
STATISTICAL ANALYSIS PLAN

An Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of AMG 334

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Table of Abbreviations

In addition to the study glossaries and abbreviations defined in the protocol, here is a table of abbreviations used in this document:

Abbreviation	Definition
AE	Adverse event
ANC	Absolute neutrophil count
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Toxicity Criteria for Adverse Events
DBP	Diastolic blood pressure
DMP	Data management plan
DTP	Data transfer plan
EAS	Efficacy analysis set
ECG	Electrocardiogram
EDC	Electronic Data Capture
eDiary	Electronic diary
EOS	End of study
E-R	Exposure-Response
FAS	Full analysis set
GSO-DM	Global Study Operations-Data Management
IP	Investigational product
IPD	Important protocol deviation
IVR	Interactive Voice Response
MedDRA	Medical Dictionary for Regulatory Activities
MIDAS	Migraine Disability Assessment
MO	Medication overuse
MPFID	Migraine Physical Function Impact Diary
MSQ	Migraine-Specific Quality of Life Questionnaire
OLE	Open-label Extension
PD	Pharmacodynamics
PK	Pharmacokinetics
PRO	Patient reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System

Abbreviation	Definition
QM	Dosed monthly
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SAS	Safety analysis set
SD	Standard deviation
SSAP	Supplemental statistical analysis plan
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal
WHODRUG	World Health Organization Drug Dictionary

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 3 for Study 20130255 AMG 334, dated 31 March 2016**. The scope of this plan includes the final analysis that is planned and will be executed by the Biostatistics department unless otherwise specified. **For the CHU substudy, please refer to the CHU substudy SAP.**

2. Objectives

Primary

To characterize the safety and tolerability of long-term administration of AMG 334

Secondary

To characterize the efficacy of long-term administration of AMG 334 as assessed by:

- Change from baseline in monthly migraine days
- Proportion of subjects with at least 50% reduction from baseline in monthly migraine days
- Change from baseline in monthly acute migraine-specific medication treatment days
- **Change from baseline in monthly cumulative hours of headache**

Exploratory

- **To evaluate the effect of AMG 334 as measured by reduction from baseline in monthly migraine attacks, in subjects with chronic migraine**
- To evaluate the effect of AMG 334 as measured by the reduction from baseline in
 - monthly headache (migraine and non-migraine headache) days
 - headache days with moderate or severe intensity
 - monthly average severity of migraine pain
- To evaluate the effect of AMG 334 as measured by the change from baseline in monthly average severity of migraine related symptoms (nausea, vomiting, phonophobia and photophobia) for qualified migraine headaches
- To evaluate the effect of AMG 334 on
 - migraine-specific quality of life as measured by the Migraine-Specific Quality of Life Questionnaire (MSQ), version 2.1
 - migraine-related disability, as measured by the Migraine Disability Assessment (MIDAS)
 - pain interference with daily activities and migraine-specific impact, as measured by the Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Interference Scale short form and single pain and migraine symptom interference questions

- To evaluate effect of AMG 334 on change in physical impairment over time as measured by the Migraine Physical Function Impact Diary (MPFID).
- To evaluate the effect of AMG 334 on change in impact on everyday activities over time as measured by the MPFID
- To evaluate AMG 334 pharmacokinetic (PK) in subjects with migraine
- To investigate potential biomarker development by analysis of blood samples

3. Study Overview

3.1 Study Design

This is a multicenter, open-label study designed to assess the long-term safety and efficacy of AMG 334. Subjects who complete the 12-week double-blind treatment phase (DBTP) of the AMG 334 20120295 parent study and meet all AMG 334 20130255 eligibility criteria will be enrolled into the study. Enrollment should occur within 14 days after the parent study's week 12 visit. **Subjects who enroll in the AMG 334 20130255 study will end the AMG 334 20120295 study and will not participate in the parent study safety follow-up visit.**

All subjects who have enrolled in the study under Protocol Amendment 3 or later, will receive open-label AMG 334 140 mg every month (QM) SC for 13 months. Subjects who enrolled in the 20130255 study, prior to Protocol Amendment 3, will increase the open-label dose from 70 mg QM to 140 mg QM at the first available opportunity at either week 4, 8, 12, 16, 20, 24, or 28 visits. Subjects who have already completed the week 28 visit will continue to receive 70 mg QM.

All subjects will receive open-label AMG 334 QM SC for 13 months followed by a 12-week safety follow up visit (16 weeks after the last dose of investigational product [IP]).

Investigational product AMG 334 70 mg or 140 mg will be dosed QM, SC.

