Statistical Analysis Plan

Protocol Title:	A Phase 2a Randomized Double-blind Placebo Controlled Study to Evaluate the Efficacy and Safety of AMG 301 in Migraine Prevention
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Protocol Number:	20150308
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List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BDI-II	Beck Depression Inventory - II
BMI	body mass index
CAPS	Cranial Autonomic Parasympathetic Symptom
CGRP	Calcitonin gene-related peptide
CM	chronic migraine
COAs	Clinical Outcome Assessments
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DBTP	Double-blind Treatment Period
DRE	Disease-Related Event
EAS	efficacy analysis set
ECG	electrocardiogram
eDiary	Electronic diary
EM	episodic migraine
End of Study (end of trial)	defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
Enrollment	when the investigator decides that the subject has met all Part 1 and Part 2 eligibility criteria
EOS	end of study
ET	Early termination
FAS	full analysis set
HbA1c	glycosylated hemoglobin
HIT-6	Headache Impact Test-6
IC_{50}	half maximum inhibitory concentration
ICH	International Council for Harmonisation

Abbreviation or Term	Definition/Explanation
ICHD	International Classification of Headache Disorders
ICHD-IIIb	ICHD, third edition beta
IV	Intravenous
IVR	Interactive Voice Response
IWR	Interactive Web Response
MedDRA	Medical Dictionary for Regulatory Activities
MIDAS	Migraine Disability Assessment
MPFID	Migraine Physical Function Impact Diary
MMPFID	Modified Migraine Physical Function Impact Diary
PACAP	Pituitary adenylate cyclase-activating polypeptide
PD	pharmacodynamic
PK	Pharmacokinetics
PRO	patient-reported outcome
Q2W	every 2 weeks
Q4W	every 4 weeks
Randomization	A subject will be randomized to treatment assignment
SAS	safety analysis set
SC	Subcutaneous
SSAP	Supplement Statistical Analysis Plan
Study Day 1	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
TBL	total bilirubin
ULN	upper limit of normal
VIP	vasoactive intestinal polypeptide

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol amendment 2 for Study 20150308, AMG 301 dated 17 October 2017. The scope of this plan includes the primary analysis and the final analysis that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified. Full details of the independent, unblinded interim analyses are described in a separate Supplemental Statistical Analysis Plan (SSAP) and the Interim Analysis Review Steering Committee (IARSC) charter.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of AMG 301 compared to placebo on the change from the baseline period in monthly migraine days in subjects with migraine	• Change from the baseline period in monthly migraine days. The monthly migraine days will be calculated using the migraine days over the last 4 weeks of the 12-week double-blind treatment period
The primary estimand consists of: • **The target population, which is patients with chronic or episodic migraine who have failed at least one prophylactic treatment for migraine** • The variable, which is the change in monthly migraine days from the baseline period over the last 4 weeks of the 12-week double-blind treatment period • The population-level summary measure, which is the difference in the mean of the variable between each AMG 301 treatment group and the placebo group • **The intercurrent event, adherence to treatment will be ignored and the primary endpoint will be assessed for all subjects who receive at least 1 dose of investigation product and have at least 1 postbaline mothly eDiary measurement regardless of adherence to treatment** **The primary estimand is the difference in means between each AMG 301 treatment group and placebo in the change in monthly migraine days from the baseline period over the last 4 weeks of the 12-week double-blind treatment period for patients with chronic or episodic migraine who have failed at least one prophylactic treatment for migraine who are randomised, receive at least one dose of investigation product and have at least 1 post baseline mothly eDiary measurement.**	
Secondary	
• To evaluate the effect of AMG 301 compared to placebo on the proportion of subjects with at least 50% reduction from the baseline period in monthly migraine days	• Achievement of at least a 50% reduction from the baseline period in monthly migraine days in the last 4 weeks of the 12-week double-blind treatment period
• To evaluate the effect of AMG 301 compared to placebo on the change from the baseline period in monthly acute migraine-specific medication treatment days	• Change from the baseline period in monthly acute migraine-specific medication days in the last 4 weeks of the 12-week double-blind treatment period.
• To evaluate the effect of AMG 301 compared to placebo on the change from the baseline period in monthly physical impairment domain score as measured by the Migraine Physical Function Impact Diary (MPFID)	• Change from the baseline period in physical impairment domain scores as measured by the MPFID over the last 4 weeks of the 12-week double-blind treatment period

Objectives	Endpoints
• To evaluate the effect of AMG 301 compared to placebo on the change from the baseline period in monthly impact on everyday activities domain score as measured by the MPFID	• Change from the baseline period in impact on everyday activities domain scores as measured by the MPFID over the last 4 weeks of the 12-week double-blind treatment period.
• To evaluate the safety and tolerability of AMG 301	• **Incidence of treatment-emergent adverse events** • **Change from baseline in clinical laboratory values and vital signs**
The secondary estimands for each of the secondary objectives except the last one are similar to the primary estimand but differ in the following ways: • The variables are the endpoints listed above for each secondary objective • The population-level summary measure for the first secondary objective is the difference in proportions of subjects who achieve at least a 50% reduction in monthly migraine days between each AMG 301 group and the placebo group **The estimands for the last secondary objective is similar to the primary estimand but differ in the following ways:** • The variables are the incidence of adverse events and change from baseline in clinical laboratory values and vital signs during the 12-week double-blind treatment period • The population-level summary measures for the incidence of adverse events is the count of adverse events during the 12-week double-blind treatment period and the difference in means for the change from baseline variables for each AMG 301 treatment group and the placebo group • **The intercurrent event, adherence to treatment will be ignored and the secondary endpoint will be assessed for all subjects in the target population**	

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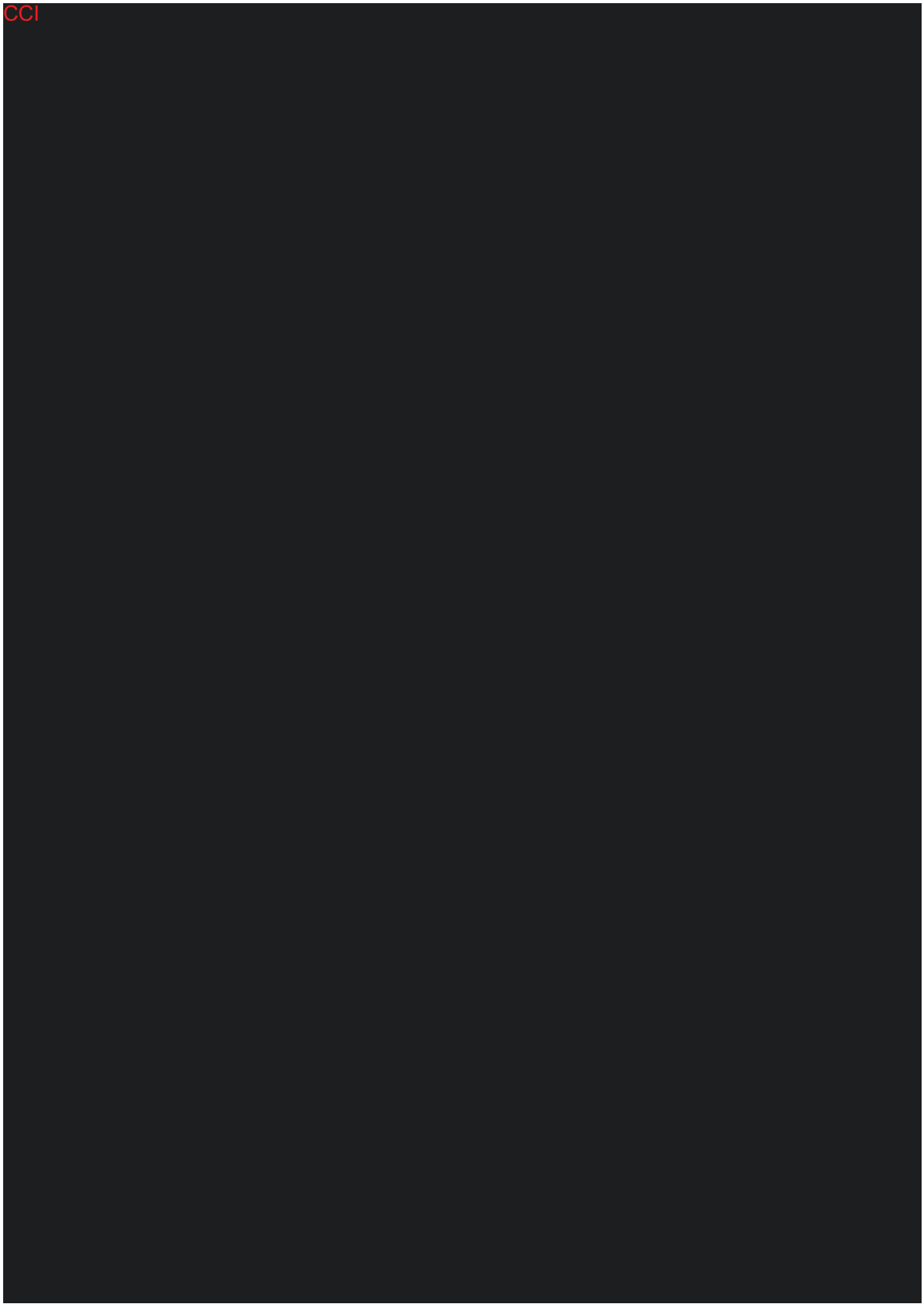

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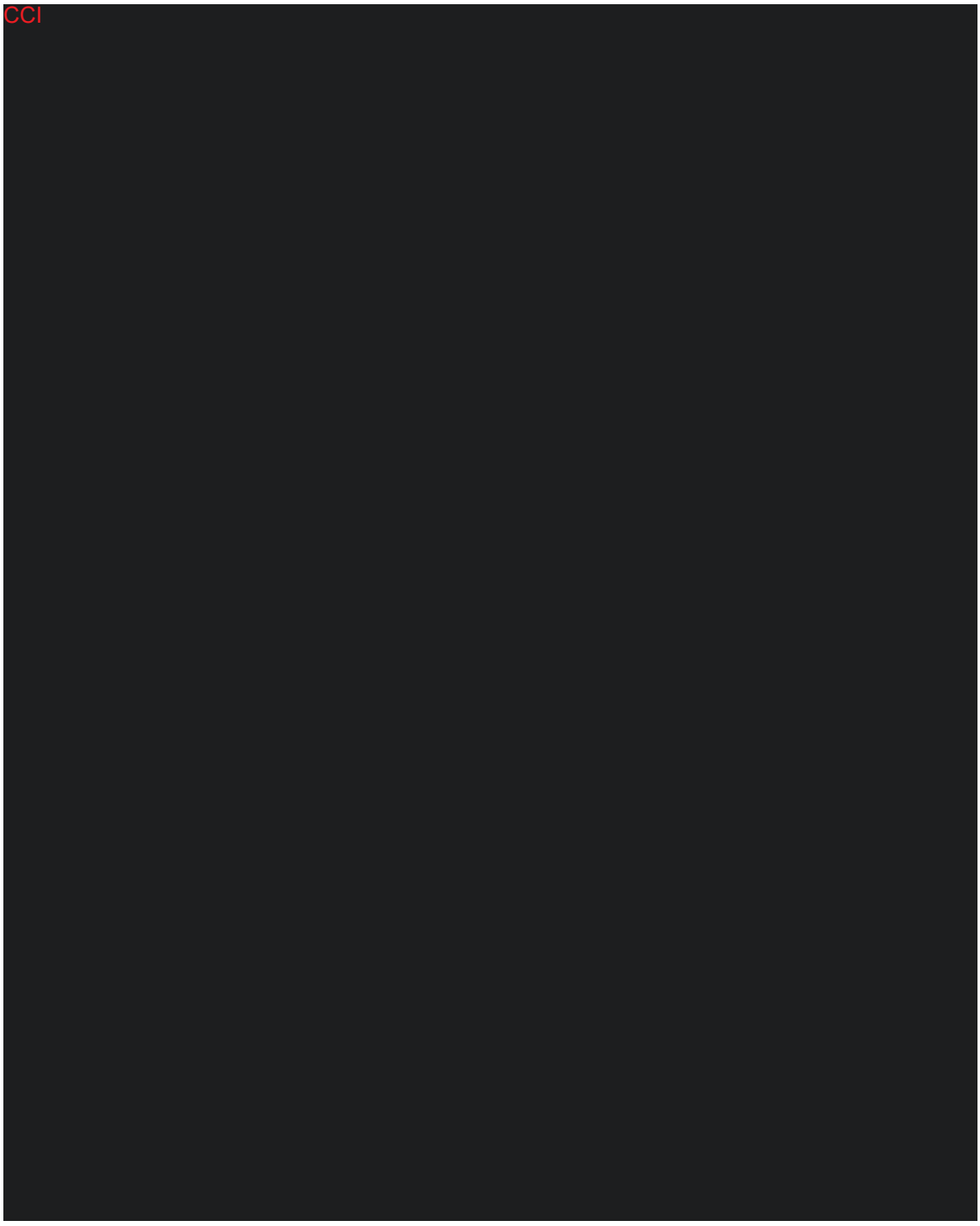

2.2 Hypotheses and/or Estimations

In subjects with migraine, AMG 301 provides a greater reduction from the baseline period in monthly migraine days, compared to placebo.

The primary endpoints of the study will be tested for each of the AMG 301 210 mg and AMG 301 420 mg groups compared to placebo, respectively, at significance levels of 0.05 and 0.05, respectively, to maintain a familywise type I error of 0.10.

- Null Hypothesis: In subjects with migraine, the AMG 301 treatment group is not different from placebo, in terms of the reduction of the monthly migraine days from baseline.
- Alternative Hypothesis: In subjects with migraine, the AMG 301 treatment group is different from placebo, in terms of the reduction of the monthly migraine days from baseline.

3. Study Overview

3.1 Study Design

This is a phase 2a, multicenter, randomized, double-blind, placebo-controlled, 3-arm parallel-group study of subjects with chronic migraine (CM) or episodic migraine (EM). Approximately 335 subjects will be randomized 4:3:3 to placebo, AMG 301 210 mg via SC injections QM, or AMG 301 420 mg via SC injections Q2W, respectively. The randomization will have 2 stratification factors: baseline migraine frequency (CM versus EM) and region (North America versus Rest of World).

Interactive Voice Response (IVR)/Interactive Web Response (IWR) system will be used to facilitate randomization and stratification and investigational product assignment.

Stratification at Randomization:

Baseline migraine frequency (CM versus EM; limit both CM and EM randomization to approximately 50% each of total sample size) and Region (North America versus Rest of World; neither region will enroll more than 60% of the total sample size).

