")	Time to event: [event date – start date + 1]/30.4375 for each qualifying relapse reported during the Parent and Extension Study Period and [censoring date – start date + 1]/30.4375 with censoring at Extension Study completion/discontinuation date for all participants	The MCF estimate for recurrent events will be calculated and plotted for all qualifying relapses. The MCF Nelson estimates will be presented for every month along with their 95% CIs. The increase in MCF in each month, defined as MCF(t) - MCF(t-1) will also be displayed.	
Secondary endpoint: Time from M24 Visit to MRI activities, 6MCDP, qualifying relapse, and treatment start with other DMDs			
Secondary (FAS)	Time to event: [event date or censoring date as applicable – start date + 1]/30.4375 for first active T2 lesion identified during the Extension Study Period	Same as in Section 14.2.2	Same as in Section 14.2.2
Secondary (FAS by subgroup "Previous treatment with DMDs")			
Secondary (FAS)	Time to event: [event date or censoring date as applicable – start date + 1]/30.4375 for first T1 Gd+ lesion identified during the Extension Study Period		
Secondary (FAS by subgroup "Previous treatment with DMDs")			
Secondary (FAS)	Time to event: [event date or censoring date as applicable – start date + 1]/30.4375 for first 6MCDP started during the Extension Study Period		
Secondary (FAS by subgroup "Previous treatment with DMDs")			
Secondary (FAS)			

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Secondary (FAS by subgroup "Previous treatment with DMDs")	Time to event: [event date or censoring date as applicable – start date + 1]/30.4375 for first qualifying relapse reported during the Parent and Extension Study Period		
Secondary (FAS)	Time to event: [event date or censoring date as applicable – start date + 1]/30.4375 for other DMDs started during the Extension Study Period		
Secondary (FAS by subgroup "Previous treatment with DMDs")			
Secondary (FAS)	Time to event: [event date – start date + 1]/30.4375 for each qualifying relapse reported during the Extension Study Period and [censoring date – start date + 1]/30.4375 with censoring at Extension Study completion/discontinuation date for all participants	The MCF estimate for recurrent events will be calculated and plotted for all qualifying relapses. The MCF Nelson estimates will be presented for every month along with their 95% CIs. The increase in MCF in each month, defined as MCF(t) - MCF(t-1) will also be displayed.	Same as Section 14.2.2
Secondary (FAS by subgroup "Previous treatment with DMDs")			

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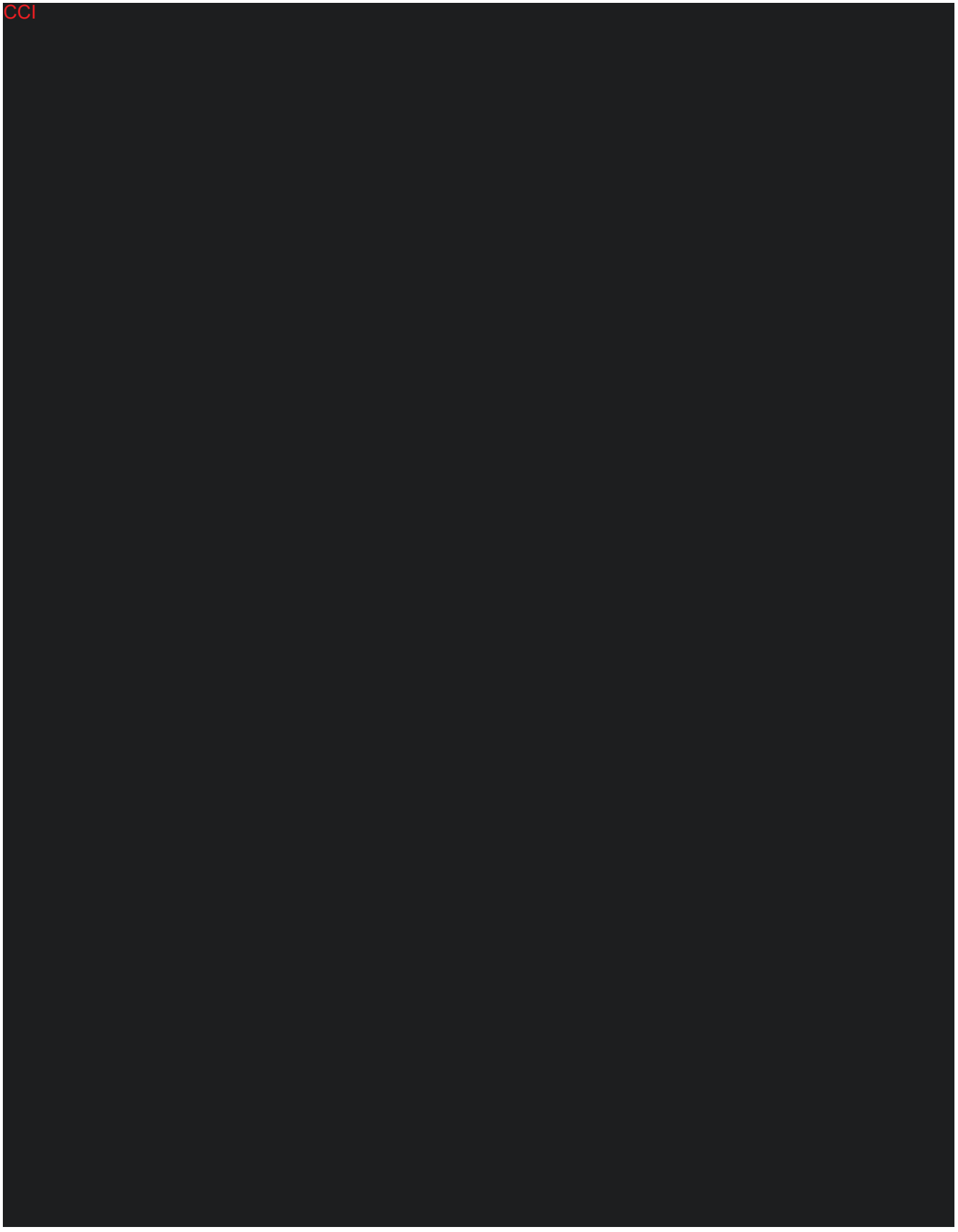

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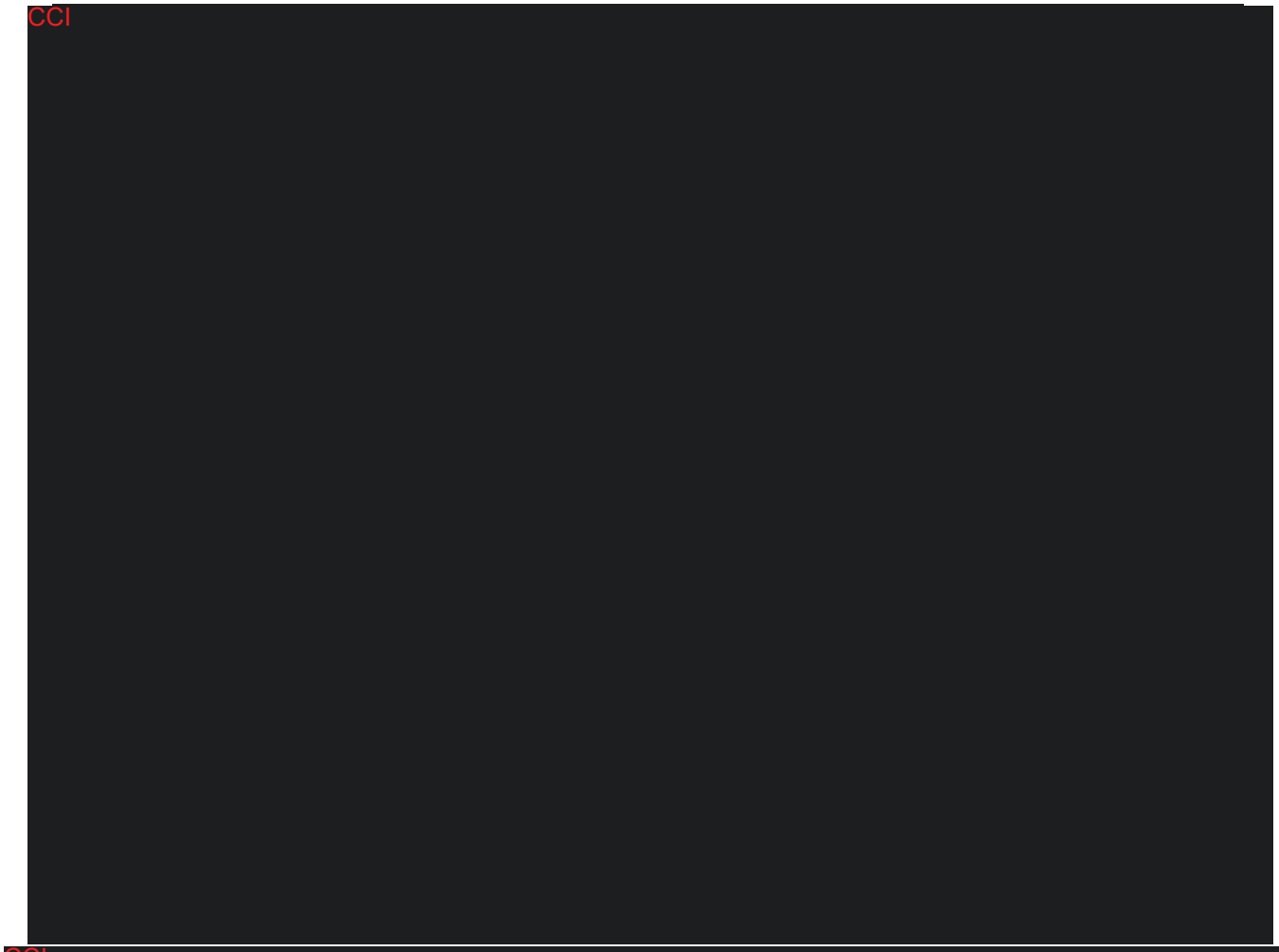