3.2 Sample Size

All subjects who completed the 12-week DBTP of the parent study, meet the inclusion and exclusion criteria for the 20130255 OLE study, and consent to receive IP will be eligible to be enrolled. Up to **651** subjects may participate in the study.

4. Study Endpoints and Covariates

4.1 Study Endpoints

Primary Endpoint

The primary endpoint for the study is subject incidence of adverse events.

Secondary Endpoints

- change from baseline in monthly migraine days at assessment time points
- achievement of at least a 50% reduction from baseline in monthly migraine days at assessment time points
- **change from baseline in monthly acute migraine-specific medication treatment days at assessment time points**
- **change from baseline in cumulative monthly headache hours at assessment time points**

Exploratory Endpoints

Change from baseline in

- monthly migraine attacks at assessment time points
- monthly headache (migraine and non-migraine headache) days at assessment time points
- monthly moderate and severe headache (migraine and non-migraine headache) days at assessment time points
- monthly average severity of migraine pain at assessment time points
- monthly average severity of migraine related symptoms (nausea, vomiting, phonophobia, photophobia) for qualified migraine headaches at assessment time points
- migraine-specific quality of life, as measured by the MSQ, version 2.1 at assessment time points
- migraine-related disability, as measured by the MIDAS at assessment time points
- pain interference with daily activities and migraine-specific impact, as measured by the PROMIS Pain Interference Scale short form and single pain and migraine symptom interference questions at assessment time points
- **change in physical impairment over time as measured by the MPFID**
- **change in impact on everyday activities over time as measured by the MPFID**
- AMG 334 pharmacokinetic (PK) concentration
- monthly acute medication use at assessment time points

4.2 Planned Covariates

There are no planned covariate analyses.

Region (North America vs. Other) and medication overuse (Yes vs. No) as collected on the eCRF in the parent study 20120295, if available, and if not available as collected per the parent study randomization stratification factors may be used for subgroup analysis of the appropriate endpoints.

5. Hypotheses and/or Estimations

This is a single-arm estimation study. No hypotheses will be tested.

6. Definitions

6.1 Definition of Terms Included in Study Endpoints

6.1.1 Safety Endpoints

Serious Adverse Event (SAE)

SAEs determined by the flag indicating if the adverse event is serious on the Adverse Events (AE) eCRF page will include those that occur after signing of the informed consent and up to and including end of study.

Treatment-Emergent Adverse Event

Adverse Events (AEs) recorded on the Adverse Events eCRF page that occur on or after first dose of investigational product as determined by the flag indicating if the adverse event started prior to the first dose on the Adverse Events eCRF and up to and including 112 days after the end of investigational product (16 weeks after the last dose of IP) or end of study, whichever comes earlier.

An AE that started in parent study 20120295 is only considered treatment emergent in the OLE study 20130255 if there is a worsening of the event. If the event is ongoing with no changes in severity, then it will not be considered an AE in 20130255.

Treatment-Related Adverse Event

A treatment-related AE is defined as a treatment-emergent adverse event that is considered by investigators to have reasonable possibility that it may have been caused by IP as determined by the flag indicating if the event is caused by investigational product on the Adverse Events eCRF page.

Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a clinician rating of suicidal behavior and ideation. The version "Since Last Visit" will be used for this study. The C-SSRS consists of a maximum of 20 items to evaluate suicidal behavior and suicidal ideation. Please refer to [Appendix B](#) for more details.

6.1.2 Efficacy Endpoints

eDiary Day

Day in which a subject uses the eDiary.

Migraine Day

A migraine day is any calendar day in which the subject experiences a qualified migraine headache. A qualified migraine headache is defined either as a migraine with or without aura as outlined below:

1. A migraine without aura is defined as a headache lasting continuously for ≥ 4 hours, and meeting criteria a and/or b:
 - a) ≥ 2 of the following pain features:
 - Unilateral
 - Throbbing
 - Moderate to severe
 - Exacerbated with exercise/physical activity
 - b) ≥ 1 of the associated symptoms:
 - Nausea and/or vomiting
 - Photophobia and phonophobia

OR

2. A migraine with aura and meeting criteria c and d:
 - c) The occurrence of ≥ 1 of the following fully reversible aura symptoms:
 - Visual
 - Sensory
 - Speech and/or language
 - Retinal
 - Brainstem
 - d) Aura is accompanied, or followed within 60 minutes, by headache lasting continuously for ≥ 4 continuous hours (see [Appendix C](#)).