CM is defined as:

- ≥ 15 headache days of which ≥ 8 headache days meet criteria as migraine days during the baseline period based on the electronic diary (eDiary) calculations

EM is defined as:

- < 15 headache days of which at least 4 or more headache days meet criteria as migraine days during the baseline period based on the eDiary calculations

After signing the informed consent form, subjects will enter the screening period. The entire screening period includes a screening period (up to 3 weeks) followed by a 4-week baseline period. At the day 1 visit (the day 1 visit must occur 28 to 35 days after the week -4 baseline period visit date), eligible subjects will be randomized into the 12-week DBTP) and will begin to receive double-blind investigational product. At the week 10 visit, subjects will take the last dose of investigational product. At the week 12 visit, subjects will end the DBTP. A safety follow-up period will be conducted 18 weeks after the last dose of investigational product (16 weeks after DBTP). Subjects will use an eDiary every day throughout the baseline period, DBTP, and safety follow-up period to report information about the migraine and non-migraine headaches and acute medication use. Subjects will have in-clinic study visits Q2W after day 1 through the week 12 visit and then Q4W.

The overall study design is described by a study schema in Section 2.1 of the protocol.

3.2 Sample Size

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3.3 Adaptive Design

Not applicable.

4. Covariates and Subgroups

4.1 Planned Covariates

Region (North America versus Rest of World) and baseline migraine frequency (CM versus EM) will be included in the repeated measures linear mixed models models as stratification factors. In addition, the baseline value corresponding to the endpoint being analyzed will also include.

4.2 Subgroups

The primary and secondary endpoints may also be explored using subgroup analyses of region (North America, Rest of World), migraine frequency type (EM, CM), prior anti-CGRP medication use (Yes, No), prior migraine prophylactic treatment failure (1, ≥ 2), medication overuse (Yes, No), CAP score (0, ≥ 1), age (<Median, ≥ Median), sex (Female, Male), race (White, Other), response status to AMG 334 (Yes, No), and other subgroup variables as deemed appropriate.

5. Definitions

5.1 Endpoints

5.1.1 Efficacy Endpoints

The baseline period for efficacy analysis is defined as the period between week -4 visit (date on which the eDiary device is set up) and the day prior to study day 1 (study day 1 is not included).

eDiary Day

A day in which a subject uses the eDiary and data are entered for that day.

Migraine Day

A migraine day is any calendar day from the eDiary in which the subject experiences a qualified migraine headache (onset, continuation or recurrence of the migraine headache). A qualified migraine headache is defined as a migraine with or without aura, lasting for ≥ 4 hours, and meeting at least one of the following criteria:

a) ≥ 2 of the following pain features:
- Unilateral
- Throbbing
- Moderate to severe
- Exacerbated with exercise/physical activity

b) ≥ 1 of the following associated symptoms:
- Nausea and/or vomiting
- Photophobia and phonophobia

If the subject took a migraine-specific medication (ie, triptan or ergotamine) during aura or to treat headache on a calendar day, then it will be counted as a migraine day regardless of the duration and pain features/associated symptoms.

Monthly Migraine Days

Number of migraine days during a 28-day period. Monthly migraine days at baseline are the number of migraine days in the baseline period. Days without eDiary data in each monthly interval are handled by proration according to Section 8.3.

Headache Day

A headache day is any calendar day from the eDiary in which the subject experiences a qualified headache (initial onset, continuation or recurrence of the headache). A qualified headache is defined as**:**

- a qualified migraine headache (including an aura-only event that is treated with acute migraine-specific medication), or
- a qualified non-migraine headache, which is a headache that lasts ≥ 4 hours and is not a qualified migraine headache, or
- A headache of any duration for which acute headache treatment is administered.

Monthly Headache Days

Number of headache days during a 28-day period**.** Monthly headache days at baseline are the number of headache days in baseline period. Days without eDiary data in each monthly interval are handled by proration according to Section 8.3.

Information Day

A day which is either a headache day or an eDiary day.

Migraine Attack

A migraine attack is an episode of any qualified migraine headache or migraine specific medication intakes for aura only. The following rules will be used to distinguish an attack of long duration from two attacks, or to distinguish between attacks and relapses:

a) A migraine attack that is interrupted by sleep, or temporarily remits, and then recurs within 48 hours will be considered as one attack and not two.

b) An attack treated successfully with medication but with relapse within 48 hours will be considered as one attack.

A migraine attack lasting more than 48 hours will be counted as one attack.

Monthly Migraine Attacks

Number of migraine attacks during each 28-day period. Monthly migraine attacks at baseline are the number of migraine attacks in baseline period. Days without eDiary data are handled by proration according to Section 8.3.

Response

At least a 50% (or at least 75% or 100%) reduction from baseline in monthly migraine days over the last 4 weeks of the DBTP.

Monthly Acute Headache Medication Treatment Days

Number of days on which acute headache medications are used as recorded in eDiary during each 28-day period. Monthly acute headache medication treatment days at baseline are the number of acute headache medication treatment days in the baseline period. Days without eDiary data are handled by proration according to Section 8.3.

Monthly Acute Migraine-specific Medication Treatment Days

Number of days on which migraine specific medications are used during each 28-day period. Migraine-specific medications include two categories of medications: triptan-based migraine medications and ergotamine-based migraine medications. Monthly migraine-specific medication treatment days at baseline are the number of migraine-specific medication treatment days in the baseline period. Days without eDiary data are handled by proration according to Section 8.3.

Monthly Average Severity of Migraine Pain

Severity of migraine pain is graded as 1=mild, 2=moderate or 3=severe and is rated as its worst or peak intensity per migraine headache. The monthly average severity of migraine pain is defined as the sum of the severity of each observed qualified migraine headache during each 28-day period divided by the total number of observed qualified migraine headaches (as one record in eDiary with start and end time) in that interval. If fewer than 14 days of eDiary data in each interval is recorded, then the monthly average severity of migraine pain will be set as missing. Monthly average severity of migraine pain at baseline is the average severity of migraine pain in the baseline period.

Clinical Outcomes Assessments (COA) and Electronic Diaries (eDiaries)

The Clinical Outcomes Assessments (COAs) will be collected by subjects using a handheld eDiary at various frequencies. The eDiary will collect the following COAs daily at home:

- Date and time of start of headache (ie, migraine or non-migraine headache)
- Date and time of end of each headache
- Worst pain severity per headache
- Pain features (eg, 1-sided, throbbing, worsens with exercise/physical activity)
- Symptoms (eg, aura, nausea, vomiting, photophobia, phonophobia)
- Use of acute medications (medication name [from pre-entered list] date of dosing, number of times taken of each date, number of units taken)

The subject's eDiary will also be used for the completion of the following patient-reported outcomes (PROs) measures:

- HIT-6, monthly in clinic
- Modified MIDAS questionnaire; monthly in clinic
- MPFID, daily at home

Headache Impact Test (HIT-6)

The Headache Impact Test (HIT-6) is a short-form self-administered questionnaire based on the Internet-HIT question pool. The HIT-6 was developed as a global measure of adverse headache impact to assess headache severity in the previous month and change in a patient's clinical status over a short period of time. Six questions cover:

- severe pain,
- limitation of daily activity (household, work, school and social),
- wanting to lie down when headache is experienced,
- feeling too tired to work or do daily activities because of headache,
- feeling fed up or irritated because of headache,
- headache limiting ability to concentrate or work on daily activities.

Each of the 6 questions is responded to using 1 of 5 response categories: "never," "rarely," "sometimes," "very often," or "always."

For each HIT-6 item, 6, 8, 10, 11, or 13 points, respectively, are assigned to the response provided. These points are summed to produce a total HIT-6 score that ranges from 36 to 78. The HIT-6 score is categorized into 4 grades, representing little or no impact (49 or less), some impact (50-55), substantial impact (56-59), and severe impact (60-78) due to headache. No recall period is specified for the first 3 items. The recall period is the past 4 weeks for the last 3 items. Subjects will complete the HIT-6 using the eDiary at the clinical assessment visit. Please refer to Appendix E for scoring algorithm.

Modified Migraine Disability Assessment (MMIDAS)

The modified Migraine Disability Assessment Questionnaire (MMIDAS) is a 5-item self-administered questionnaire that sums the number of productive days lost over the past month in two settings: the workplace and the home. The MMIDAS also assesses disability in family, social, and leisure activities. The MMIDAS score is the sum of missed days due to a headache from paid work, housework, and non-work (family, social, leisure) activities; and days at paid work or housework where productivity was reduced by at least half**. The original MIDAS was a 3-month recall assessment.**

In order to categorize severity of subjects with the MMIDAS, the total score is multiplied by 3 and categorized into 4 severity grades: Grade I = 0 - 5 (defined as minimal or infrequent disability), Grade II = 6 - 10 (mild or infrequent disability), Grade III = 11 - 20 (moderate disability), and Grade IV = 21 and over (severe disability). The recall period is the past one month.

Subjects will complete the modified MMIDAS monthly using the eDiary. Please refer to Appendix E for scoring algorithm.

Migraine Physical Function Impact Diary (MPFID)

The MPFID is a self-administered 13-item instrument measuring physical functioning. It has 2 domains, Impact on Everyday Activities (7 items) and Physical Impairment (5 items), and 1 stand-alone global question that provides an assessment of the overall impact of migraine on subjects' everyday activities. The recall period for each item is the past 24 hours.

Subjects respond to items using a 5-point scale, with difficulty items ranging from "Without any difficulty" to "Unable to do" and frequency items ranging from "None of the time" to "All of the time". These are assigned scores from 1 to 5, with 5 representing the greatest burden. For each domain, the scores will be calculated as the sum of the item responses and the sum will be rescaled to a 0 to 100 scale, with higher scores representing greater impact of migraine (ie, higher burden). There will be a score for each of the 2 domains and a third score for the stand-alone item.

The recall period is the past 24 hours.

Please refer to Appendix E for more information.

Subjects will complete the MPFID every day using the eDiary.

Monthly Days with Impairment as Measured by MPFID

If ≥ 50% of the 13 daily items are completed, this is the number of days with a response of 3, 4, or 5 on any item of the MPFID between each monthly IP dose. Monthly days with impairment at baseline is the number of impairment days during the baseline period. Days with < 50% of the 13 daily items completed are handled by proration according to Section 8.3.

Monthly Days with Physical Impairment as Measured by MPFID Physical Impairment (PI) Domain

If ≥ 50% of the daily items within the PI domain are completed, this is the number of days with a response of 3, 4, or 5 on any of the 5 daily items on the PI domain between

each monthly IP dose. Monthly days with physical impairment at baseline is the number of impairment days during the baseline period. Days with < 50% of the 5 daily items in the PI domain completed are handled by proration according to Section 8.3.

Monthly Day with Impact on Everyday Activities as Measured by MPFID Everyday Activities (EA) Domain

If ≥ 50% of the daily items within the EA domain are completed, this is the number of days with a response of 3, 4, or 5 on any of the 7 daily items on the EA domain between each monthly IP dose. Monthly days with impact on everyday activities at baseline is the number of impairment days during the baseline period. Days with < 50% of the 7 daily items in the EA domain completed are handled by proration according to Section 8.3.

Achievement of at least a 50% reduction from baseline in monthly migraine days over the last 4 weeks of the DBTP

Calculated based on the following: if (monthly migraine days over the last 4 weeks of the DBTP - baseline monthly migraine days) * 100 / baseline monthly migraine days is less than or equal to - 50%

Change from baseline in monthly acute migraine-specific medication treatment days over the last 4 weeks of the DBTP

Calculated based on the following: (monthly acute migraine-specific medication treatment days over the last 4 weeks of the DBTP) – (baseline monthly acute migraine-specific medication treatment days)

Change from baseline in monthly average physical impairment scores as measured by the MPFID over the last 4 weeks of the DBTP

Calculated based on the following: (monthly average physical impairment scores as measured by the MPFID over the last 4 weeks of the DBTP) – (baseline monthly average physical impairment scores as measured by the MPFID)

Change from baseline in monthly average impact on everyday activities scores as measured by the MPFID over the last 4 weeks of the DBTP

Calculated based on the following: (monthly average impact on everyday activities scores as measured by the MPFID over the last 4 weeks of the DBTP) – (baseline monthly average impact on everyday activities scores as measured by the MPFID)

Achievement of at least a 5-point reduction from baseline in monthly average impact on everyday activities/physical impairment domain scores over the last 4 weeks of the DBTP

The achievement of at least a 5-point reduction from baseline in monthly average impact on everyday activities/physical impairment domain scores as measured by the MPFID is calculated based on the following:

If (monthly average impact on everyday activities/physical impairment domain score over the last 4 weeks of the DBTP - baseline monthly average impact on everyday activities/physical impairment domain score) is less than or equal to -5

Cranial Autonomic Parasympathetic Symptom (CAPS) Scale

The CAPS Scale is a 5-item questionnaire that assesses whether migraine subjects experience each of the following 5 CAPS based on the ICHD, third edition beta (ICHD-IIIb), **with headaches: 1) lacrimation, 2) conjunctival injection, 3) eyelid edema, 4) sensation of fullness in the ear and 5) nasal congestion and/or rhinorrhea. Each CAPS (eg, consider all headaches experienced over the past 4 weeks) is graded as either 0 (absent), 1 (present but mild) or 2 (present and conspicuous). The CAPS total score ranges from 0 to 10 points. (Riesco et al, 2016).**

The CAPS scale will be administered by clinical study center staff as described in Table 2-1 of the protocol.

5.1.2 Safety Endpoints

Treatment-emergent Adverse Event (TEAE)

An adverse Event (AE) recorded on the Events eCRF page that occurs on or after the date of the first dose of investigational product (IP), as determined by the flag indicating the event did not start before first dose of IP on the Events eCRF, and up to and including **126 days** after the end of IP (ie. **18 weeks** after the last dose of IP).

Serious TEAE

A serious treatment-emergent adverse event is an SAE considered to be treatment-emergent.

Disease-Related Event (DRE)

Disease-related Events (DREs) are events determined by the flag on the Event CRF.

Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a clinician rating of suicidal behavior and ideation. Two versions depending on the type of visits will be used in this study: Screening and Since Last Visit. The C-SSRS consists of a maximum of 20 items, which defines 5 subtypes of suicidal ideation and behavior in addition to self-injurious behavior with no suicidal intent. The C-SSRS will be administered by the principal investigator or qualified designee to evaluate suicidal behavior and suicidal ideation. For the baseline assessment, for measurements with multiple individual items, all individual items from the same set of measurement will be used for analysis.

For C-SSRS, the last complete assessment prior to first IP administration will be used as the baseline. If subject completes C-SSRS form on Day 1 then all individual items from Day 1 visit will be used as baseline. If subject does not complete C-SSRS form on Day 1 then all individual items from Week -4 visit will be used as baseline. Please refer to Appendix E for more information.

Beck Depression Inventory (BDI)-II

The BDI-II is a 21-item questionnaire that assesses severity of depression. Each item is scored from 0 to 3. The total score is categorized into 4 severity grades: Minimal depression (0-13), mild depression (14-19), moderate depression (20-28) and severe depression (29-63). Please refer to Appendix E for more information.

5.2 Study Dates

Informed Consent Date

The date on which subject signs the informed consent form.

eDiary Device Assignment Date

The date on which an eDiary device is assigned to a subject for the first time after completion of initial screening at week -4 visit and which is the beginning of the baseline period.

Enrollment Date

The date on which the investigator decides that the subject has met all Part 1 and Part 2 eligibility criteria. The subject is also randomized per IVRS on this date.

Randomization Date

Randomization date is the date on which a subject is assigned to one of the treatments through the Interactive Voice Response System (IVRS). The randomization date is the same as the enrollment date.