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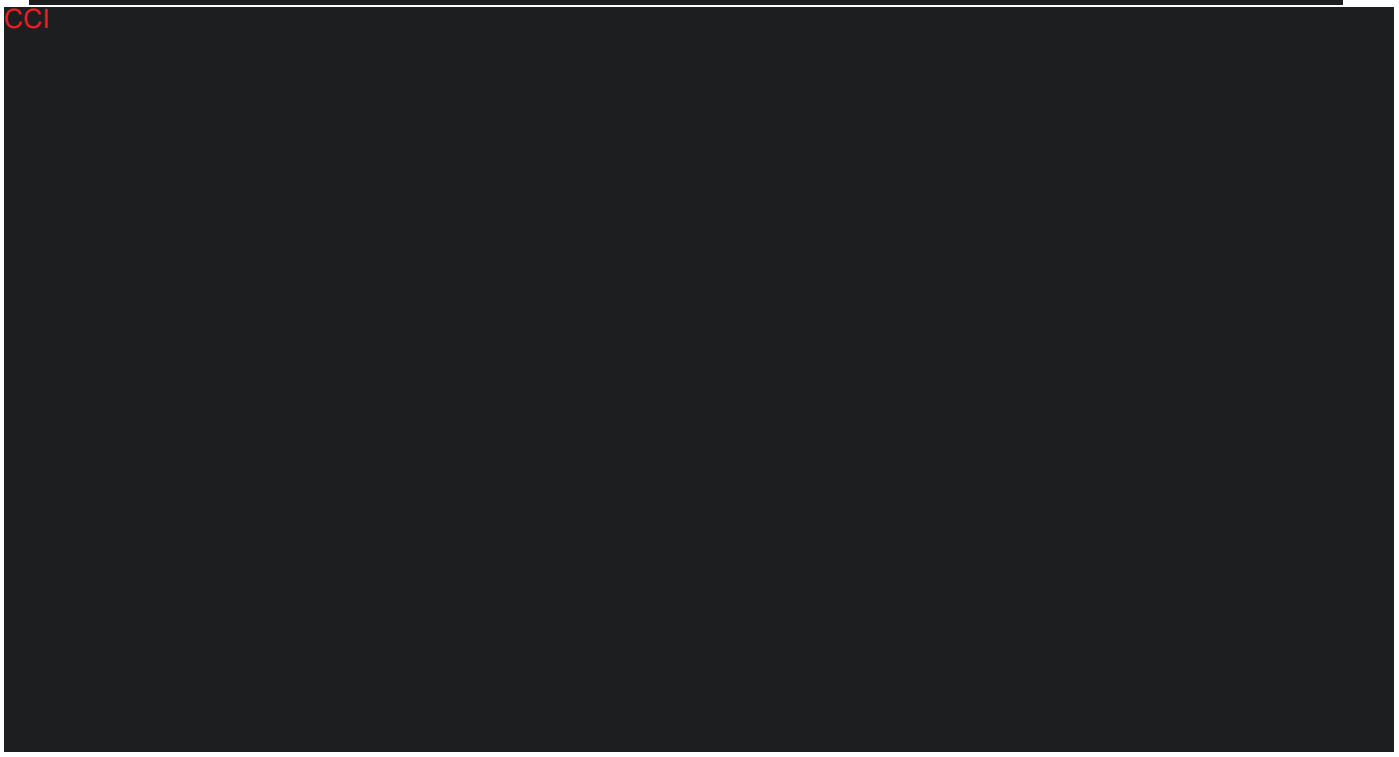

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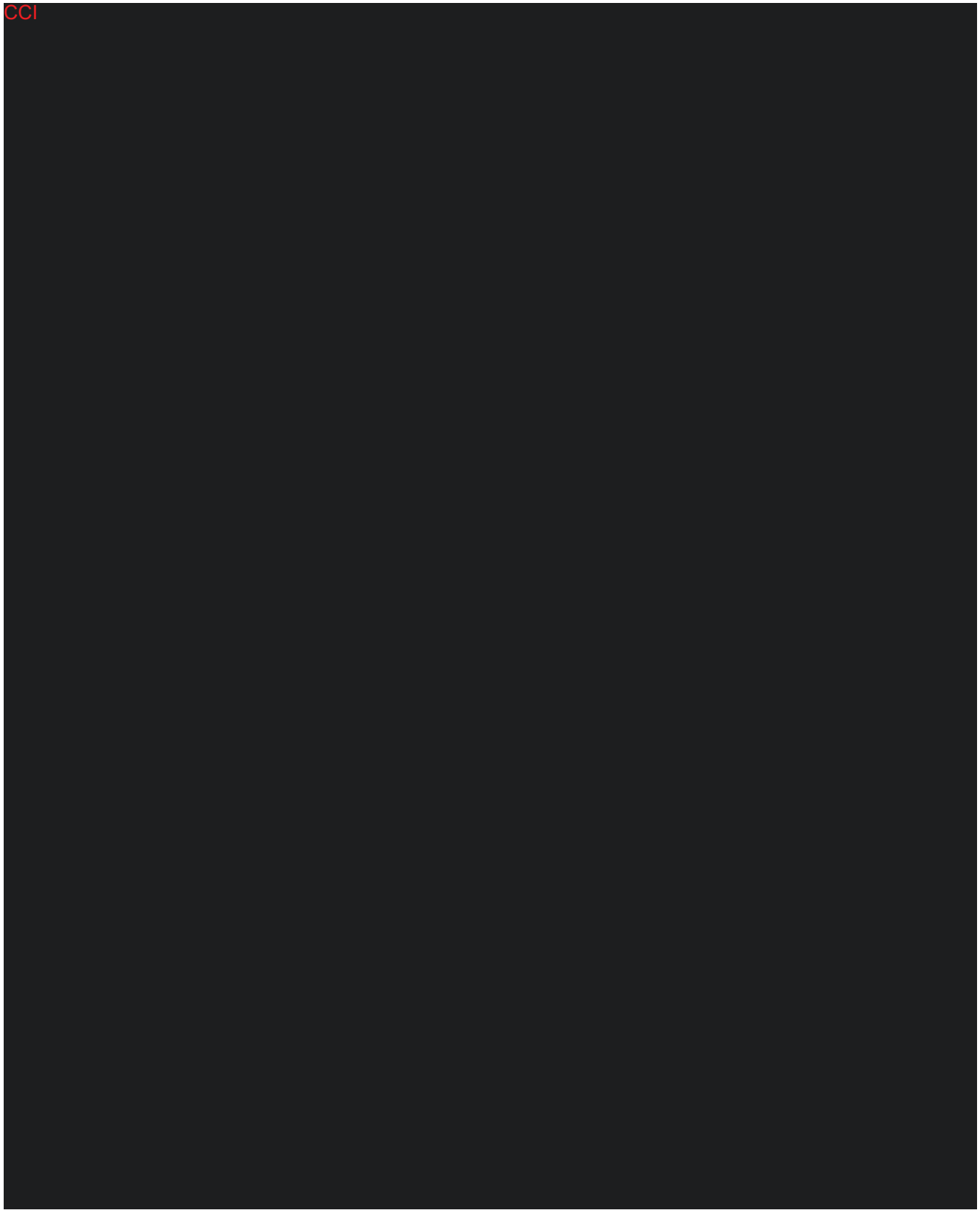