If the subject took a triptan or ergot-derivative 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 or associated symptoms.

Monthly Migraine Days

Monthly migraine days is the number of migraine days **between each monthly IP dose normalized to 28 day equivalents**, relative to study day 1 in the first 3 months, between the month 5 and 6 visit, between the month 9 and 10 visit and **between the month 12 and 13 visit**. Hereafter, the corresponding visits for these intervals will be reported/presented as/referred to month 1, month 2, month 3, month 6, month 10 and

month 13 visit, respectively. All available eDiary data for the visits will be used and prorated to 28-day equivalents.

Qualified Headache

A migraine or non-migraine headache which lasts ≥ 4 continuous hours, or a headache of any duration for which acute medication was administered for treatment of headache.

In particular, a qualified headache is:

- 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 continuously for ≥ 4 hours and is not a qualified migraine headache, or
- a headache of any duration for which acute medication is administered.

Headache Day

Any calendar day in which the subject experiences a qualified migraine or non-migraine headache.

Monthly Headache Days

Number of headache days in **between each monthly IP dose intervals and normalized to 28 day equivalent** relative to study day 1 in the first 3 months, or between the month 5 and 6 visit, or between the month 9 and 10 visit, **or between the month 12 and 13 visit. Days without eDiary data are handled by proration according to [Section 9.3](#).**

Migraine Attack

An episode of any qualified migraine headache or episode for which the subject took a triptan or ergot-derivative to treat headache or aura. The following rules will be used for distinguishing an attack

of long duration from two attacks or for distinguishing between attacks and relapses:

- a) A migraine attack that is interrupted by sleep, or temporarily remits, and then recurs within 48 hours after onset of the attack will be considered as one attack and not two.
- b) An attack primarily treated successfully with medication but with relapse within 48 hours **of onset of attack** will be considered as one attack.
- c) **A migraine attack lasting more than 48 hours will be counted as one attack.**

Monthly Migraine Attacks

Number of migraine attacks **between each monthly IP dose and normalized to 28 day equivalent** relative to study day 1 in the first 3 months, or between the month 5 and 6 visit, or between the month 9 and 10 visit or **between the month 12 and 13 visit**. **Days without eDiary data are handled by proration according to [Section 9.3](#)**. For the definition of a migraine attacks, see above.

Fifty Percent Responder Rate

At least 50% reduction from baseline in monthly migraine days. **Percentage change from baseline in monthly migraine days is used to determine 50% responder (see [Section 6.6](#))**.

Monthly Cumulative Hours of Migraine Headache

Cumulative duration of any qualifying migraine headache which occurs during each migraine day **between each monthly IP dose and normalized to 28 day equivalent** relative to study day 1 in the first 3 months, or between the month 5 and 6 visit, or between the month 9 and 10 visit, or **between the month 12 and 13 visit**, regardless of acute treatment use. **Days without eDiary data are handled by proration according to [Section 9.3](#)**.

Monthly Acute Medication Use in Days

Number of days on which medications are used for acute treatment of headache **between each monthly IP dose and normalized to 28 day equivalent** relative to study day 1 in the first 3 months, or between the month 5 and 6 visit, or between the month 9 and 10 visit, or **between the month 12 and 13 visit**. **Days without eDiary data are handled by proration according to [Section 9.3](#)**.

Monthly Acute Migraine-specific Medication Use in Days

Number of days on which migraine-specific medications are used **between each monthly IP dose and normalized to 28 day equivalent** relative to study day 1 in the first 3 months, or between the month 5 and 6 visit, or between the month 9 and 10 visit, or **between the month 12 and 13 visit**. **Days without eDiary data are handled by proration according to [Section 9.3](#)**.

Monthly Average Severity of Migraine Pain

Severity of migraine pain is graded as 1=mild, 2=moderate or 3=severe and was rated as its worst or peak intensity per migraine headache. Monthly average severity of migraine pain was defined as the sum of the severity of each observed qualified

migraine day **between each monthly IP dose and normalized to 28 day equivalent** relative to study day 1 in the first 3 months, or between the month 5 and 6 visit, or between the month 9 and 10 visit, **or between the month 12 and 13 visit** divided by the total number of observed qualified migraine days (**as one record in eDiary with start and end time**) in the corresponding interval. **If less than 14 days of eDiary in each interval is recorded, then the monthly average severity of migraine pain will be set as missing.**

Monthly Average Severity of Migraine Symptoms

Migraine Symptoms include nausea, vomiting, photophobia and phonophobia. Severity of these symptoms is graded as 1=mild, 2=moderate or 3=severe and 0 if not reported for qualified migraine headache. Monthly average severity of each migraine symptom was defined as the sum of the severity of corresponding migraine symptom **between each monthly IP dose and normalized to 28 day equivalent** relative to study day 1 in the first 3 months, or between the month 5 and 6 visit, or between the month 9 and 10 visit, **or between the month 12 and 13 visit** divided by the total number of observed qualified migraine days in the corresponding interval. **If less than 14 days of eDiary in each interval is recorded, then the monthly average severity of migraine symptom will be set as missing.**

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6.2 Study Dates

Informed Consent Date

The date on which the subject signs the study informed consent form.