First IP Dose Date

The first IP dose date is the date on which a subject is administered the first dose of IP following randomization, which may be the same day or after the randomization date. For subjects who are randomized but not dosed with double-blind IP after randomization, the first IP dose date is considered missing.

Last IP Dose Date

The last IP dose date for each subject is defined as the latest date IP is administered.

End of IP Admin Date

The end of IP admin date for each subject is defined as the date the decision was made to end IP as recorded on the End of IP eCRF page.

Subject-level End of Study (EOS) Date

The end of study (EOS) date for each subject is defined as the last date on which the subject participated in the study. The date will be recorded on the End of Study eCRF page.

Subject-level End of Double Blind (EODB) Treatment Phase Date

The end of double blind (EODB) treatment phase date for each subject is defined as the last date on which the subject participated in the double-blind treatment phase. The date will be recorded on the End of Double Blind eCRF page.

Study Completion Date (Study-level EOS Date)

The study completion date is the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, when the last subject completes the study, which includes the safety follow-up visit 18 weeks after the last dose of IP, or is discontinued from the study).

5.3 Study Points of Reference

Baseline Period

The 4-week baseline period starts when the subject has met all Part 1 eligibility criteria (refer to Section 6.1 of the protocol) and is entered in the baseline period (refer to Section 6.6 of the protocol) and ends when the subject is considered a screen failure (discontinuation before randomization and/or subject does not meet all baseline eligibility criteria, refer to Section 6.3) or randomized.

The first day of the baseline period is the day that the subject records the first assessment in the eDiary and the last day of this period is the date the subject records the last assessment prior to the first dose of IP on Study Day 1.

The baseline assessment is defined as the last non-missing measurement for the endpoint of interest taken before the first dose of IP. In cases where baseline measurements are taken on the same day as the first dose of IP, it will be assumed that these measurements are taken prior to IP being administered. For subjects who are randomized but not dosed after the randomization, the baseline of the study is defined as the last non-missing measurement prior to or on the date of randomization. Above definition applies to safety measurements and PROs collected at office **visits** (HIT-6, CAPS and MMIDAS).

For measurements with multiple individual items such as C-SSRS and ECG, all individual items from the same set of measurement will be used for analysis. If some items from the same set are missing, then the latest complete set of measurement prior to the first dose of IP will be used as baseline. A similar rule holds for post-baseline measurements.

Baseline assessment of data collected from eDiary will be summarized as monthly measurements using data collected during baseline period.

Study Day 1

Study Day 1 is defined as the first IP dose date. For subjects who are randomized but not dosed after randomization, the Study Day 1 is defined as the date of randomization.

Study Day

Study Day is defined as the number of days from Study Day 1.

Before Study Day 1:

Study Day = (date of interest – date of Study Day 1)

On or after Study Day 1:

Study Day = (date of interest – date of Study Day 1) + 1

Therefore the day prior to Study Day 1 is -1.

5.4 Study Time Intervals

Monthly Interval for Efficacy Endpoints

Monthly efficacy measurements will be calculated based on the 2-week IP dosing schedule defined below using eDiary data collected from the beginning of the baseline phase (week -4 visit) up to the end of the safety follow-up phase (week 28 end of eDiary use). Any eDiary data occurring after EOS date or after the end date of the last monthly interval defined below, whichever comes earlier, will not be included in the analysis.

Table 5-1. Monthly Interval for Efficacy Endpoints Derived From Daily eDiary Data

Study Phase	Assessment Time Point	Monthly Interval	
		Start Date/Day	End Date/Day
Baseline Phase	Baseline	eDiary device assignment date (week -4 visit)	The day of or prior to Study Day 1
Double-blind Treatment Phase	Week 4	Study Day 1	• Week 4 dose date – 1 • Else MIN(Study Day 28, EOS) if Week 4 dose was not received
	Week 8	• Week 4 dose date • Else Study Day 29 if Week 4 dose was not received	• Week 8 dose date – 1 • Else MIN(Study Day 56, EOS) if Week 8 dose was not received
	Week 12	• Week 8 dose date • Else Study Day 57 if Week 8 dose was not received	• MIN(Study Day 84, EOS)
Safety Follow-up Period	Week 16	• Study Day 85	• MIN(Study Day 112, EOS)
	Week 20	• Study Day 113	• MIN(Study Day 140, EOS)
	Week 24	• Study Day 141	• MIN(Study Day 168, EOS)
	Week 28	• Study Day 169	• MIN(Study Day 196, EOS)

Study Visit

Since the actual visit for a subject may not exactly coincide with their targeted visit date, the actual visit date is mapped to the study visit as following. The study day window will be utilized to define study visit for lab, vital signs, physical measurements and PROs collected during office visits including HIT-6, and MMIDAS. Any data occurring after the EOS date will not be included in the analysis with the exception of lab shift analyses and antibody data.

Table 5-2. Study Visit Windows for HIT-6, MMIDAS, C-SSRS, and CAPS Scale

Study Phase	Study Visit	Target Day	Study Day
Double-blind Treatment Period	Baseline	Please refer to Section 5.3 Baseline Assessment of the Study	
	Week 4	29	• 2 – 43
	Week 8	57	• 44 – 71
	Week 12	85	• 72 – 99
Safety Follow-up Period	Week 16	113	• 100 – 127
	Week 20	141	• 128 – 155
	Week 24	169	• 156 – 183
	Week 28	197	• 184 – 211

Table 5-3. Study Visit Windows for Lab (Except HbA1C and Urinalysis)

Study Phase	Study Visit	Target Day	Study Day
Double-blind Treatment Period	Baseline	Please refer to Section 5.3 Baseline Assessment of the Study	
	Week 4	29	• 2 – 36
	Week 6	43	• 37 – 64
	Week 12	85	• 65 – 99
Safety Follow-up period	Week 20	141	• 100 – 169
	Week 28	197	• 170 – 211

Table 5-4. Study Visit Windows for HbA1C

Study Phase	Study Visit	Target Day	Study Day
Double-blind Treatment Period	Baseline	Please refer to Section 5.3 Baseline Assessment of the Study	
	Week 6	43	• 2 – 64
	Week 12	85	• 65 – 99
Safety Follow-up period	Week 20	141	• 100 – 169
	Week 28	197	• 170 – 211

Table 5-5. Study Visits for Vital Signs

Study Phase	Study Visit	Target Day	Study Day
Double-blind Treatment Period	Baseline	Please refer to Section 5.3 Baseline Assessment of the Study	
	Day 1	1	• 1
	Week 2	15	• 2 – 22
	Week 4	29	• 23 – 36
	Week 6	43	• 37 – 50
	Week 8	57	• 51 – 64
	Week 10	71	• 65 – 78
	Week 12	85	• 79 – 99
Safety Follow-up period	Week 16	113	• 100 – 127
	Week 20	141	• 128 – 155
	Week 24	169	• 156 – 183
	Week 28	197	• 184 – 211

Table 5-6. Study Visits for Physical Examination

Study Phase	Study Visit	Target Day	Study Day
Double-blind Treatment Period	Baseline	Please refer to Section 5.3 Baseline Assessment of the Study	
	Week 12	85	• 1 – 99
Safety Follow-up period	Week 28	197	• 100 – 211

Table 5-7. Study Visits for PK

Study Phase	Study Visit	Target Day	Study Day
Double-blind Treatment Period	**Baseline**	**Please refer to Section 5.3 Baseline Assessment of the Study**	
	Week 1	**8**	• **2 – 15**
	Week 4	**29**	• **16 – 43**
	Week 8	**57**	• **44 – 60**
	Week 9	**64**	• **61 – 67**
	Week 10	**71**	• **68 – 78**
	Week 12	**85**	• **79 – 99**
Safety Follow-up period	**Week 16**	**113**	• **100 – 141**
	Week 24	**169**	• **142 – 183**
	Week 28	**197**	• **184 – 211**

Table 5-8. Study Visits for Antibody

Study Phase	Study Visit	Target Day	Study Day
Double-blind Treatment Period	**Baseline**	**Please refer to Section 5.3 Baseline Assessment of the Study**	
	Week 8	**57**	• **2– 71**
	Week 12	**85**	• **72 – 99**
Safety Follow-up period	**Week 16**	**113**	• **100 – 141**
	Week 24	**169**	• **142 – 183**
	Week 28	**197**	• **184 – 211**

Note:

If more than one visit (including the unscheduled visits, ie, CPEVENT = 'UNSCHED') falls within the same defined window with non-missing measurements, **the closest visit to the target day will be considered for analysis.** If two assessment dates are equidistant from the target date, the latter visit will be considered for analysis. The baseline assessment is defined as the last non-missing measurement for the endpoint of interest taken before the first dose of IP. In cases where baseline measurements are taken on the same day as the first dose of IP **and the measurement time is not collected**, it will be assumed that these measurements are taken prior to IP being administered

5.5 Subject Disposition

Enrolled

Individuals are considered enrolled when they have met Part 1 and Part 2 eligibility criteria Enrolled individuals are referred as “subjects”.

Randomized

Individuals are considered randomized if they have been assigned a randomization number. Randomized individuals are referred to as “subjects”.

Completing the DBTP

Subjects are defined as completing the DBTP if they complete the week 12 assessment. It will be derived from the End of Double-blind Treatment Phase eCRF with “Completed” as the reason for ending study phase.

Completing Study

Subjects are defined as completing study if they complete the whole 28 weeks of study evaluation. It will be derived from the End of Study eCRF page with “Completed” as the primary reason for ending study.

Exposed to IP

Subjects are defined as exposed if they receive at least one dose of IP.

Completing the Double-Blind IP

Subjects are defined as completing double-blind IP if they complete **week 10** IP dose. **It will be derived from the End of Investigational Product Administration eCRF page with “Completed” as the reason for ending IP.**

On-study

Subjects are considered on-study if they have been randomized and have not yet had their end of study visit.

5.6 Arithmetic Calculations

Duration of Migraine

The number of years from the diagnosis date (DXDT) of migraine (migraine with aura or migraine without aura, whichever is earlier) to the date informed consent is signed.

If month or day of the diagnosis date is missing, follow the formula below to calculate the duration:

Observed portion	Missing portion	Formula to Calculate Duration
Year, Month, Day		(Informed Consent Day – DXDT)/365.25
Year, Month	Day	[Year(Informed Consent Day)-Year(DXDT)]+ [Month(Informed Consent Day)-Month(DXDT)]/12 if it equals 0, add 1 month or 1/12 years (this is to avoid a disease duration of 0)
Year	Month, Day	[Year(Informed Consent Day)-Year(DXDT)] if it equals 0, add 1 month or 1/12 years (this is to avoid a disease duration of 0)

Exposure

For all calculations of exposure, dose date refers to receiving dose > 0, but can include partial dose.

Age at Onset of Migraine

Age at enrollment – [date at enrollment in years-DXDT of migraine in years (migraine with aura or migraine without aura]

Duration of DB IP Exposure

Duration = Minimum (Last DB Dose Date + 27, EOS Date) – First DB Dose Date + 1

Change from Baseline in Monthly Efficacy Measurement

The change from baseline in monthly efficacy measurement is the monthly efficacy measurement in the monthly interval prior to the given time point minus the baseline monthly efficacy measurement. Please refer to the Monthly Interval for Efficacy Endpoints defined in Section 5.4. For example, change from baseline in monthly migraine days for Week 12 will be calculated based on the following:

(Monthly migraine days during the week 12 interval) – (monthly migraine days during the baseline phase)

If the baseline or post-baseline value is missing, then the change from baseline is set to missing.

The following efficacy endpoints will be calculated as above:

- Change from baseline in monthly migraine days
- Change from baseline in monthly acute migraine-specific medication treatment days

- Change from baseline in monthly physical impairment domain score as measured by the MPFID
- Change from baseline in monthly impact on everyday activities scores as measured by the MPFID
- Change from baseline in monthly headache (migraine and non-migraine headache) days
- Change from baseline in monthly average severity of migraine pain
- Change from baseline in monthly acute headache medication treatment days
- Change from baseline in monthly mean overall impact on everyday activities as measured by the MPFID stand-alone item
- Change from baseline in monthly days with impact on everyday activities as measured by the MPFID domain
- Change from baseline in monthly days with physical impairment as measured by the MPFID domain
- Change from baseline in the Cranial Autonomic Parasympathetic Symptom (CAPS) scale total score
- Change from baseline in monthly migraine-related disability and productivity as measured by MMIDAS
- Change from baseline in daily activity impact of headache as measured by HIT-6
- Change from baseline in the first 4 weeks in monthly migraine days

Change from Baseline in Mean Monthly Efficacy Measurement over Multiple Months

- The Change from Baseline in Mean Monthly Efficacy Measurement is the Arithmetic mean of monthly values for the months considered - baseline monthly value

Percent Change from Baseline

The change from baseline divided by baseline and multiplied by 100:

(Post-baseline – Baseline) * 100 / Baseline

If the baseline value is 0 and the post-baseline value is also 0, then the percent change from baseline is set to 0. If the baseline value is 0 and the post-baseline value is non-zero, then the percent change from baseline is set to be missing

Percent change from baseline in (mean) monthly migraine days which is used to determine 50%, 75%, and 100% responder will be calculated as above.

Subject Incidence

The subject incidence for a given event in a given period is defined as the number of subjects with at least one reported occurrence of the event divided by the number of

subjects who entered that period. For subjects with multiple occurrences of the same event, the event will only be counted once per subject.

Medication Overuse at baseline

Medication overuse at baseline will be considered if any of the following criteria are present:

- **≥ 15 days of simple analgesic,**
- **≥ 10 days of triptans,**
- **≥ 10 days of ergotamines,**
- **≥ 10 days of combination therapy intake of any combination of ergotamines, triptans, opiates, combination-analgesic medication (includes the case of more than 1 medication category within one visit).**

Medication Overuse during the DBTP

Medication overuse will be considered present if any of the following criteria are met during a **single** month of the DBTP: ≥ 15 days of simple analgesics; ≥ 10 days of triptans; ≥ 10 days of ergotamines; ≥ 10 days of combination therapy intake of any combination of ergotamines, triptans, opiates, **combination-analgesic medications.**

5.7 Disease Characteristics

Migraine-Specific Medications

Migraine-specific medications include two categories of medications: triptan-based and ergotamine-based migraine medications collected from the subject's eDiary.

Treatment Failure of Migraine Prophylactic Medications

Treatment failure of prior migraine prophylactic medications is determined by "Reason for stopping" as "Intolerance" or "Lack of efficacy" in the Migraine Prophylactic Medication eCRF page.

Response Status to AMG 334

At least a 50% reduction from baseline in monthly migraine days at month 3 for subjects who received consecutive 3 doses of AMG334 since the first dose of AMG334.

6. Analysis Sets

6.1 Full Analysis Set

The Full Analysis Set (FAS) consists of all subjects who were randomized in the study. The FAS will be used to tabulate subject disposition, demographic data, baseline disease characteristics, and important protocol deviations for all randomized subjects.