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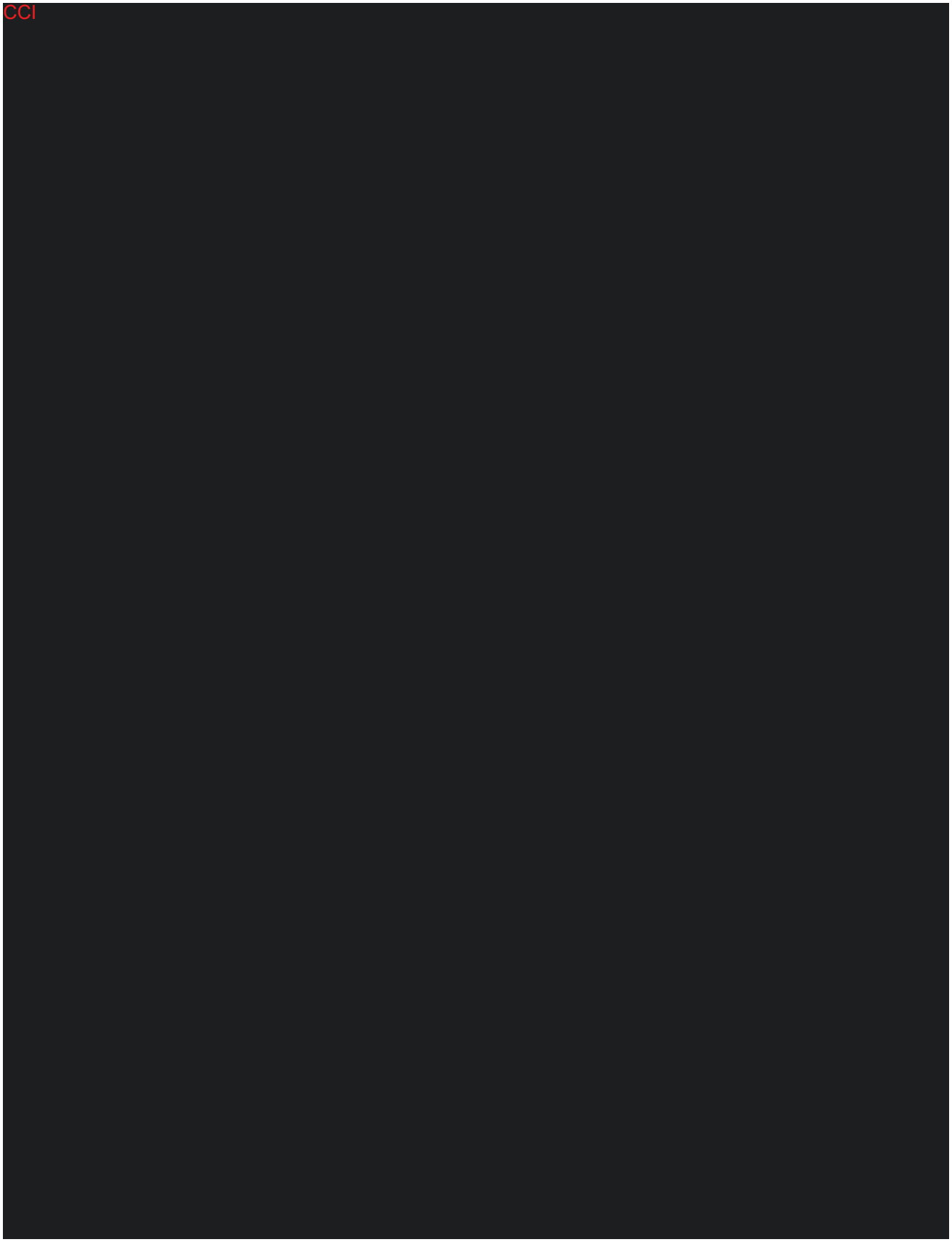

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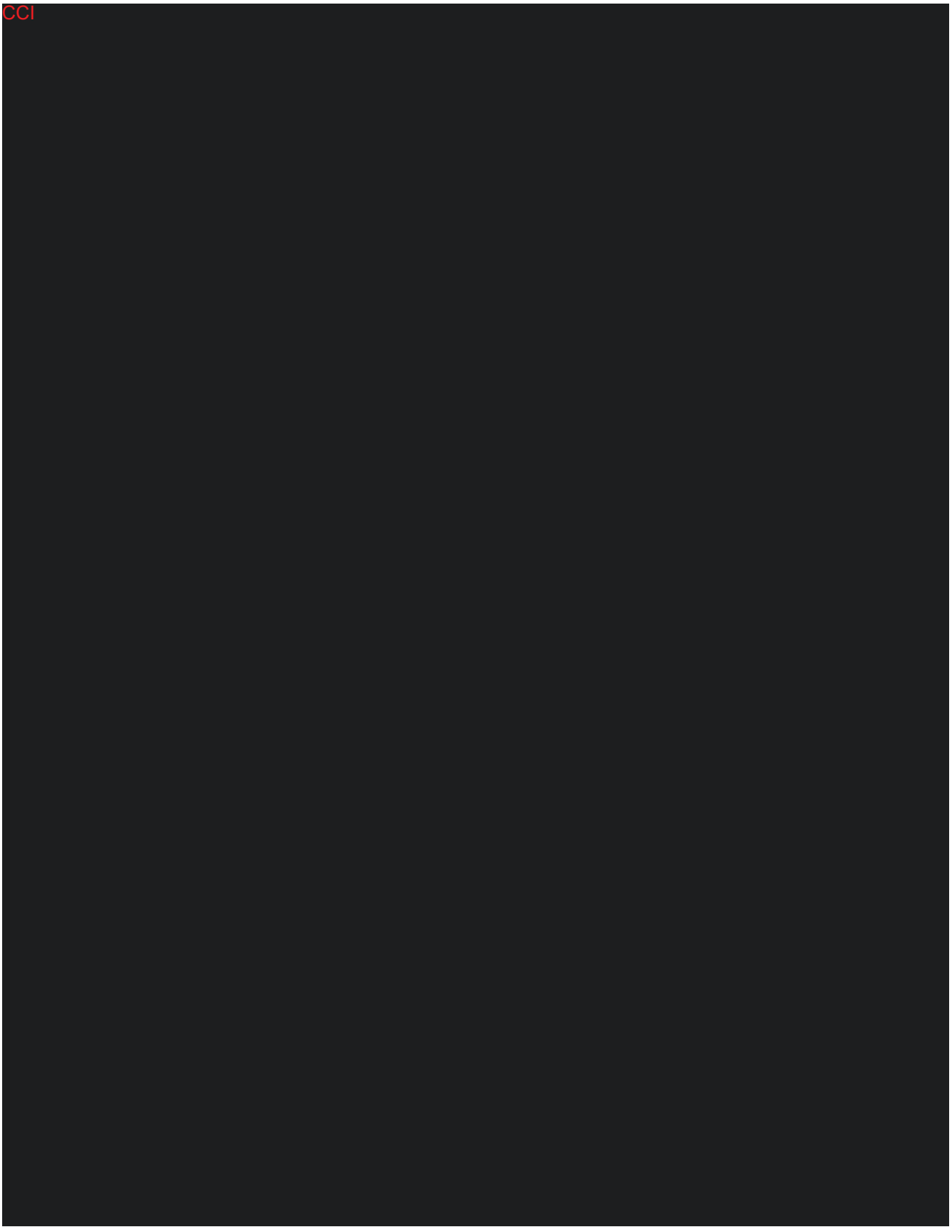

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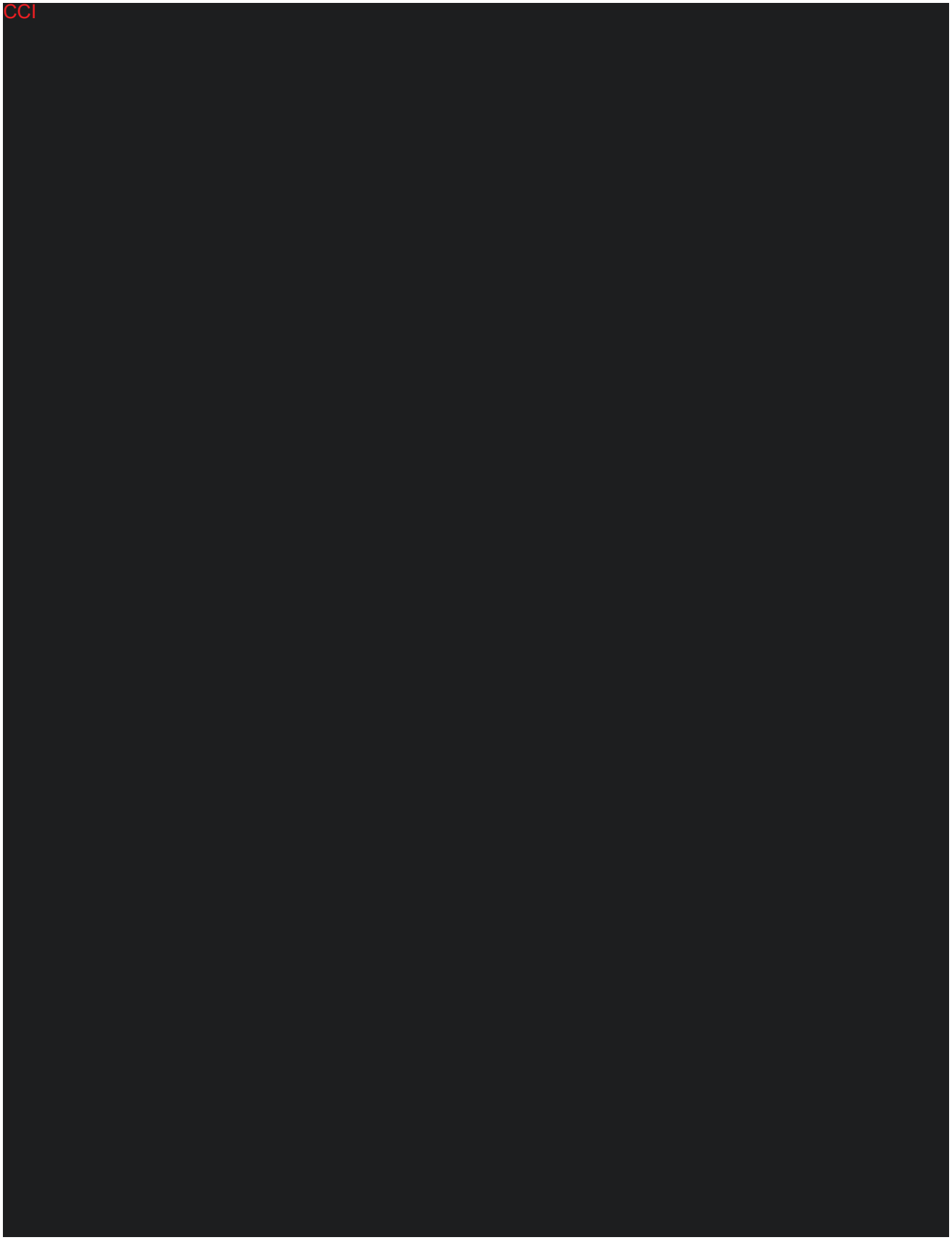