Enrollment Date

The date on which the subject is enrolled in the study.

First IP Dose Date

First IP dose date is the date on which a subject is administered the first dose of IP in study 20130255, which may be the same or after the enrollment date. Subjects who are enrolled should be dosed at least on day 1. If a subject is enrolled but not dosed, first IP dose date is set to first available dose date.

Last IP Dose Date

End of IP dose date for each subject is defined as the latest date IP is administered.

End of IP Admin Date

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 CRF page.

Subject-level End of Study (EOS) Date

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.

Study Completion Date

The study completion date is the EOS date of the last subject in the study.

6.3 Study Points of Reference

Baseline

There are two baselines for this study: one is based on the 20120295 parent study baseline and other is based on the 20130255 study baseline.

The 20120295 parent study baseline is the baseline defined in the 20120295 parent study. For monthly efficacy endpoints, the baseline is derived using the parent study data from the first day subject used eDiary in baseline phase at week-4 study visit through the day prior to study day 1 of the parent study 20120295. For safety endpoints, the baseline is the last non-missing assessment for the endpoint of interest taken before day 1 IP dose in the parent study 20120295.

In addition, for monthly rate or monthly average of migraine and non-migraine headache related efficacy endpoints, 20130255 study baseline is also used and derived using the parent study 20120295 month 3 data (ie, week 8 through week 12 data). For safety endpoints, 20130255 study baseline is the last non-missing measurement (including measurements taken from 20120295) for the endpoint of interest taken before day 1 IP dose in the study 20130255. For C-SSRS, all individual items from the parent

study 20120295 week 12 visit will be used as 20130255 study baseline if available, **otherwise baseline as defined in the parent study will be used.**

Study Day 1

Study day 1 is defined as the first IP dose date in the study 20130255. For subjects who are enrolled but not dosed after enrollment, the study day 1 is defined as the date of enrollment.

Study Day

Study day is defined as the number of days from study day 1.

Before study day 1:

$$\text{Study day} = (\text{date of Interest} - \text{date of study day 1})$$

On or after study day 1:

$$\text{Study day} = (\text{date of Interest} - \text{date of study day 1}) + 1$$

The day prior to study day 1 is -1.

6.4 Study Time Intervals

Monthly Interval for Efficacy Endpoints

Monthly efficacy measurements will be calculated based on the subject's monthly IP dosing schedule defined below using eDiary data collected from day 1 up to week 48 (end of eDiary use). Any eDiary data occurring after EOS date will not be included in the analysis.