6.2 Primary Analysis Set

The Primary Analysis Set (PAS) (ie, Efficacy Analysis Set) will be used to carry out the primary analyses of the efficacy endpoints. **It consists of all subjects who were randomized,** received at least 1 dose of investigational product, and have at least 1 postbaseline monthly eDiary measurement. Subjects will be analyzed according to their randomized treatment group, regardless of treatment received. The PAS will be used to analyze all efficacy and PRO endpoints.

6.3 Safety Analysis Set

The Safety Analysis Set (SAS) consists of all enrolled subjects who received at least 1 dose of investigational product. Subjects will be analyzed according to the randomized treatment unless a subject has received the incorrect dose during the entire DBTP period. Where a subject has received the incorrect dose during the entire DBTP, the subject will be analyzed according to treatment received. Analyses for safety endpoints and summary of investigational product administration will use this analysis set.

6.4 Pharmacokinetic/Pharmacodynamic Analyses Set(s)

All subjects who received AMG 301 and had at least one PK sample collected will be included in the Pharmacokinetic Analysis Set. These subjects will be evaluated for pharmacokinetics unless significant protocol deviations affect the data analysis or if key dosing, dosing interruption or sampling information is missing.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

After about 50% of the subjects have been enrolled in the DBTP and completed the week 12 visit, multiple independent, unblinded interim analyses will be performed for administrative purposes for future study planning and development based on the interim effect size results for the primary endpoint. The results of these interim analyses will not affect the execution of this study. The maximum number of interim analyses will be no more than 5.

These administrative interim analyses will be conducted by an independent group that is internal to Amgen (eg, Clinical Therapeutic Area Head and 2 statisticians) and separate from the study team; the study team will remain blinded to the specific results. Subject-level treatment group assignment will only be available to Amgen personnel who comprise the external team until the study has been unblinded for the primary analysis.

The primary endpoint (ie, change from baseline period in monthly migraine days) and the following secondary endpoints will be included: achievement of at least 50% reduction in monthly migraine days, and change from baseline period in monthly acute migraine-specific medication days. No safety data will be included.

An internal unblinded team will perform the interim analyses and provide the interim report. Members will review all available safety and efficacy data periodically after at least 50% of the subjects have been enrolled and have completed the week 12 visit. The internal team will have access to subjects' individual treatment assignments. To minimize the potential introduction of bias to the conduct of the study, members of the interim analysis group will not have any direct contact with study center personnel or subjects.

An independent Data Review Team (DRT) will review and make recommendations regarding the safety of the study participants throughout the DBTP and until treatment assignment is unblinded to the study team. The DRT will be composed of Amgen staff that are external to the study team and will include a clinician, a safety physician, and a biostatistician. Summaries of data at the treatment group level will be prepared and presented by an independent biostatistician at the DRT meeting. A study DRT charter will be developed to guide membership, procedures, and meeting timing.

7.2 Primary Analysis

The objective of the primary analysis will be to test the primary efficacy endpoint once the primary completion milestone is achieved after the last subject reaches the last visit in the DBTP, and all data are collected for the primary endpoint. At this time, the study will be unblinded and all efficacy and safety analyses will be conducted and reported by treatment group for both CM and EM. **Safety data collected during safety follow-up before the data cutoff date for the primary analysis will also be summarized.**

The following hypothesis for the primary endpoint will be tested for each AMG 301 treatment group (420 mg SC injections Q2W, 210 mg SC injections Q4W) compared to placebo using the generalized linear mixed effects model:

- Clinical Hypothesis: In subjects with CM **and** EM, AMG 301 reduces the monthly migraine days from the baseline period, compared to placebo

To maintain a family-wise type I error at 0.10 for the testing of the primary endpoint, the pair-wise comparison will be tested for both (1) AMG 301 420 mg SC injections Q2W versus placebo and (2) AMG 301 210 mg SC injections Q4W versus placebo, each at an alpha level of 0.05.

7.3 Final Analysis

The final analysis will be completed after study completion is reached, after the last subject reaches the last visit during the safety follow-up period, and all data are collected for the study. **The safety analyses will be summarized for both the DBTP and safety follow-up phase combined.** In addition, any changes made in the database for data from the double-blind treatment period and following the completion of the primary analyses will be noted. Any changes to data from the double-blind phase will be listed and an assessment will be made to determine if any of the primary analyses should be rerun. Where this is the case, any changes in results and/or study conclusions will be documented in the clinical study report (CSR).

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database.

8.3 Handling of Missing and Incomplete Data

Subjects may miss specific data points for a variety of causes. In general, data could be missing due to a subject's early withdrawal from study, a missed visit, or inability to evaluate an endpoint at a particular point in time. For this study, most of the efficacy endpoint will be collected via eDiary and subjects could miss entering several days of data in each monthly interval. The general procedures outlined below describe what will be done when a data point is missing.

In general, the PAS will be used without any subject-level imputation for missing data for the primary and secondary endpoints, except for proration performed for the eDiary measurements, as described below. The sensitivity analyses for both primary and secondary analyses will use non-responder imputation for categorical endpoints and multiple imputation with the assumption of missing not at random (MNAR) (with control- based pattern imputation) for the continuous endpoints.

Missing eDiary data in the calculation of monthly measurements about subjects' migraine and non-migraine headaches and missing daily scores of impairment day based on MPFID will be handled based on the degree of completion during the month.

For the eDiary, if at least 14 out of 28 monthly days are not missing, then the monthly frequency measurements (eg, migraine days, headache days, migraine attacks) will be prorated based on the number of days with available information using the following formula:

> Number of observed migraine days *28/Number of information days in interval, where an information day is a diary day or headache day.

For each MPFID daily diary domain, if greater than 50% of the items within a domain are not missing, the mean of the item scores that are present for that day will be used to impute a score for the missing item(s). Otherwise, no domain score will be calculated; the domain score will be considered missing.

Table 8-1. Handling of Missing and Incomplete eDiary Data

Monthly Endpoint	Condition	Proration Method (does not need to be rounded)
Monthly frequency measurements (including migraine days, headache days, migraine attacks, acute headache medication treatment days, acute migraine-specific medication treatment days)	If diary days in entire baseline or interval post baseline >=14 (including retrospective eDiary days), then do proration; Else monthly measurement is set to missing [A diary day is a day with all headache related questions completed retrospectively or not]	Number of observed migraine days * 28/ Number of information days in interval [information day is a diary day or headache day]
Monthly average of severity of migraine pain (1-3 scale)	If diary days in entire baseline or interval post baseline >=14 (including retrospective eDiary days), then calculate the average; Else missing	Arithmetic mean of the observed pain scores of qualified migraine headaches over the monthly interval
Monthly average of MPFID domain scores	If days with observed daily domain score in interval >=14 then calculate the average; Else missing	Arithmetic mean of the observed daily domain score over the monthly interval
Monthly impairment day for Everyday Activity and Physical Impairment domains and overall	If days with observed daily domain score in interval >=14 then do the proration; Else missing	Number of observed impairment days * 28/ Number of days with domain score in monthly interval

Completely missing COAs and subject-completed assessments (eg, HIT-6, MIDAS) scheduled to be collected at office visit at certain assessment will not be imputed.

Missing safety endpoints and antibody data will not be imputed, except for adverse event dates as described in Section 8.3.

8.3.1 Missing and Incomplete Dates

Missing or incomplete dates will be listed unless imputed as follows:

Incomplete start date of an adverse event or concomitant medication taken will be handled by following rule:

	Missing	Imputation	Exception
Start date (Adverse event, concomitant medication)	Day	01	Default to Study Day 1 if an adverse event starts the same year and month as Study Day 1 and the flag indicates that the adverse event started on or after the first dose on the Adverse Events eCRF
	Day/Month	01 JAN	Default to Study Day 1 if an event started the same year as Study Day 1 and the flag indicates that the adverse event started on or after the first dose on the Adverse Events eCRF
	Day/Month/Year	No imputation	

8.3.2 Missing Baseline Evaluation

Baseline values are defined in Section 5.3 “Baseline Assessment”. Missing baseline evaluations will not be imputed.

All subjects included in the primary analysis set will have baseline monthly rate or monthly baseline average of migraine and non-migraine headaches related measurements after applying proration rule defined in Section 8.3 since only subjects with ≥ 80% compliance of eDiary use during baseline will be eligible for randomization.

8.3.3 Missing Post-baseline Evaluation in the DBTP

Primary analysis of continuous efficacy endpoints during the 12-week randomized DBTP will be conducted using the generalized linear mixed model on observed data without subject-level imputation.

In sensitivity analyses of primary and secondary efficacy endpoints during the 12-week DBTP, missing continuous monthly efficacy endpoints will be handled using multiple imputation (MI) with the assumption of missing not at random (MNAR) (with control-based pattern imputation). The continuous monthly efficacy endpoints will be computed as the mean over the last four weeks of the DBTP based on the observed and imputed values.

In the non-responder imputation (NRI) method, post-baseline missing dichotomous efficacy endpoints **(responder [Yes/No] based on ≥50%, ≥75% and 100% reduction from baseline in monthly migraine days)** during the DBTP will be imputed as

non-responder at each corresponding time point. The dichotomous endpoints derived based on the mean change from baseline over the last 4 weeks of the DBTP will be imputed as non-responder if the mean change from baseline over the last 4 weeks of the DBTP is missing.

If the proportion of missing data for the primary endpoint is high (eg, > 20%), further analyses will be performed to

- examine the frequency and reason of missing data
- determine if there are any patterns in the missing data
- distinguish true missing values from other unknown values (eg, due to measurement or sample processing error)

8.3.4 Missing Safety-Follow up Period

Missing data in the Safety Follow-up Period will be handled in the same way as missing data in the DBTP.

8.4 Detection of Bias

This study has been designed to minimize potential bias by allocating treatment groups randomly, assessing endpoints and handling withdrawals without knowledge of the treatment. Other factors that may bias the results of the study include:

- important protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints
- inadvertent breaking of the blind before formal unblinding
- investigational product dosing non-compliance
- the timing of and reasons for early withdrawal from treatment and from study

The incidence of these factors may be assessed. Important protocol deviations will be listed and/or tabulated in the CSR. If necessary, the incidence of other factors will be tabulated.

Any breaking of the blind for individual subjects prior to formal unblinding of the study will be documented in the CSR.

The timing of and reasons for early withdrawal from treatment and from study will be tabulated and/or listed.

8.5 Outliers

Histograms will be examined to identify outliers in any of the continuous variables used in the analyses. Unexpected and/or unexplained values in categorical data will be identified by utilizing frequency tables.

Outliers due to data entry errors will be corrected by the study team before final database lock. The validity of any questionable values or outliers will be confirmed. Outliers or any questionable values with confirmed validity will be included in the analyses. However, ad-hoc sensitivity analyses may be conducted to evaluate the influence of extreme values in the data.

8.6 Distributional Characteristics

Continuous endpoints of change from baseline value will be analyzed under normality assumption. If they deviate appreciably from normality, appropriate transformations or the non-parametric alternatives, may additionally be considered.

8.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 7.1 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

The primary objective of this study is to evaluate the effect of AMG 301 compared to placebo on the change from the baseline period in monthly migraine days, in subjects with CM or EM.

The primary analysis will be performed when the last randomized subject completes the week 12 assessment or is discontinued from the study and all data are collected for the primary endpoint. The final analysis for the study including DBTP and safety follow-up phase will be performed at the end of the study.

Subjects will be analyzed based on their randomized treatment group assignment.

Summary statistics by each treatment group will be tabulated at each visit. For continuous endpoints, the descriptive statistics include: number of observations, means, medians, standard deviations, standard errors, first and third quartiles, minimums and maximums, and 2-sided 95% confidence intervals of the means (confidence intervals will be provided for efficacy endpoints only). For categorical endpoints, the summaries will contain the number and percentage of subjects in each category.

Change from baseline for efficacy endpoints during the DBTP will be summarized using the study baseline.

Primary analyses for efficacy endpoints are based on a linear mixed effects model including treatment group, baseline value, stratification factors, scheduled visit, and the interaction of treatment group with scheduled visit in the model. Unadjusted p-values (not adjusted for multiple comparisons) will be provided for the comparisons between each AMG 301 treatment group vs. the placebo group for efficacy endpoints. For continuous efficacy endpoints, the adjusted mean change from baseline for each treatment group, and the adjusted treatment difference compared to placebo, associated 95% confidence intervals, and p-values for pairwise comparisons will be reported. For dichotomous efficacy endpoints, adjusted odds ratios compared to placebo, associated 95% confidence intervals, and p-values will be reported. Values for stratification factors as used during randomization will be utilized in the efficacy analysis instead of the subject's actual value. However, the actual value will be used in analyses of baseline characteristics or in the subgroup analyses of the efficacy endpoints.

To maintain a family-wise type I error rate at 0.10 for the primary endpoint, the AMG 301 210 mg treatment group and the AMG 301 420 mg treatment group will each be tested separately vs placebo at a significance level of 0.05.

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[redacted]

9.2 Subject Accountability

The disposition of all randomized (enrolled) subjects will be tabulated by randomized treatment group. The summary for the DBTP will include the number of subjects who are randomized, the number and percent of subjects who receive/never receive the double-blind IP, who complete double-blind IP, discontinue double-blind IP and reasons for discontinuing, who complete the 12-week DBTP, and who withdraw prematurely from the study before completion of the 12-week DBTP and their reasons for withdrawal.

In addition, the number of subjects who complete the study or are continuing in the study and who withdraw prematurely from the study and their reasons for withdrawal will be summarized.

A footnote on the subject disposition tables will include the number of subjects screened.

A summary of the study reporting period including a description of key dates will also be provided, including dates of the first and last subject enrolled, the primary completion date (for the primary analysis) and the last subject's end of study date (for the final analysis).

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol.

All IPDs will be reported in the clinical study report.

9.4 Demographic and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized using descriptive statistics by randomized treatment group and overall study population using FAS. If multiple races have been reported for a subject, the subject will be categorized as multiple races.