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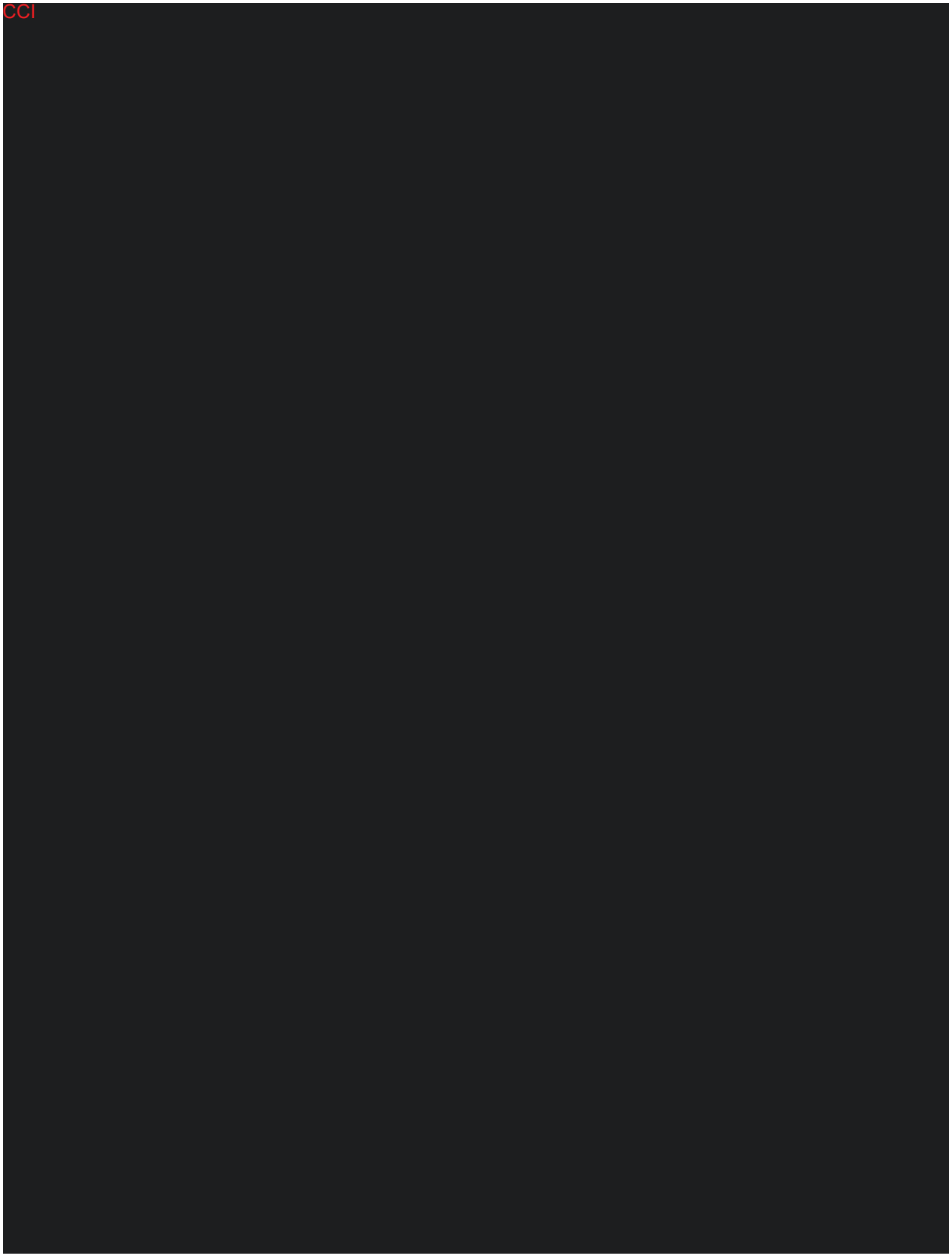

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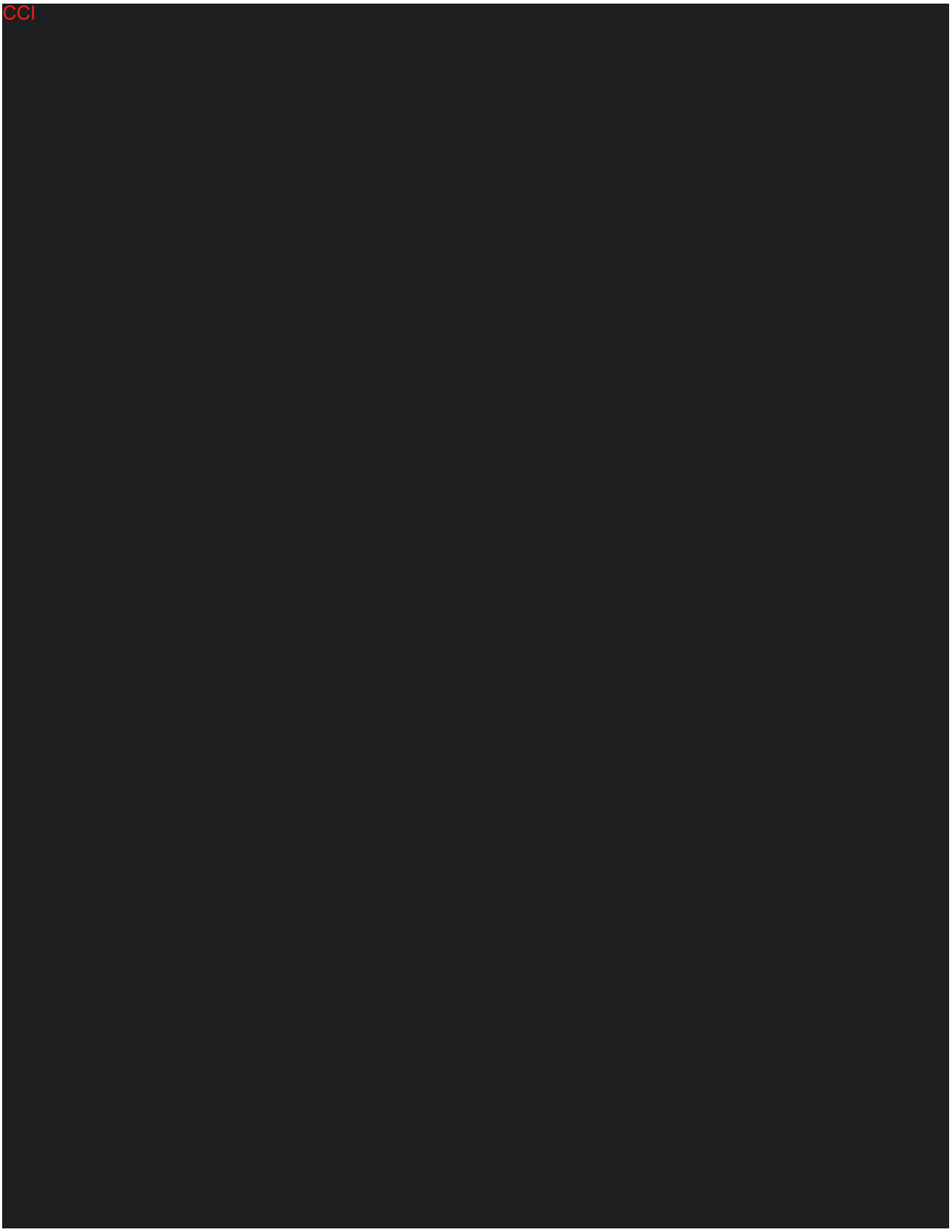