The following demographic and baseline characteristics will be summarized:

- Sex (categorical)
- Ethnicity (categorical)
- Race (categorical)
- **Age (continuous, categorical)**
- Region (categorical, North America vs. Rest of World)
- Height (continuous, cm)
- Weight (continuous, kg)
- Body Mass Index (continuous, BMI, kg/m^2)
- **Baseline migraine type (categorical, CM vs. EM)**
- **Prior participation in CGRP trial (categorical)**
- **≥ 50% reduction in MMD after receiving erenumab for 3 months (Categorical)**
- **Targeted neurological disease diagnosis at baseline (categorical: migraine with aura, migraine without aura, depression, anxiety, other)**
- **Acute headache medication use during baseline phase:**
    - **a) Migraine-specific**
    - **b) Non migraine-specific**
- **Monthly acute migraine-specific medication days in subjects who received acute migraine-specific treatment (continuous)**
- **Monthly acute migraine-specific medication days (continuous)**
- **Number of prior migraine prophylactic treatment category failed (categorical)**
- **Beck Depression Inventory (BDI)-II total score severity grade (categorical)**
- **Age at onset of migraine (continuous)**
- **Disease duration of migraine with or without aura (continuous)**
- **Monthly migraine days (continuous)**
- **Monthly headache days (continuous)**
- **Modified Migraine-specific and Migraine Disability Assessment (MMIDAS) (continuous, categorical)**

- **Headache Impact Test-6 (HIT-6) (continuous, categorical)**
- **Migraine Physical Function Impact Diary (MPFID) (continuous)**
- **Cranial Autonomic Parasympathetic Symptom (CAPS) (continuous, categorical [0, ≥ 1)**

9.5 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary endpoint, change in monthly migraine days from the baseline period to the last 4 weeks of the 12-week DBTP, will be analyzed using the generalized linear mixed effects **model including treatment group, baseline value, stratification factors, scheduled visit, and the interaction of treatment group with scheduled visit** using the PAS without any subject-level imputation for missing data. The primary endpoint will be tested for each AMG 301 treatment group (AMG 301 420 mg SC injections Q2W and AMG 301 210 mg SC injections Q4W) compared to the placebo group using appropriate contrasts for pairwise comparisons. Each AMG 301 dose will be compared to placebo at an alpha of 0.05 to maintain the family-wise type I error at 0.10. The mean change from the baseline period for each treatment group, and the treatment difference, 95% confidence intervals, and p-values will be reported. Sensitivity analyses for the primary endpoint include an analysis of covariance model using data through week 12, in which missing values will be imputed using multiple imputation assuming MNAR up to week 12.
Secondary	• At least a 50% reduction from the baseline period in monthly migraine days in the last 4 weeks of the 12-week double-blind treatment period: Comparison between treatment groups will be performed using CMH tests on observed data with stratification factors. The odds ratio for each AMG 301 treatment group versus placebo group, associated 95% confidence intervals, and unadjusted p-values will be reported. Sensitivity analyses for response include: a logistic regression model using data from week 9 through week 12, adjusting for baseline values where missing values will be imputed as non-responders. • Change from the baseline period in monthly acute migraine-specific medication days in the last 4 weeks of the 12-week double-blind treatment period: The same analysis methods will be used as for the primary endpoint. Refer to Table 5 for details on other secondary endpoints.
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The primary analysis of efficacy endpoints will utilize the PAS. Subjects will be analyzed according to their randomized treatment group regardless of the actual treatment received during the study.

For primary analysis at week 12, the continuous change from baseline efficacy endpoints calculated by the method as specified in Section 5.6 will be analyzed using generalized linear mixed effect models including treatment group, stratification factors, scheduled visit, the interaction between treatment group and scheduled visit and the baseline value on observed data. The dichotomous efficacy endpoints will be analyzed using the stratified Cochran-Mantel-Haenszel (CMH) test after the missing data are imputed as non-response. Detailed primary analysis methods, sensitivity analyses, and covariates included in the models are summarized in the table below.

Table 9-1. Summary of Efficacy Endpoints and Analysis Methods

Endpoint	Primary Summary and Analysis Method	Sensitivity Analysis
Primary Endpoint		
Change in monthly migraine days from baseline to the last 4 weeks of the 12-week DBTP (Note: Results from time points other than week 12 during the DBTP will also be generated in the same generalized linear mixed effect model.)	**Analysis Method I:** 1. Summary statistics by visit using observed data 2. Least squares means from a generalized linear mixed effect model including treatment group, baseline values, stratification variables, scheduled visit, and interaction of treatment and scheduled visit using observed data	**1. Summary statistics by visit and analyze using an ANCOVA model with multiple imputation assuming MNAR(control-based pattern imputation)** **2. Summary statistics by visit and analyze using an ANCOVA model with observed data** 3. **Subgroup analyses: Same as primary summary and analysis method.**

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Footnotes defined on last page of the table

Table 9-1. Summary of Efficacy Endpoints and Analysis Methods

Endpoint	Primary Summary and Analysis Method	Sensitivity Analysis
Secondary Endpoints		
At least a 50% reduction from baseline in monthly migraine days in the last 4 weeks of the 12-week DBTP (Note: Results from time points during DBTP will also be generated in the same model.)	1. Summary statistics by visit using observed data 2. Stratified Cochran-Mantel-Haenszel (CMH) Test	1. Summary statistics by visit and analyze using a logistic regression model, and using responder rate calculated using monthly migraine days 2. A stratified Cochran-Mantel-Haenszel (CMH) test will be used after the missing data are imputed as non-response **3. A generalized linear mixed effects model will be used on observed data** 4. **Subgroup analyses: Same as primary summary and analysis method.**
Change from baseline in monthly acute migraine-specific medication treatment days in the last 4 weeks of the DBTP (Note: Results from individual time point during the DBTP will also be generated in the same generalized linear mixed effect model.)	**Analysis Method I (see above)**	**Analysis Method II:** 1. Summary statistics by visit and analyze using an ANCOVA model with multiple imputation, assuming MNAR
Change from baseline in monthly physical impairment scores as measured by MPFID at assessment time points (Note: Results from individual time point during the DBTP will also be generated in the same generalized linear mixed effect model.)	**Analysis Method I**	N/A

Footnotes defined on last page of the table

Table 9-1. Summary of Efficacy Endpoints and Analysis Methods

Endpoint	Primary Summary and Analysis Method	Sensitivity Analysis
Change from baseline in monthly impact on everyday activities scores as measured by MPFID at assessment time points (Note: Results from individual time point during the DBTP will also be generated in the same generalized linear mixed effect model.)	**Analysis Method I**	N/A
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	Analysis Method I	N/A
	• Summary statistics by visit using observed data • Stratified CMH test	N/A

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[a] The same analyses methods will be applied to the endpoints:
Change from baseline in headache impact scores as measured by HIT-6
Change from baseline in monthly average severity of migraine pain
Change from baseline in monthly acute headache medication treatment days.
Change from baseline in migraine-related disability and productivity as measured by MMIDAS
Change from baseline in monthly days with physical impairment as measured by the MPFID
Change from baseline in monthly days with impact on everyday activities as measured by the MPFID
Change from baseline in the monthly average overall impact on everyday activities score as measured by the MPFID
Change from baseline in the Cranial Autonomic Parasympathetic Symptom (CAPS) scale total score

[b] The same analyses methods will be applied to the endpoints:
Response defined as a 100% reduction from baseline in mean monthly migraine days
Achievement of at least a 5-point reduction from baseline in mean monthly average physical impairment scores as measured by MPFID
Achievement of at least a 5-point reduction from baseline in monthly average impact on everyday activities scores as measured by MPFID

9.5.1 Analyses of Primary Efficacy Endpoint(s)

For the primary analyses, the continuous primary endpoints will be tested using a generalized linear mixed model based on observed monthly data from 12-week DBTP with appropriate contrasts provided in Appendix B for pairwise treatment comparisons and overall linear trend.

The model will include treatment group, baseline value, stratification factors which include region (North America vs Rest of World) and **baseline migraine frequency type (CM vs. EM)**, scheduled visit, the interaction of treatment group with scheduled visit using the PAS without any imputation for missing data. If applicable, the first-order autoregressive covariance structure is assumed. Least squares means (LSMs) for each treatment group, standard errors, associated 95% confidence intervals, difference of LSMs compared to placebo group, associated 95% confidence intervals and unadjusted two-sided p-values will be tabulated by visit and treatment, as well as for the mean monthly values over the last month in the DBTP.

The primary endpoint, change in monthly migraine days from baseline to the last 4 weeks of the 12-week double-blind treatment phase, will be tested for each AMG 301 treatment group (the AMG 301 420 mg SC injections Q2W and AMG 301 210 mg SC injections Q4W) compared to the placebo group using appropriate contrasts for pairwise comparisons. Each AMG 301 dose will be compared to placebo at an alpha of 0.05 to maintain the family-wise type I error at 0.10. The mean change from the baseline period for each treatment group, and the treatment difference, 95% confidence intervals, and p-values will be reported.

Sensitivity analyses for the primary endpoint include subgroup analyses and an analysis of covariance model using data through week 12 data, in which missing values for continuous variables will be imputed by multiple imputation with the assumption of MNAR up to week 12. For dichotomous endpoints, missing values will be imputed by the NRI method. Sensitivity analysis described below will be performed for the primary endpoint:

Summary statistics and ANCOVA model for continuous endpoint. Factors of treatment, baseline covariate and stratification variables will be included in the model. MI with assumption of MNAR (control-based pattern imputation) for continuous endpoints.

1. **Primary endpoint will be summarized by the subgroup of**
    - **Region (North America, Rest of World)**
    - **Migraine type (EM, CM)**

- **Prior use of anti-CGRP medication (yes, no)**
- **Prior migraine prophylactic treatment failures (1, ≥ 2)**
- **Medication overuse (yes, no)**
- **CAPS score (0, ≥ 1)**
- **Age (< median, ≥ median)**
- **Sex (female, male)**
- **Race (White, Other)**
- **Response status to AMG 334 (yes, no)**

The purpose of the subgroup analyses is to explore if the treatment effect varies across subgroups of interest. Subgroup analyses are performed for primary efficacy endpoint using the same method as primary analysis method but performed within each interested subgroup. The treatment difference (or odds ratio) with associated 95% confidence intervals and p-values will be reported within each subgroup.

Note: if the subgroup is one of the stratification factors, the stratification factor will not be included in the model, but the other randomized stratum will be included (ie, if the subgroup is prophylactic migraine medication, then randomized region would be included in the model instead of randomized strata which combined both stratification factors). **These subgroups will be re-examined for appropriateness and may be re-categorized (due to small sample size, for example, if there are < 10% of subjects within a subgroup) before unblinding. The analyses of these subgroups will be exploratory in nature.**

The heterogeneity of the treatment effect across the subgroups will be evaluated for the primary endpoints by examining the treatment by subgroup interaction and a p-value will be presented. For continuous endpoints, the primary analysis model with the addition of treatment group by subgroup interaction will be used.

Primary summary and analysis method with treatment and stratification interaction for continuous endpoints: the interaction of treatment group by stratification variable will be tested with significant level of 0.15. If the interaction term is significant, the interaction term will be included in the model as sensitivity analysis for the primary analysis method.

Time from last dose of study drug to loss of response will be evaluated during the Safety Follow-up period. For responders, loss of response is defined as the first time the subject returns to < 50% reduction from the baseline period in monthly migraine days. For non-responders, loss of response will be evaluated by

percentage of reduction from the baseline period in monthly migraine days over time.

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

For continuous secondary efficacy endpoints, summary statistics and primary analysis method will be conducted in the same way as that for the primary endpoints as specified in Section 9.5.1.

For dichotomous secondary endpoints, comparison between treatment arms will be performed using a stratified CMH test for the primary analysis. Sensitivity analyses will use generalized linear mixed effects model on observed data, adjusting for baseline values and stratification factors with appropriate contrasts for pairwise comparisons. The odds ratio for each AMG 301 treatment group versus placebo group, associated 95% confidence intervals, and unadjusted p-values will be reported. Sensitivity analyses for response include: a logistic regression model using data through week 12, adjusting for baseline values where missing values will be imputed as non-responders.

Subgroup analyses are performed for secondary efficacy endpoints using the same method as primary analysis method but performed within each interested subgroup. The treatment difference (or odds ratio) with associated 95% confidence interval and p-values will be reported within each subgroup.

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9.5.4 Analyses of Clinical Outcome Assessments (COAs) and Patient Reported Outcomes (PROs)

The COAs and PROs include MPFID, HIT-6, MMIDAS and CAPS. Change from baseline in total score (or subscale if applicable) of each COA and PRO (except endpoints described in the Section 9.5.1 above) will be reported during the DBTP.

For HIT-6, in addition to the analysis of continuous change from baseline value, proportions of subject with a ≥ 5-point reduction from baseline and proportions of subject with HIT-6 ≥ 60 (severe impact) will be analyzed similarly as the primary analysis method for dichotomous efficacy endpoints described in Section 9.5.2 above. No sensitivity analysis will be conducted for COA and PROs except for MPFID. The PAS will be used to analyze COA and PRO endpoints.

Table 9-2. Summary of COA and PRO Endpoints and Analysis Methods

Endpoint	Primary Summary and Analysis Method
Change from baseline in the daily activity impact of a headache as measured by the HIT-6 total score	1. Summary statistics by visit using observed data 2. Least squares mean at each time point calculated based on a linear mixed effects model including treatment group, baseline value, stratification factors, scheduled visit, and the interaction of treatment group with scheduled visit, without any subject-level imputation for missing data.
Change from baseline in CAPS	Same as above
Change from baseline in migraine-related disability and productivity as measured by the modified MIDAS (Note: MIDAS scores are collected every month. The first post-baseline measurement of the modified MIDAS scores are at week 4)	Same as above; using ANCOVA model instead of generalized linear mixed effect model.
Change from baseline in monthly mean overall impact on everyday activities score as measured by MPFID stand-alone item	Same as above; using ANCOVA model instead of generalized linear mixed effects model.
Change from baseline in monthly days with physical impairment as measured by MPFID	Same as above; using ANCOVA model instead of generalized linear mixed effects model.
HIT-6 severity grade shift from baseline	Summary statistics for DBTP only. Shift table will also be provided to compare baseline values vs the most extreme post-baseline values through the DBTP.
MMIDAS severity grade shift from baseline	Summary statistics for DBTP only. Shift table will also be provided to compare baseline values vs the most extreme post-baseline values through the DBTP.

9.5.5 Pharmacokinetic Endpoints

AMG 301 exposure parameters of mean concentration over the DBTP will be estimated.

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

For safety endpoints, all randomized subjects who received at least one dose of IP (ie, SAS) will be analyzed based on the randomized treatment unless a subject has received the incorrect dose during the entire DBTP.

No statistical testing comparing treatment groups will be performed in the safety analyses.

Table 9-3. Safety Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)
Secondary	For safety endpoints, data for all enrolled subjects who received at least 1 dose of investigational product (ie, SAS) will be analyzed based on the randomized treatment unless a subject has received the incorrect dose the entire period of interest (period or study). The Medical Dictionary for Regulatory Activities (MedDRA) **version 21.1** or later will be used to code all adverse events to a system organ class and a preferred term. All adverse events will be graded using the CTCAE Version 4 as described in Appendix 4 of the protocol. All adverse event tables will be summarized by treatment group. Subject incidence of adverse events will be summarized for all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product, and fatal adverse events. Adverse events will be tabulated by system organ class and preferred term in alphabetical order. In addition, subject incidence of all treatment-emergent adverse events and serious adverse events will be tabulated by system organ class, preferred term and CTCAE grade in alphabetical order. Subject incidence of all treatment-emergent adverse events and serious adverse events will also be tabulated by preferred term in descending order of frequency. No statistical testing comparing treatment groups will be performed for the safety analyses. Descriptive statistics will be provided for all safety endpoints.

9.6.2 Adverse Events and Disease-related Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, and significant treatment emergent adverse events will also be provided. Subject incidence of disease-related events and fatal disease-related events, if applicable, will be tabulated by system organ class and preferred term. Disease-related events will be combined with other adverse events for the tabulations.

The Medical Dictionary for Regulatory Activities (MedDRA) version **21.1** or later will be used to code all events categorized as adverse events, disease-related events, endpoints, to a system organ class and a preferred term.

The subject incidence of adverse events will be summarized for all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product, fatal adverse events, and adverse events of interest.

Subject incidence of all treatment-emergent adverse events, serious adverse events, treatment-related serious and non-serious adverse events, disease-related events, adverse events leading to withdrawal of investigational product, and fatal adverse events will be tabulated by system organ class and preferred term in alphabetical order.

Summaries of treatment-emergent and serious adverse events occurring in at least 5% of the subjects by preferred term in any treatment arm will be provided in descending order of frequency.

Summaries of treatment-emergent and serious adverse events will be tabulated by system organ class, preferred term, and grade.

9.6.3 Laboratory Test Results

Shift tables of the laboratory toxicity based in CTCAE grade will be tabulated by treatment group. Subject listing of grades ≥2 laboratory toxicities will be provided. In the cases when CTCAE grading scales include numeric range in combination with clinical assessment (eg Potassium [Hypokalemia]), laboratory test results may be summarized based on standard normal ranges or by CTCAE grade utilizing investigator's input.

Summary of change from baseline in selected lab analyst will also be provided.

Subject incidence of liver function test abnormalities (including AST, ALT, Total Bilirubin (TBL) and Alkaline Phosphatase (ALP)) will also be summarized by treatment group.

Additional liver test summary table will provide the number and percentage of subjects by treatment group for the following categories:

- AST and ALT (> 3x ULN; > 5x ULN; > 10x ULN; > 20x ULN, respectively)
- AST or ALT (> 3x ULN; > 5x ULN; > 10x ULN; > 20x ULN, respectively)
- Total Bilirubin (> 1x ULN; >1.5x ULN; >2x ULN, respectively)
- ALP (>1.5 ULN)
- ALT or AST > 3x ULN and Total Bili ≥ 2x ULN and ALP < 2x ULN

Subject incidence of elevated HbA1c >=6.0% over the DBTP and safety follow-up period will also be summarized by treatment group.

9.6.4 Vital Signs

The analyses of vital signs (systolic/diastolic blood pressure, heart rate, temperature and respiratory rate) will include summary statistics of change from baseline over time by treatment group.

Systolic and diastolic blood pressure will also be analyzed by change from baseline in categories: ≥ 20 mm Hg in SBP for SBP >140 mm Hg (Yes vs. No) and ≥ 10 mm Hg in DBP for DBP>90 mm Hg (Yes vs. No) at each time point.

The number and percentage of subjects with at least one post-treatment vital sign measurement meeting any of the following criteria will be reported:

- Systolic Blood Pressure: < 90 mm Hg, > 140 mm Hg, > 160mm Hg
- Diastolic Blood Pressure: < 50 mm Hg, > 90 mm Hg, > 100 mm Hg
- Pulse Rate: < 60 bpm, > 100 bpm
- Temperature: > 38.0°C, < 36.0°C
- Respiratory rate: < 12 breaths/min, > 20 breaths/min

9.6.5 Beck Depression Inventory (BDI)-II

No statistical testing will be performed on BDI-II. The number and percentage of subjects in each of the 4 severity grade categories will be provided by treatment group.

9.6.6 Columbia Suicide Severity Rating Score (C-SSRS)

No statistical testing will be performed on C-SSRS. The number and percentage of subjects in each of the 5 categories describing suicidal behavior and ideation will be summarized by treatment group.

9.6.7 Physical Measurements

The analyses of weight will include summary statistics over time by treatment group. The number and percentage of subjects with at least one post-treatment weight measurement meeting the following criteria will be reported:

Decrease of 7% from baseline or increase of 7% from baseline

9.6.8 Electrocardiogram

The ECG measurements from this clinical study will be performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QTc effect. Since these evaluations may not necessarily be performed under the

rigorous conditions expected to lead to meaningful evaluation of QTc data, summaries and statistical analyses of ECG measurements are not planned, and these data would not be expected to be useful for meta-analysis with data from other studies.

9.6.9 Antibody Formation

The number and percentage of subjects who develop anti-AMG 301 antibodies (binding) will be tabulated by treatment group for entire study. The list of subjects with positive binding antibody at any time will be provided.

9.6.10 Exposure to Investigational Product

The total dose of investigational product and the proportion of subjects receiving each dose level will be summarized using descriptive statistics. Descriptive statistics will be produced to describe the exposure to investigational product by treatment group. The number and percentage of subjects with dose change, reason for dose change and duration of exposure to IP in days will be summarized by treatment group.

9.6.11 Exposure to Concomitant Medication

Number and proportion of subjects receiving acute headache-related will be summarized by acute medication category for each treatment group.

9.6.12 Exposure to Prior Prophylactic Medication

Number and percentage of subjects receiving prior prophylactic medication by categories and discontinuation reasons will be summarized by treatment group.

9.6.13 Cardiovascular Medical History

Number and proportion of subjects reporting cardioscular medical history will be summarized by treatment group.

9.6.14 Cardiac and Diabetes Risk Factors

Number and proportion of subjects reporting cardiac and diabetes risk factors will be summarized by treatment group.

9.7 Other Analyses

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

The pharmacokinetic analysis will be carried out for all subjects who received any AMG 301 doses for estimation of exposure parameters. The exposure parameters will be summarized by dose level and treatment time with descriptive statistics. Actual dose and actual sampling time will be used in the analysis. Dosing interruptions, sampling errors

or administration errors which may impact on the assessment will be taken into account in the analysis. Individual concentration-time data will be provided as a listing.

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PK analyses will be done by Clinical Pharmacology Modeling and Simulation (CPMS).

All PK-related tables, figures, listings and other deliverables will be generated by Clinical Pharmacology Modeling and Simulation (CPMS).

9.7.2 Analyses of Clinical Outcome Assessments

See Section 9.5.4.

10. Changes From Protocol-specified Analyses

The endpoint of change from the baseline period in monthly days with impact on everyday activities as measured by the MPFID domain at assessment time points was not included in the protocol but was added to the SAP to assess the effect of AMG 301 compared to placebo on change from the baseline period in monthly days with impact on everyday activities as measured by the MPFID domain.

The protocol stated that for secondary endpoints comparison between treatment groups for categorical data will be performed using generalized linear mixed effects model on observed data adjusting for baseline values and stratification factors with appropriate contrasts for pairwise comparisons as well as CMH test. The analysis method will be changed so that comparison between treatment groups for secondary endpoints will be performed using only CMH tests on observed data with stratification factors for categorical data.

The protocol stated that the FAS consists of all subjects who were enrolled in the study. This definition will be changed so that the FAS consists of all subjects who were randomized in the study.

Three subgroups were added: prior use of anti-CGRP medication, CAPS score at baseline, and response status to AMG 334.

11. Literature Citations / References

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12. Prioritization of Analyses

There is no prioritization for these analyses.

13. Data Not Covered by This Plan

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- ECG data
- **Efficacy data during Safety Follow up period, with the exception of change from baseline in monthly headache days from week 12 to week 16.**
- General comments
- Data from pharmacogenetics substudy.

14. Appendices

Appendix A. Technical Detail and Information Regarding Statistical Procedures and Programming

N/A

Appendix B. Code Fragment

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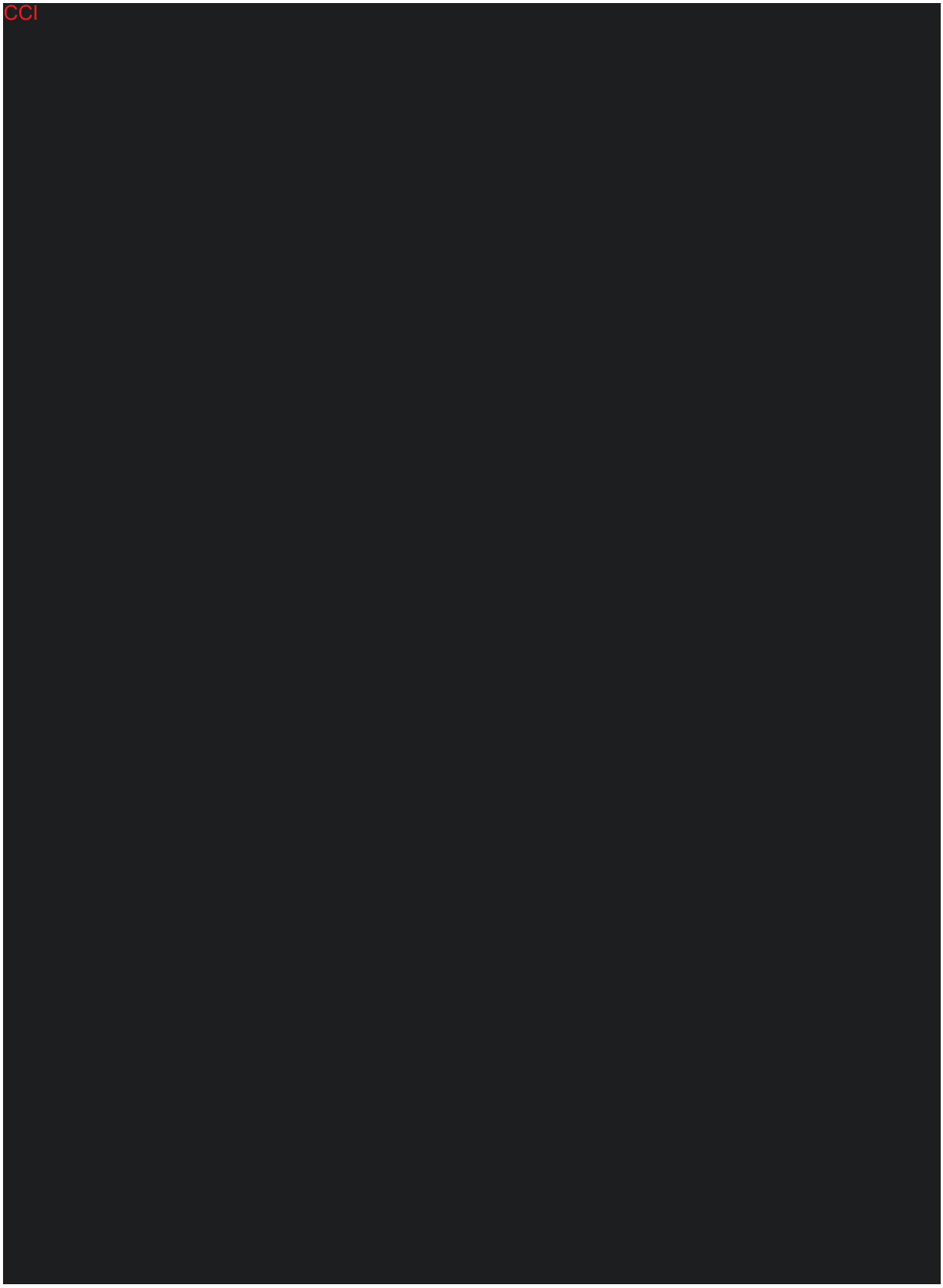

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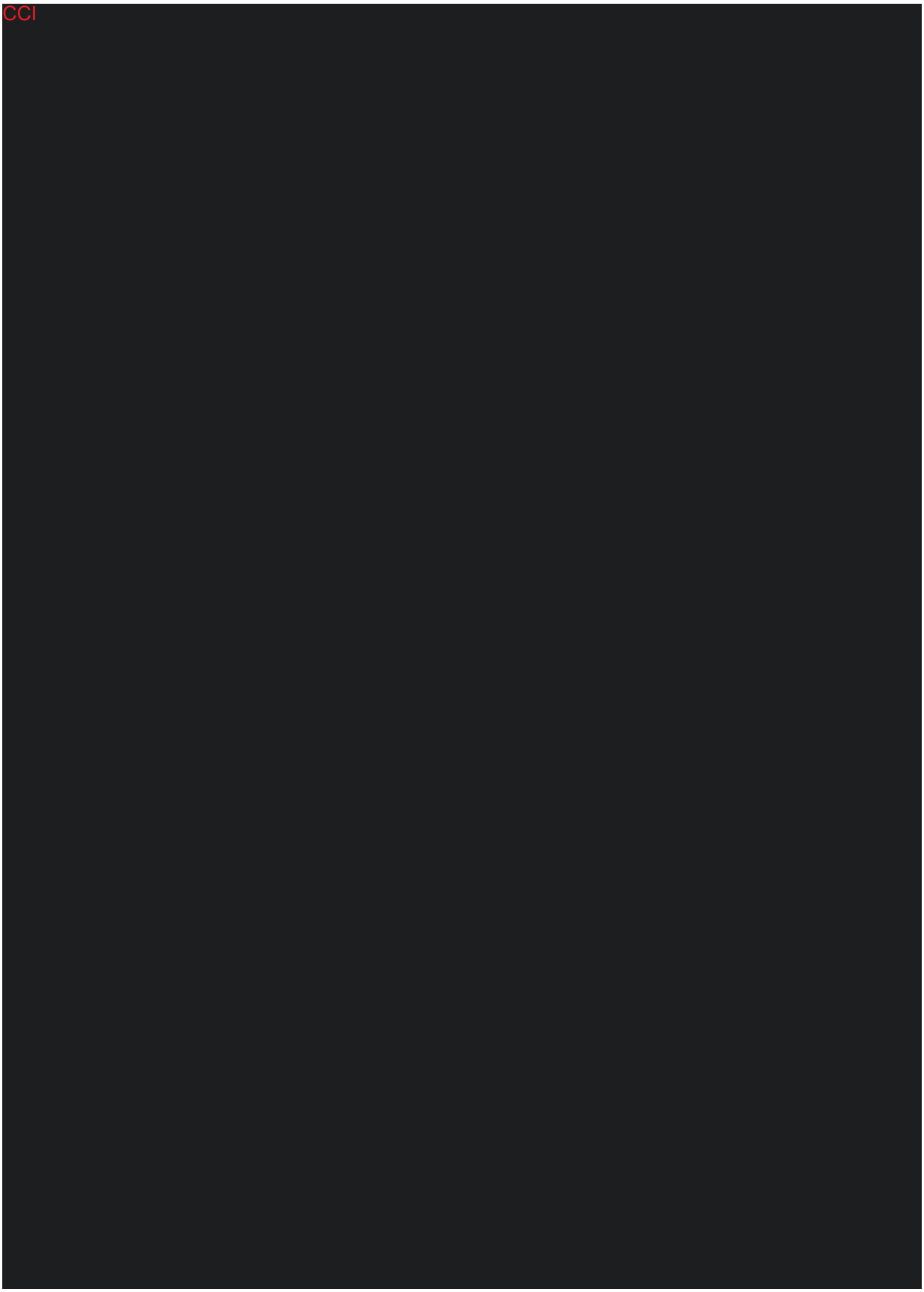