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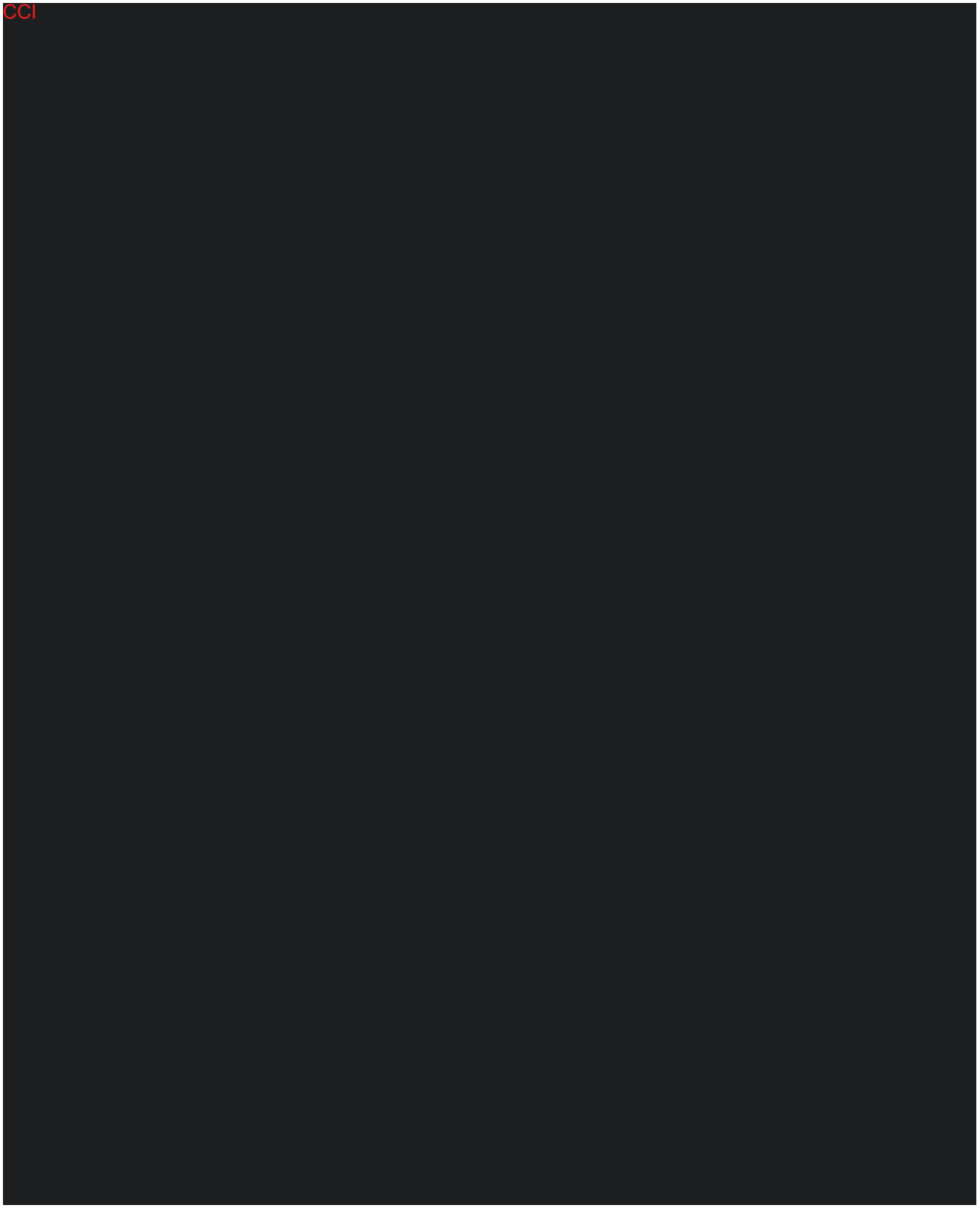

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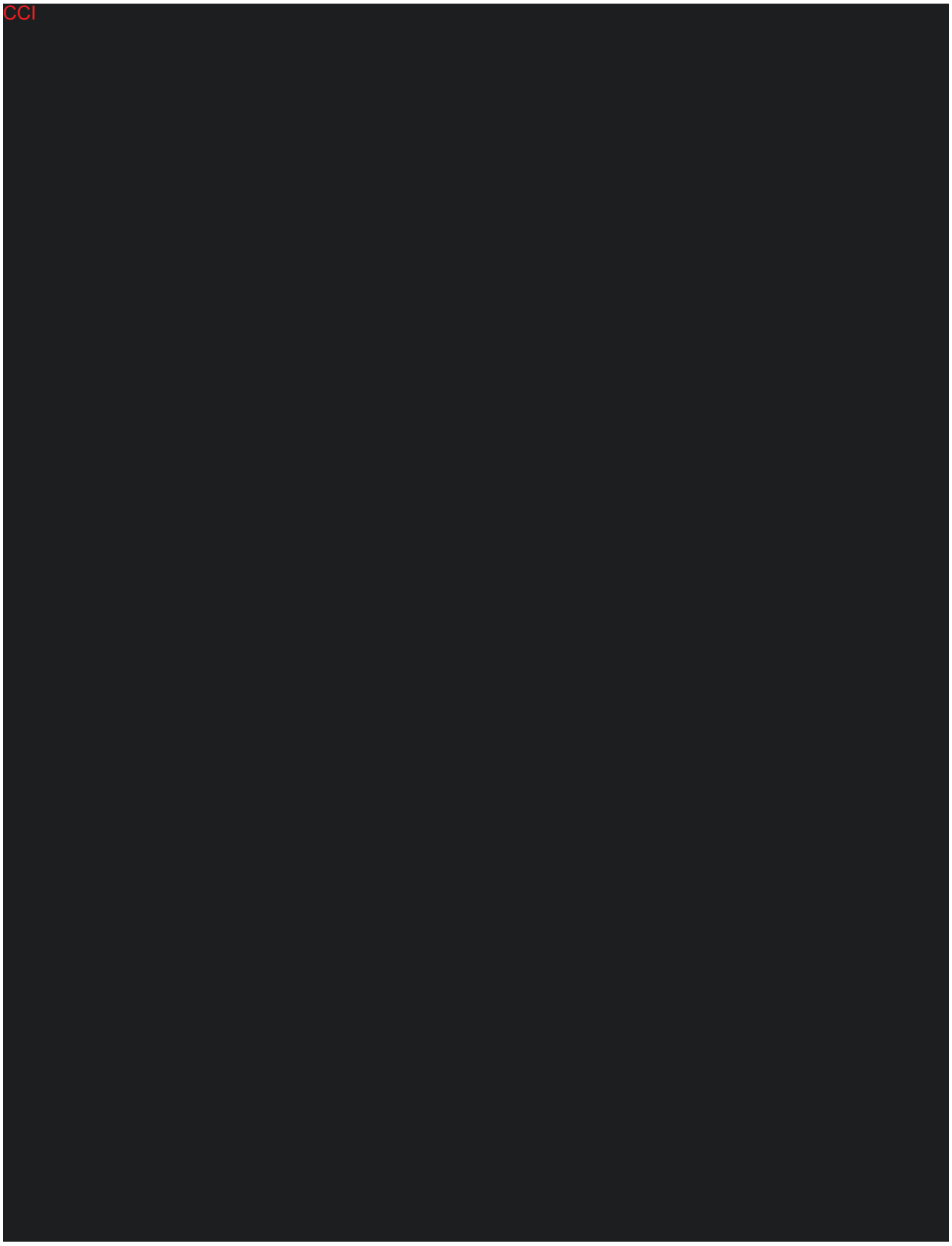

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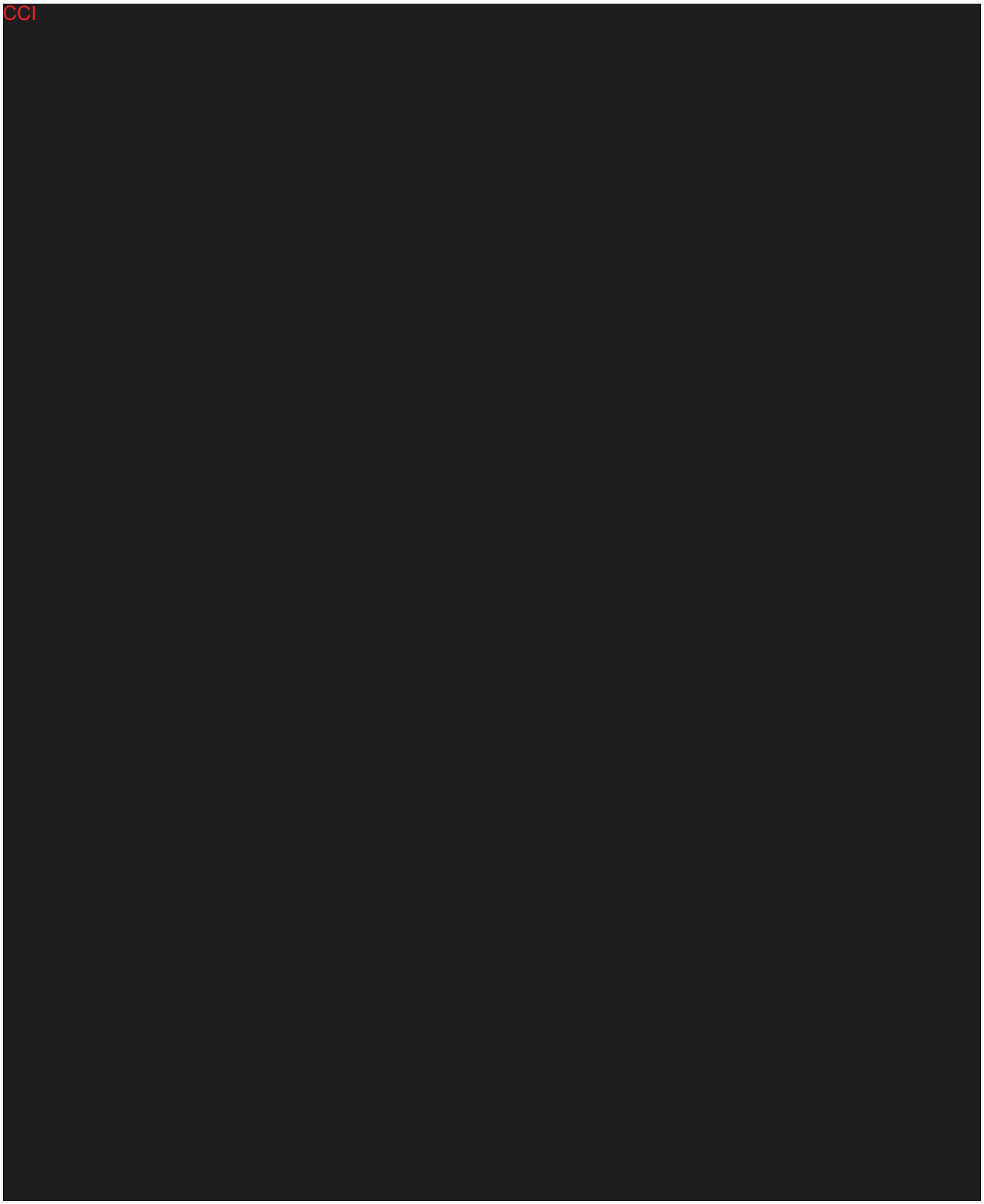