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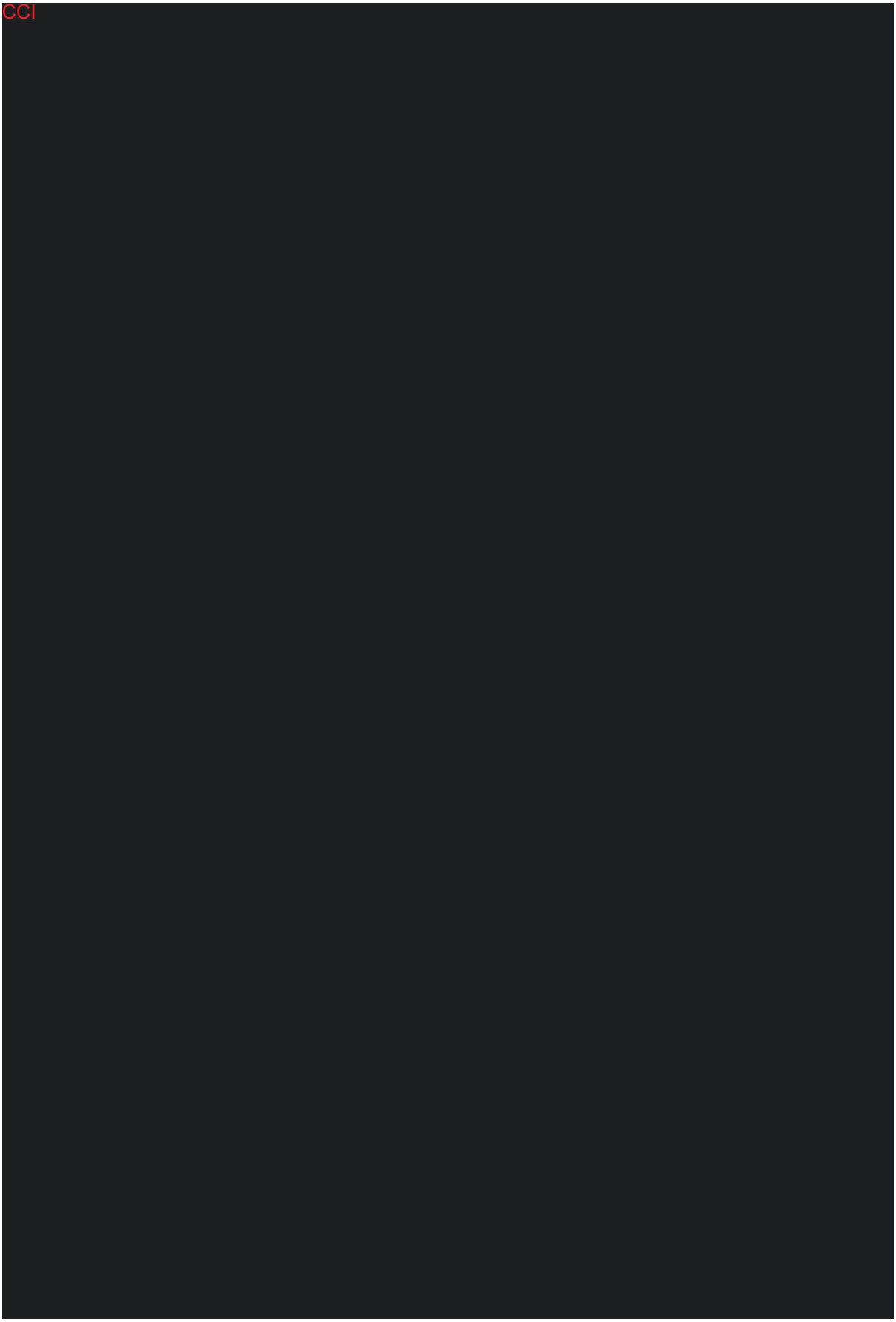

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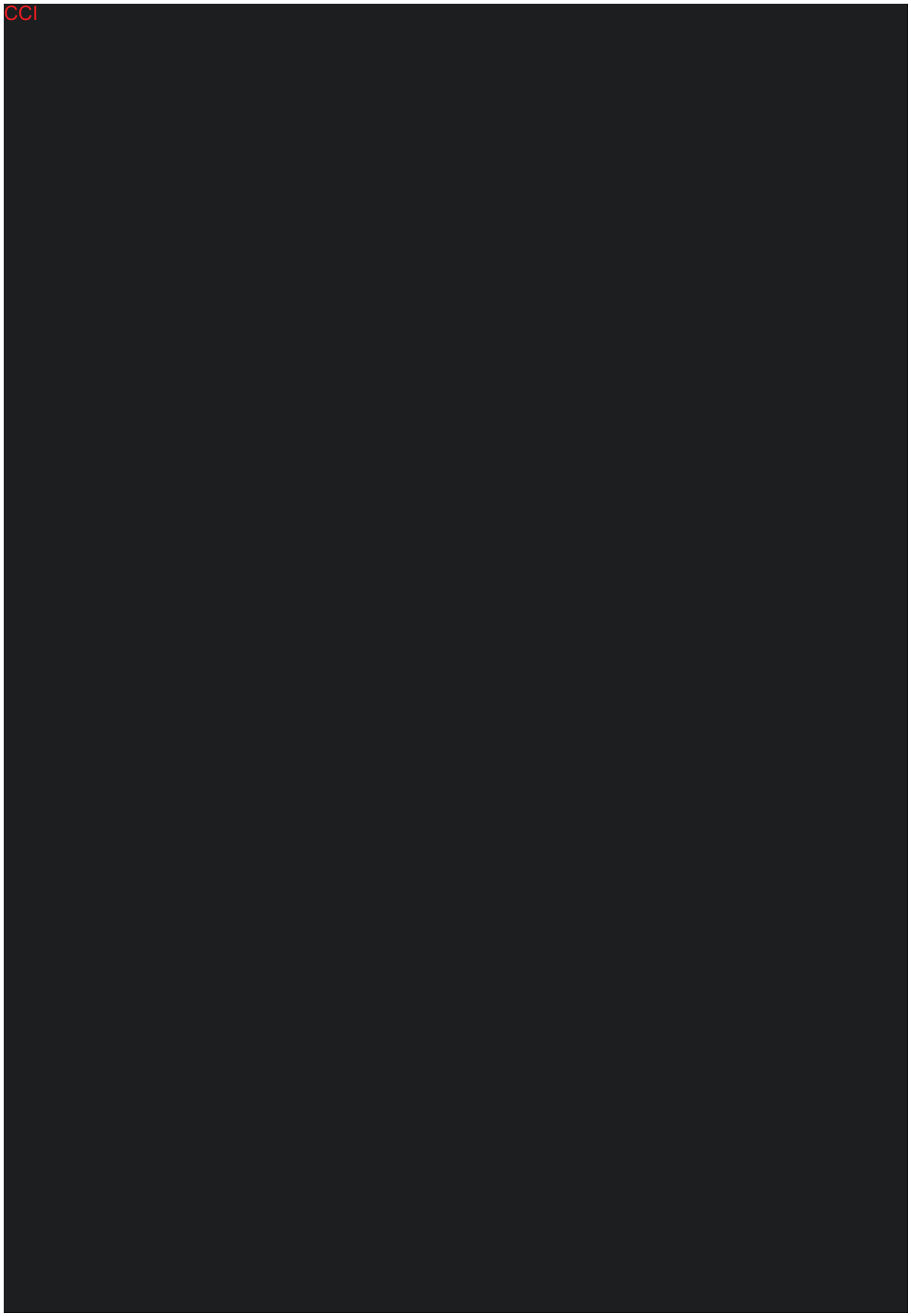

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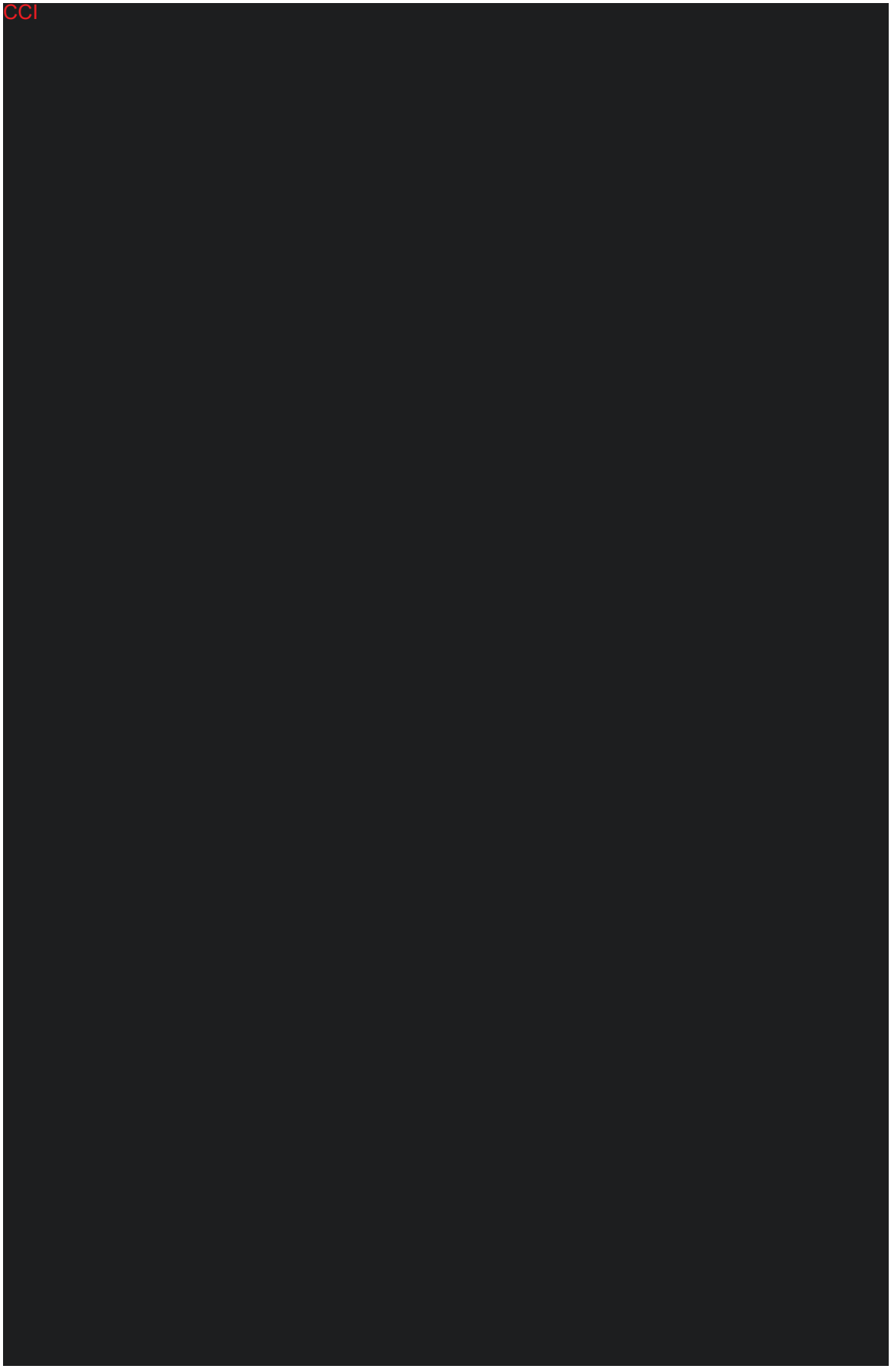

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Appendix C. Reference Values/Toxicity Grades

Adverse event severity and laboratory toxicity are graded based on NCI Common Toxicity Criteria version 4 or higher, which is available at the following:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Appendix D. Concomitant Medications

N/A

Appendix E. Clinical Outcome Assessment Forms/Instruments

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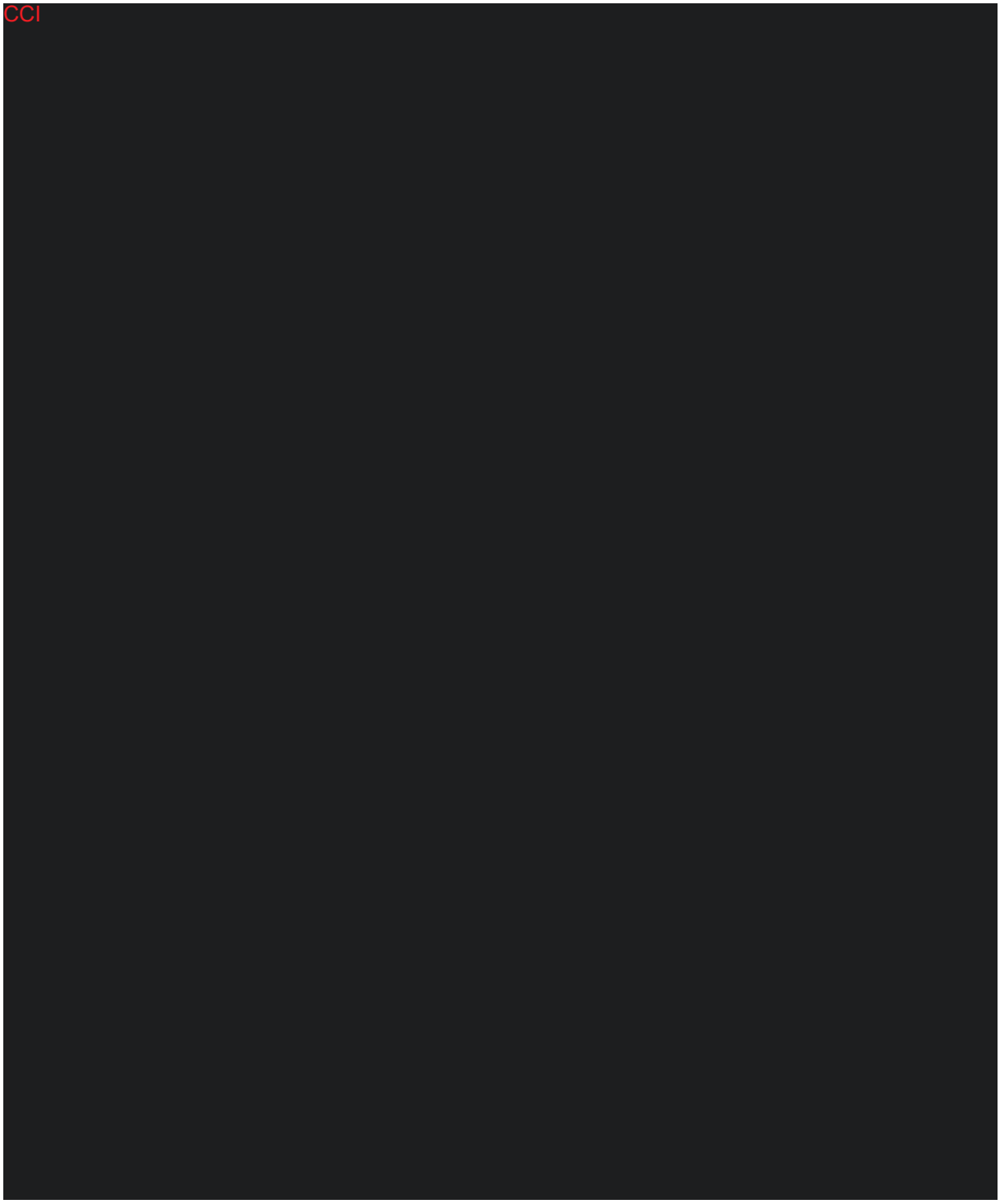

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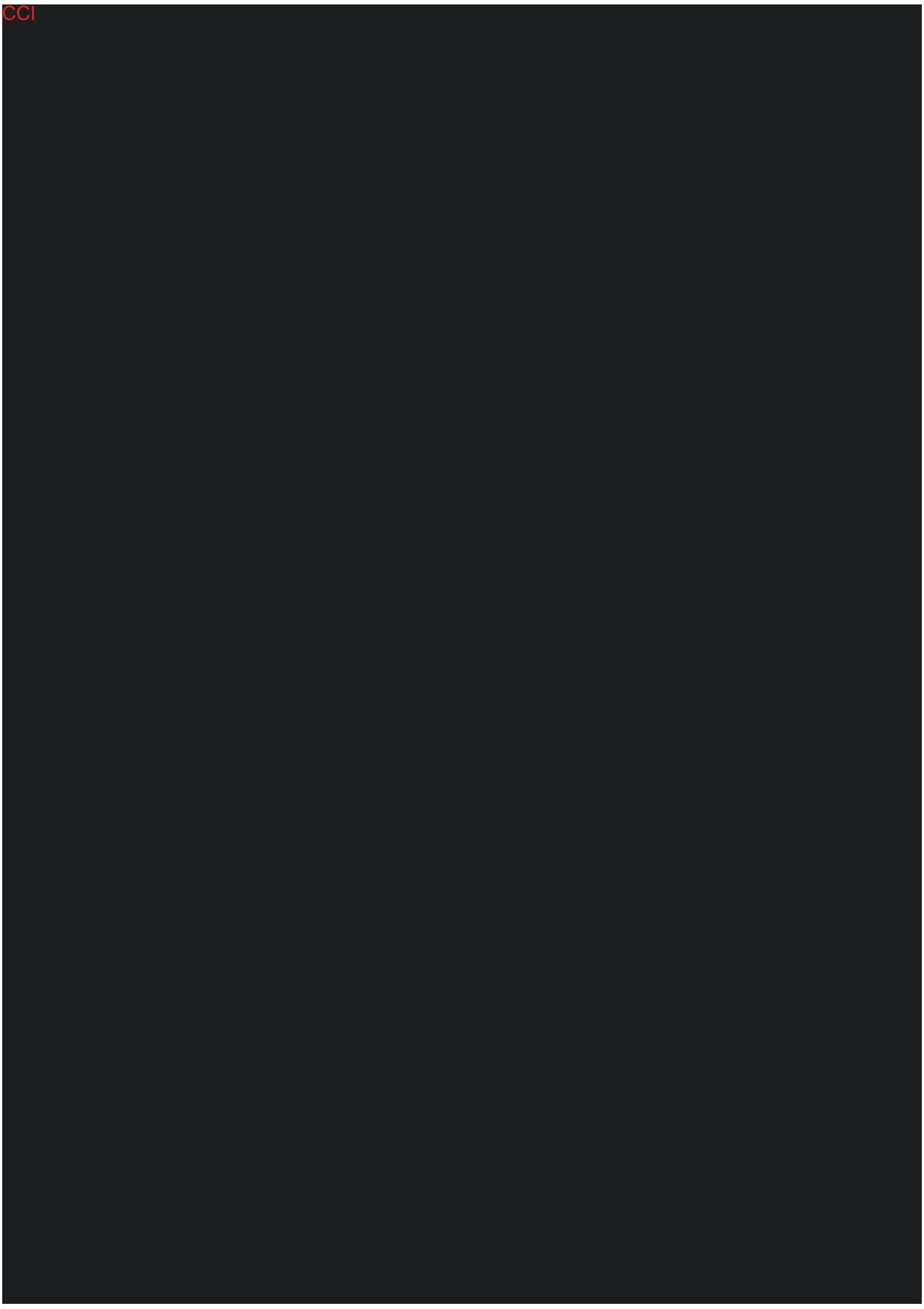

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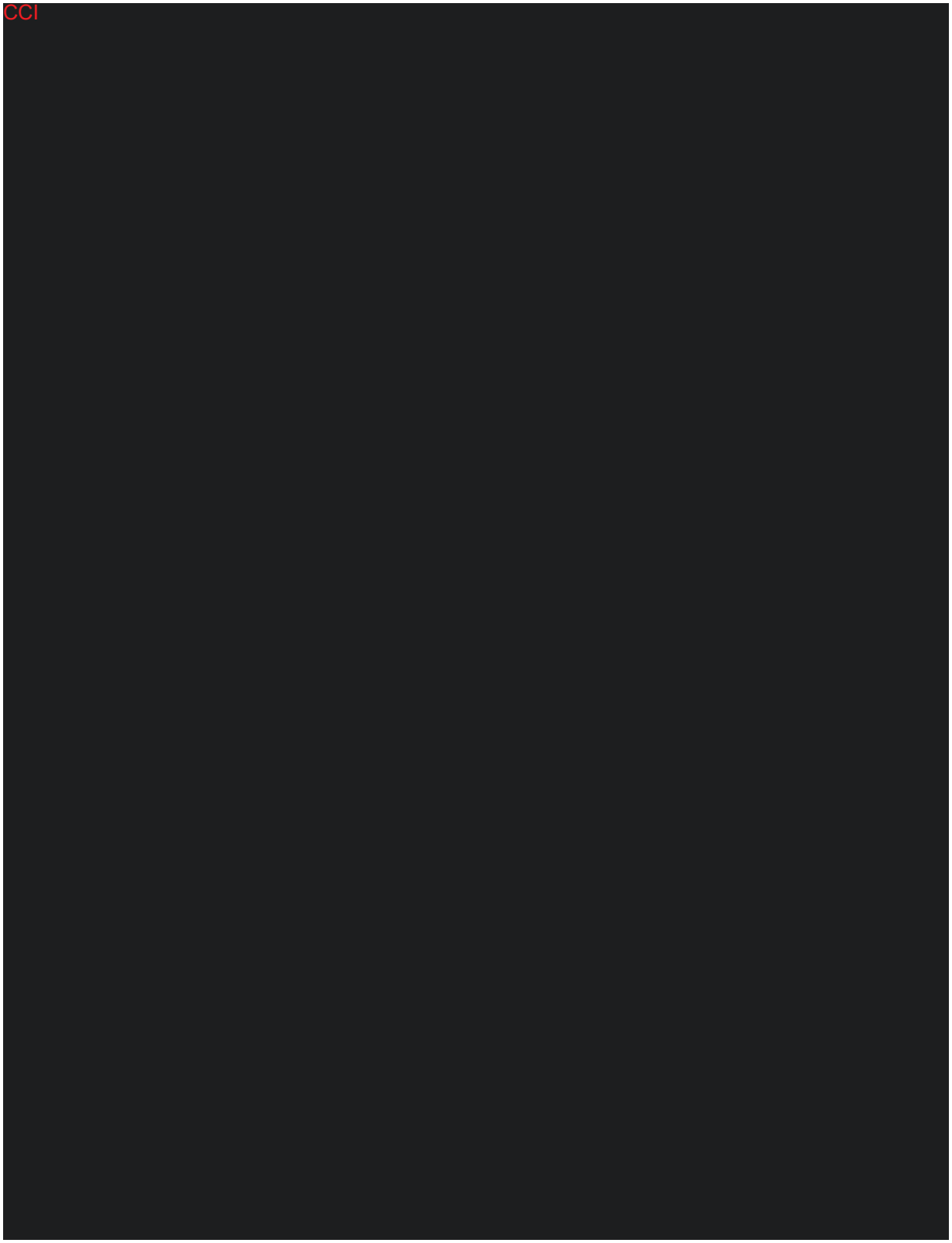

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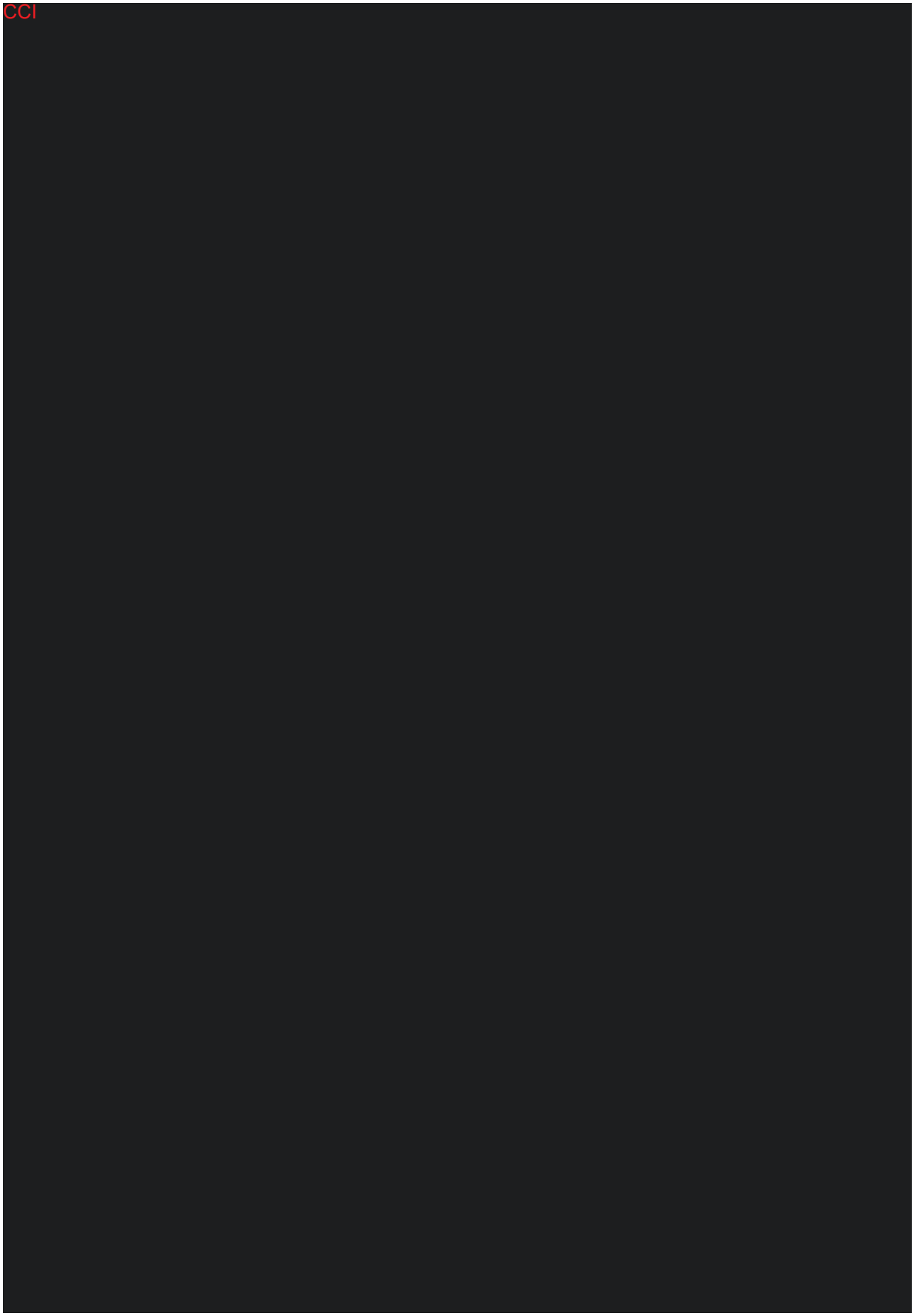

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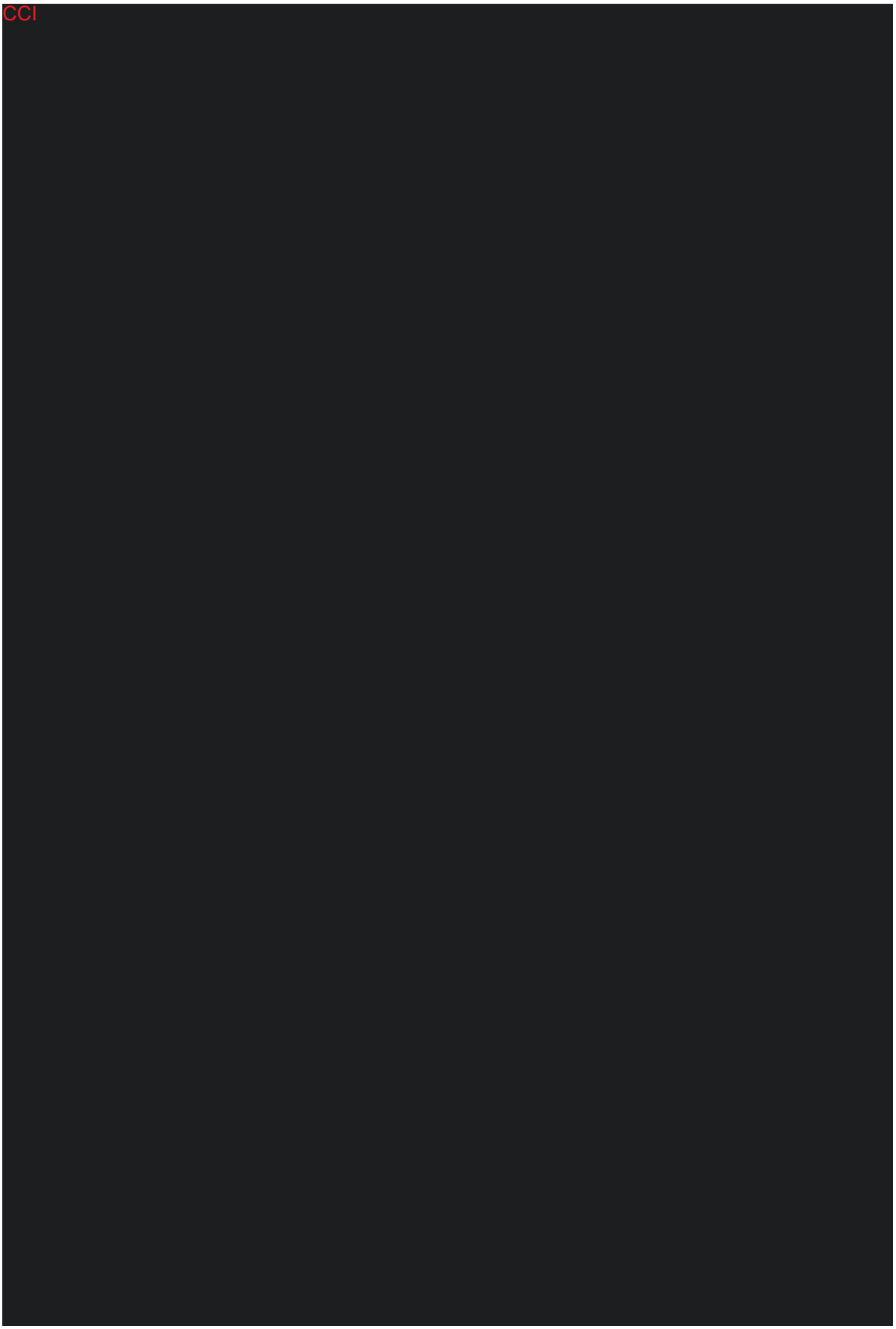

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Appendix F. Health Economic Forms/Instruments

N/A

Appendix G. Details of PK or PK/PD Methods for Modeling

N/A