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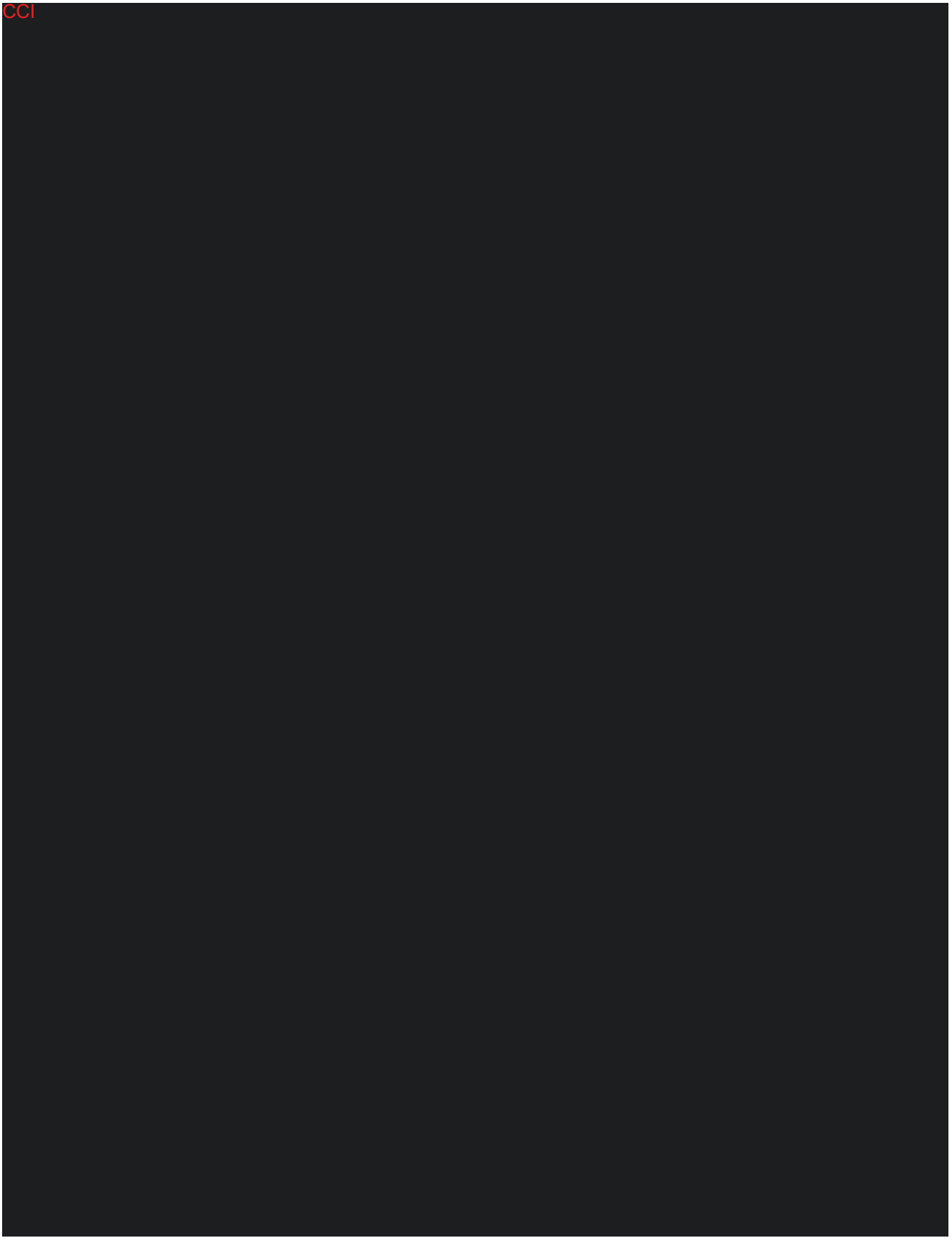


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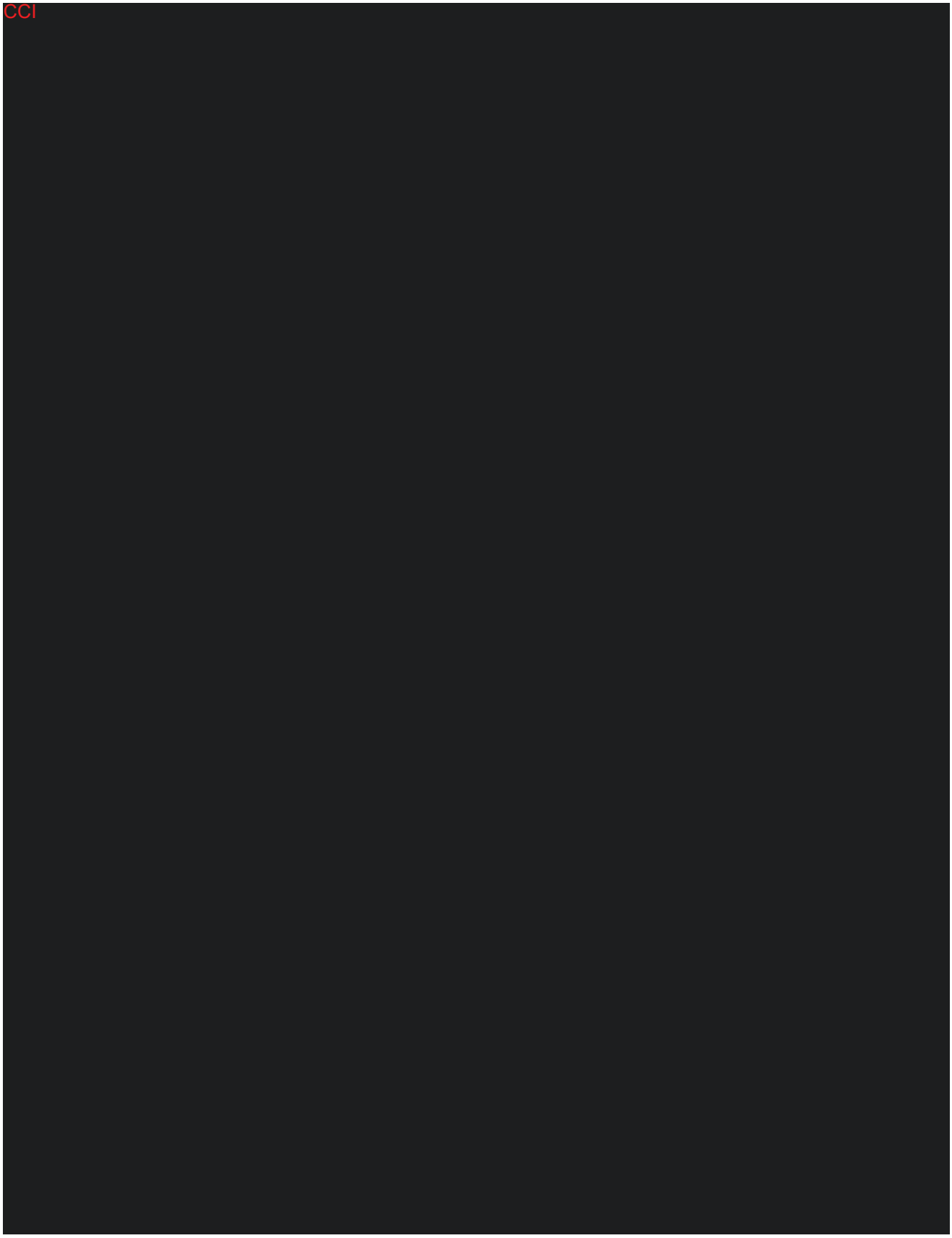

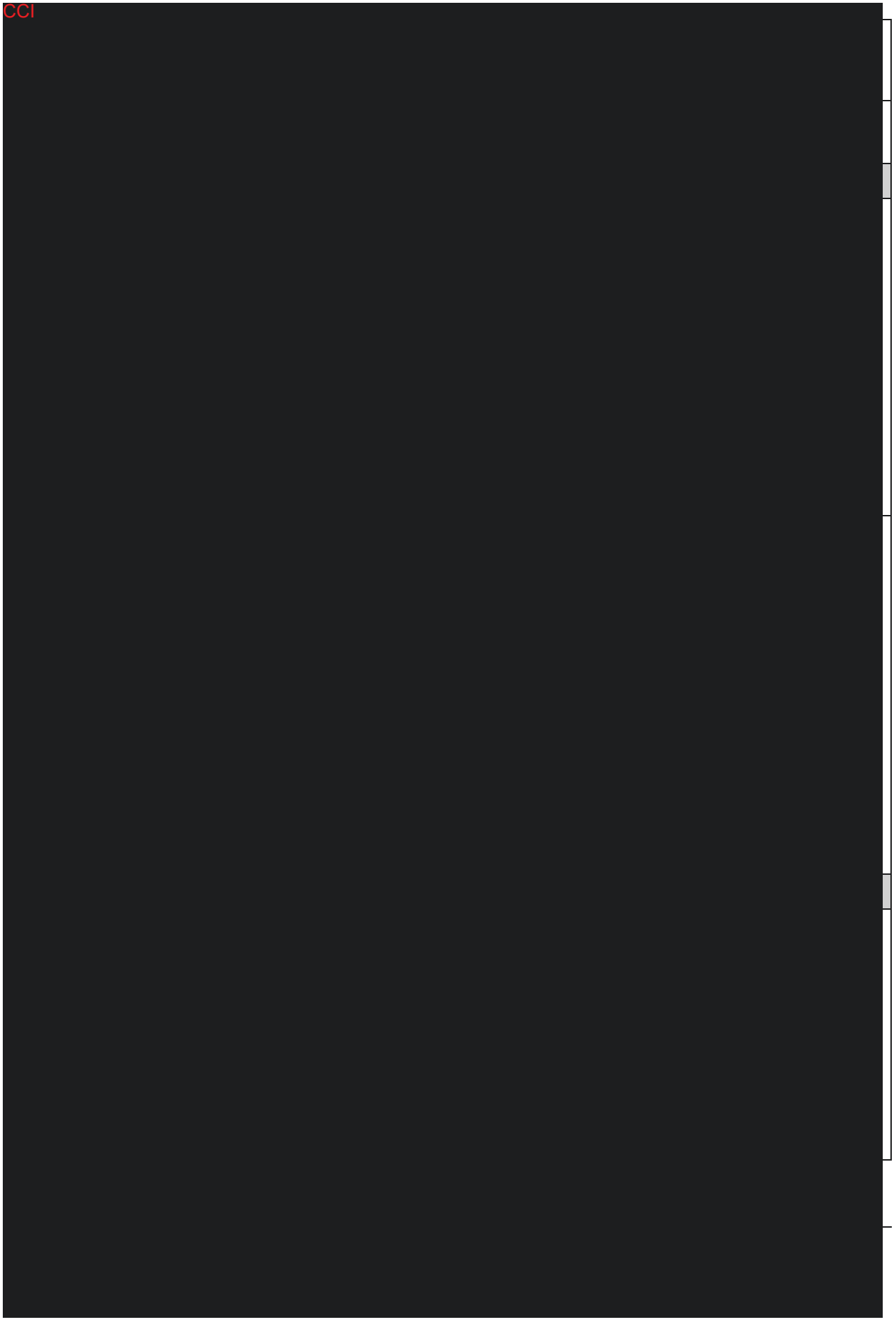
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15 Safety Analyses

This section includes specifications for summarizing safety endpoints that are common across clinical studies such as adverse events, laboratory tests and vital signs.

Safety analyses will be done on the SAF and reflect data collected during the Extension Study Period.

15.1 Adverse Events

The definition of AE has been described in Appendix 7 of the CSP. All analyses described in this Section will be based on reported AEs during the Extension Study Period.

SAEs and events of lymphopenia (also if not serious) with an onset date prior to the MAGNIFY MS exit date and are ongoing on the MAGNIFY MS Extension enrollment date will be recorded on the "Medical History" CRF. A listing comprising all ongoing SAEs and events of lymphopenia (also if not serious) from the MAGNIFY MS trial will be presented.

Each participant will be counted only once within each SOC or PT. If a participant experiences more than one AE within a SOC or PT for the same summary period, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

Incomplete AE-associated dates will be imputed as described in Section 9.7.

15.1.1 All Adverse Events

All AEs reported during the Extension Study Period will be summarized using MedDRA (latest version available) PT as event category and MedDRA primary SOC body term as Body System category overall and by DMD subgroups as defined in Section 8.2.

Unless otherwise stated, adverse events will be displayed in terms of frequency tables: PT and primary SOC in alphabetical order.

Adverse events related to study treatment are those events with relationship missing, unknown or related.

The following overall frequencies of participants with the corresponding AEs will be prepared. In addition, the tables will be provided by PT and primary SOC in alphabetical order:

- Any AE,
- Any study treatment related AEs,
- Any serious AEs,
- Any non-serious AEs,

- Any study treatment related serious AEs,
- Any AE by severity (mild, moderate, severe),
- Any study treatment related AE by severity (mild, moderate, severe),
- Any AEs leading to death (AEs with outcome "fatal"),
- Any study treatment related AEs leading to death (AEs with outcome "fatal").
- Any AEs leading to study discontinuation,
- Any study treatment related AEs leading to study discontinuation.

Summary table for non-SAEs applying frequency threshold of 5% will be provided by SOC and PT.

Summary tables for serious and non-SAEs applying frequency threshold of 5% sorted by decreasing frequency will be provided by PT.

All AEs by worst severity will be presented by SOC and PT. Missing severity will be presented in all severity groups.

All AEs collected during the Extension Study Period will be listed by participant for the SAF.

Exposure Adjusted Incidence Rate

Exposure adjusted incidence rates (EAIR) are calculated as number of participants with AE divided by the total time at risk, which is defined as a sum of the individual times in years of all participants in the safety population from start of Extension Study Period to first onset of AE or end of the Extension Study Period, whichever occurs first.

The exact Poisson 95% confidence intervals for the EAIR are calculated using the relationship between the Poisson and the Chi-square distribution (Ulm, 1990):

$$LCI = \frac{\chi^2_{2n,\frac{a}{2}}}{2 \times t},$$

$$UCI = \frac{\chi^2_{2(n+1),1-\frac{a}{2}}}{2 \times t},$$

where t is the sum of the individual times in years of all participants and n is the number of participants with a specific AE for the EAIR, which will be the basis for the number of the degrees of freedom for the chi-square quantile for the upper tail probability χ^2.

The incidence rate multiplied with 100 would give the number of AEs expected in 100 participants within 1 year.

EAIR of AEs will be presented overall, and by SOC and PT.

The following table will be provided:
- Exposure adjusted incidence rates of AEs by SOC and PT.

15.1.2 Adverse Events Leading to Discontinuation of Study Intervention

Not applicable.

15.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

15.2.1 Deaths

Any discontinuations due to death (see Section 10.1) and any AEs leading to death will be tabulated (see Section 15.1.1).

A summary table of observed Deaths (from "Study Termination" eCRF page) will be provided together with AEs with fatal outcome by PT.

15.2.2 Serious Adverse Events

The statistical analysis and reporting of SAEs are defined in Section 15.1.1. In addition, all SAEs will be listed.

15.2.3 Other Significant Adverse Events

AEs associated to COVID-19

The frequency of AEs associated to COVID-19 will be presented. The relevant events will be identified based on the SMQ COVID-19 (narrow scope) and will be presented by SOC and PT.

A listing comprising all COVID-19 related AE terms will be presented.

AEs associated to COVID-19 vaccines

The frequency of AEs associated to COVID-19 vaccines will be presented.

The safety profile of the investigational treatment and vaccine may overlap. Investigators are asked to provide all AEs with potential COVID-19 vaccine related causality AEs as part of information on "Causality factors other than study treatment" and to enter "COVID19 vaccination" as free text on the AEDT eCRF page. Per this classification a focused analysis will be possible for potential vaccination associated AEs.

A listing comprising all COVID-19 vaccines related AE terms will be presented.

AEs associated to Lymphopenia

The frequency of AEs associated to Lymphopenia will be presented. The relevant events will be identified based on the list of PTs in Appendix 18.3 and will be presented by SOC and PT.

A listing comprising all Lymphopenia related AE terms will be presented.

15.3 Clinical Laboratory Evaluation

Not applicable.

15.4 Vital Signs

The maximum changes of vital sign measurements from MAGNIFY MS Baseline during Extension Study Period will be grouped as follows:

Heart rate increase from baseline <100 bpm; ≥ 100 bpm	≤20 bpm, >20 – 40 bpm, >40 bpm
Heart rate decrease from baseline <100 bpm; ≥ 100 bpm	≤20 bpm, >20 – 40 bpm, >40 bpm
SBP increase from baseline <140 mmHg; ≥ 140 mmHg	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
SBP decrease from baseline <140 mmHg; ≥ 140 mmHg,	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
DBP increase from baseline <90 mmHg; ≥ 90 mmHg	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
DBP decrease from baseline <90 mmHg; ≥ 90 mmHg,	≤20 mmHg, >20 – 40 mmHg, >40 mmHg

For each participant, the worst change during the Extension Study Period will be considered. Missing values will be presented as a separate category.

The following summaries will be prepared for vital sign parameters as grouped above considering only participants with post-Baseline values:

- Summary of Maximal Shifts (changes in categories),
- Listing of highest change per participant.

15.5 Other Safety or Tolerability Evaluations

The results of the physical examination will not be presented in any statistical analysis or listing. Abnormalities occurring, or worsening, during the study will be reported as AE.

Pregnancies reported as AEs or SAEs will be listed for the SAF.

16 Analyses of Other Endpoints

16.1 Baseline Characteristics Compared to Parent Study

A comparison of participant baseline and background characteristics from population of the CLARIFY MS trial with population of the CLARIFY MS EXTENSION trial will be done by visual comparison. No special statistical analysis will be planned in this IAP.

17 References

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Parmenter, Brett A. et al. "The utility of regression-based norms in interpreting the minimal assessment of cognitive function in multiple sclerosis (MACFIMS)." Journal of the International Neuropsychological Society: JINS vol. 16,1 (2010): 6-16. doi:10.1017/S1355617709990750

Lipkovich, I., Ratitch, B., O'Kelly, M. "Sensitivity to censored-at-random assumption in the analysis of time-to-event endpoints." Pharm Stat vol.15, 3 (2016): 216-29. doi:10.1002/pst.1738.

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Data Transfer Specification - MS700568_0157 - MRI-based endpoint values, Version 1.0, 02 April 2022 (specification provided by SIENA imaging)

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Clinical Study Protocol, A 2-year extension study to evaluate long-term effectiveness of Mavenclad® in participants who have completed Trial MS700568_0022 (MAGNIFY MS); Version 1.0, 20 August 2020.

Clinical Study Protocol, A 2-year prospective study to evaluate the onset of action of Mavenclad ® in participants with highly active relapsing multiple sclerosis; Version 2.0, 12 February 2019.

Integrated Analysis Plan, A 2-year prospective study to evaluate the onset of action of Mavenclad® in subjects with highly active relapsing multiple sclerosis; Version 3.0.

18 Appendices

18.1 Appendix 1: List of DMDs for MAGNIFY MS Extension Study

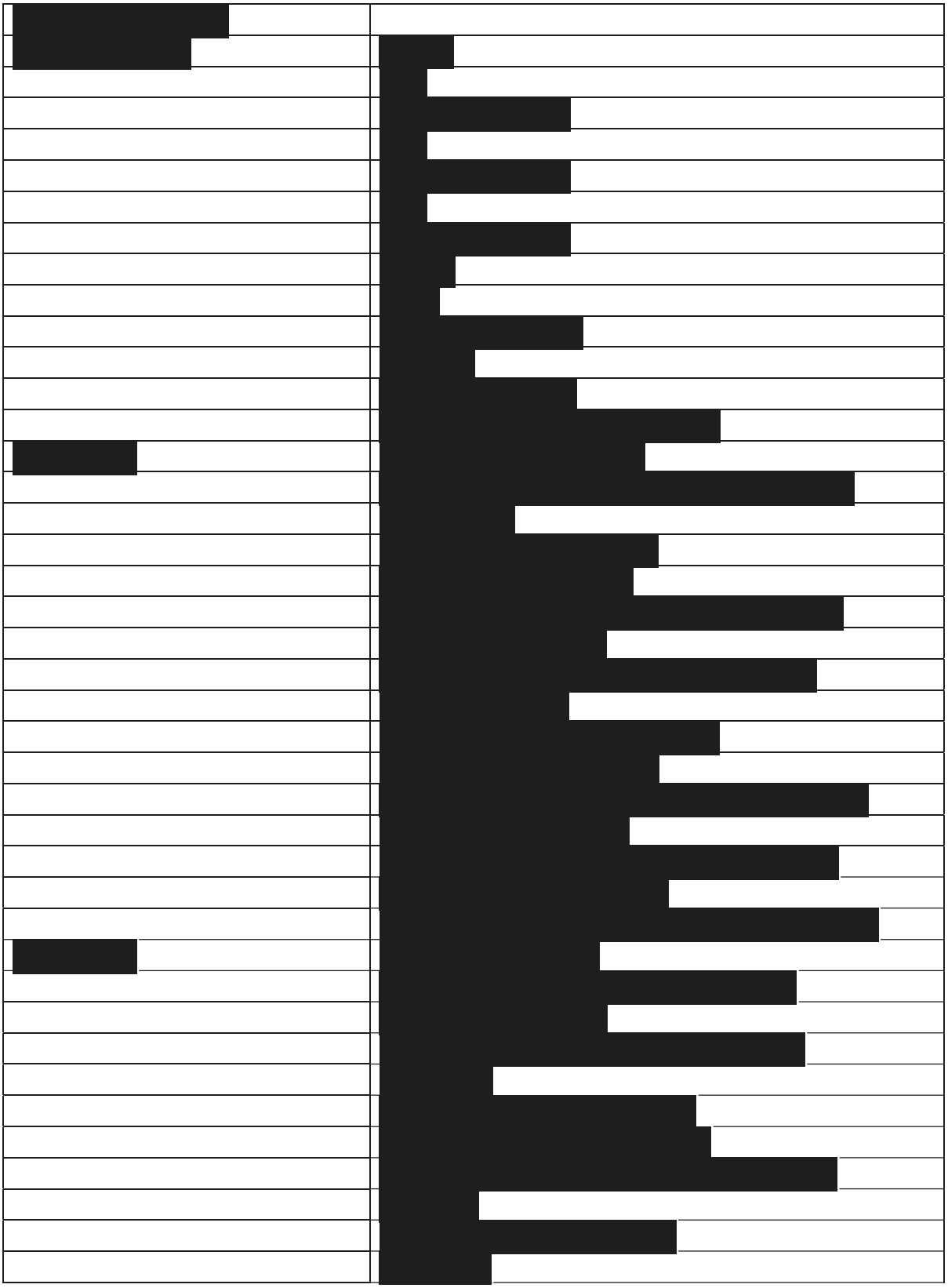
DMDs	Preferred Term
Alemtuzumab* (Campath, MabCampath, Lemtrada)	ALEMTUZUMAB
Cladribine (Mavenclad)	CLADRIBINE
Daclizumab* (Zinbryta)	DACLIZUMAB
Dimethyl fumarate (Tecfidera)	DIMETHYL FUMARATE
Diroximel fumarate (Vumerity)	DIROXIMEL FUMARATE
Fingolimod* (Gilenya)	FINGOLIMOD FINGOLIMOD HYDROCHLORIDE
Glatiramer Acetate (Copaxone)	GLATIRAMER GLATIRAMER ACETATE
Immunoglobulins	IMMUNOGLOBULIN HUMAN NORMAL IMMUNOGLOBULINS IMMUNOGLOBULINS NOS
Interferon beta (Avonex, Rebif, Betaferon, Extavia, Plegridy)	INTERFERON INTERFERON BETA INTERFERON BETA-1A INTERFERON BETA-1B PEGINTERFERON PEGINTERFERON BETA-1A
Mitoxantrone (Novantrone)	MITOXANTRONE MITOXANTRONE HYDROCHLORIDE
Natalizumab* (Tysabri)	NATALIZUMAB
Non-approved investigational DMDs* (monoclonal antibodies, antiS1PR, laquinimod etc)	INVESTIGATIONAL DRUG LAQUINIMOD OPICINUMAB OTHER ANTINEOPLASTIC AGENTS
Ocrelizumab* (Ocrevus)	OCRELIZUMAB
Ofatumumab (Kesimpta)	OFATUMUMAB
Off-label immunosuppressants (azathioprine, mycophenolate, cyclophosphamide)	AZATHIOPRINE CYCLOPHOSPHAMIDE METHOTREXATE
Ozanimod (Zeposia)	OZANIMOD
Ponesimod (Ponvory)	PONESIMOD
Rituximab	RITUXIMAB
Siponimod (Mayzent)*	SIPONIMOD SIPONIMOD FUMARATE
Teriflunomide (Aubagio)	TERIFLUNOMIDE

DMDs marked with a * are second line DMDs, which were not allowed as a previous medication in the parent study according to the study protocol.

The list may be extended during medical review in case that new or other DMDs will be applied during the study.

For categorization into DMD pre-treated group, the DMDs listed in MAGNIFY MS IAP V3.0 was used. Participants who have taken any of the listed DMDs according to the "Relevant Previous Medication" eCRF page of the parent study Baseline visit will be categorized as DMD pre-treated. All other participants will be considered as pre-treatment naïve.

CCI [redacted]



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18.3 Appendix 3: Preferred terms for selection of AEs associated to Lymphopenia

All PTs given are based on MedDRA version 25.1 and might be subject to change in future MedDRA version.

PTs for selection of "Lymphopenia"

Preferred Code	Preferred Term
10025327	Lymphopenia
10007839	CD4 lymphocytes decreased
10007843	CD4/CD8 ratio decreased
10012785	Differential white blood cell count abnormal
10025252	Lymphocyte count abnormal
10025256	Lymphocyte count decreased
10051313	B-lymphocyte count decreased
10051318	T-lymphocyte count decreased
10052231	Lymphocyte percentage decreased
10056283	CD8 lymphocytes decreased
10057284	T-lymphocyte count abnormal
10063293	CD4 lymphocytes abnormal
10063337	Lymphocyte percentage abnormal
10068497	Natural killer cell count decreased
10068500	Natural killer T cell count decreased
10071543	CD8 lymphocytes abnormal
10072798	CD4 lymphocyte percentage decreased
10078384	CD8 lymphocyte percentage decreased
10078589	B-lymphocyte count abnormal
10080721	B-cell aplasia
10083934	Idiopathic CD4 lymphocytopenia

Signature Page for CCI [redacted]

Approval Task	PPD [redacted]

Signature Page for CCI [redacted]