Week	Interval Based on Dose Dates for OLE Phase	
	Start date	End date
4	Day 1 dose date	Week 4 dose date-1; study day 28 if week 4 dose is not received (either missed or IP discontinued prior to week 4)
8	Week 4 dose date; study day 29 if week 4 dose is not received (either missed or IP discontinued prior to week 4)	Week 8 dose date-1; study day 56 if week 8 dose is not received (either missed or IP discontinued prior to week 8)
12	Week 8 dose date; study day 57 if week 8 dose is not received (either missed or IP discontinued prior to week 8)	Week 12 IP dose date-1; study day 84 if week 12 dose is not received (either missed or IP discontinued prior to week 12)
16	Week 12 dose date; study day 85 if week 12 dose is not received (either missed or IP discontinued prior to week 12)	Week 16 IP dose date-1; study day 112 if week 16 dose is not received (either missed or IP discontinued prior to week 16)
20	Week 16 dose date; study day 113 if week 16 dose is not received (either missed or IP discontinued prior to week 16)	Week 20 IP dose date-1; study day 140 if week 20 dose is not received (either missed or IP discontinued prior to week 20)
24	Week 20 dose date; study day 141 if week 20 dose is not received (either missed or IP discontinued prior to week 20)	Week 24 IP dose date-1; study day 168 if week 24 dose is not received (either missed or IP discontinued prior to week 24)
28	Week 24 dose date; study day 169 if week 24 dose is not received (either missed or IP discontinued prior to week 24)	Week 28 IP dose date-1; study day 196 if week 28 dose is not received (either missed or IP discontinued prior to week 28)
32	Week 28 dose date; study day 197 if week 28 dose is not received (either missed or IP discontinued prior to week 28)	Week 32 IP dose date-1; study day 224 if week 32 dose is not received (either missed or IP discontinued prior to week 32)
36	Week 32 dose date; study day 225 if week 32 dose is not received (either missed or IP discontinued prior to week 32)	Week 36 IP dose date-1; study day 252 if week 36 dose is not received (either missed or IP discontinued prior to week 36)
40	Week 36 dose date; study day 253 if week 36 dose is not received (either missed or IP discontinued prior to week 36)	Week 40 IP dose date-1; study day 280 if week 40 dose is not received (either missed or IP discontinued prior to week 40)
44	Week 40 dose date; study day 281 if week 40 dose is not received (either missed or IP discontinued prior to week 40)	Week 44 IP dose date-1; study day 308 if week 44 dose is not received (either missed or IP discontinued prior to week 44)
48	Week 44 dose date; study day 309 if week 44 dose is not received (either missed or IP discontinued prior to week 44)	Week 48 IP dose date-1; study day 336 if week 48 dose is not received (either missed or IP discontinued prior to week 48)
52	Week 48 dose date; study day 337 if week 48 dose is not received (either missed or IP discontinued prior to week 48)	Study day 364

Note: for the intervals in month 6, 10, and 13 all available data before the next planned IP dose or visit should be used for calculation. Also refer to the definition of Monthly Migraine Days in [Section 6.1.2](#).

Study Visit

Since the actual visit for a subject may not exactly coincide with his/her targeted visit date, the actual visit date is mapped to the study visit as follows (visit windows below only apply to visits other than safety follow-up visit):

Study Phase	Study Visit	Target Day	Study Day
Open-label Treatment Phase	Day 1	1	1
	Week 4	29	2-43
n = 2 to 13	Week 4n	28n+1	28n-12 to 28n+15
	Week 8	57	44-71
	Week 12	85	72-99
	Week 16	113	100-127
	Week 20	141	128-155
	Week 24	169	156-183
	Week 28	197	184-211
	Week 32	225	212-239
	Week 36	253	240-267
	Week 40	281	268-295
	Week 44	309	296-323
	Week 48	337	324-351
	Week 52	365	352-379
	Safety Follow-up	The nominal visit from RAVE	

Note: If more than one visit (including the unscheduled visits, ie, CPEVENT='UNSCHED') fall within the same defined window, **scheduled visit will be used regardless of the distance from the target day. Unscheduled visit will only be used when there is no scheduled visit in the defined window.** The closest visit to the target day **among the same type of visit (scheduled vs. unscheduled)** will be considered for analysis. If two assessment dates are equidistant from the target date, the latter visit will be considered for analysis.

Above study visit table will be used for lab, vital signs, C-SSRS and PROs collected during office visit.

For adverse event, analysis windows will be set up based on study phase:

Study Phase	Start Time Point	End Time Point
Screening Phase for SAE only	Informed consent date	One study day prior to the first IP dose
Open-label Treatment Phase	Study Day 1 after the 1 st IP Dose	Min(EOS date, last IP dose date + 112 days)

6.5 Subject Disposition

Enrolled

Individuals are considered enrolled if they have non-missing enrollment date. Enrolled individuals are referred to as “subjects”.

Completing the Open-label Treatment Phase

Subjects are defined as completing the open-label treatment phase if they complete the week 52 assessment, which means the subjects have completed the end of IP form and have eDiary data for the month 13.

Completing Study

Subjects are defined as completing the study if they complete the whole 64 weeks of study evaluation. It will be derived from the end of study CRF page with “completed” as the primary reason for ending study.

Exposed to Investigational Product

Subjects are defined as exposed if they receive at least one dose of investigational product in study 20130255.

6.6 Arithmetic Calculations

Exposure

For calculations of exposure, dose date refers to receiving dose > 0, but can include partial doses. The non-AE safety treatment group assignments will be based on the durations of IP exposure to AMG 334 70 mg and 140 mg as presented below (see also [Appendix C](#)).

Duration of IP Exposure for Subjects Receiving Only 70 mg or 140 mg

Duration = minimum (last dose date + 27, EOS date) – first dose date + 1.

Duration of IP Exposure for Subjects Receiving Both 70 mg and 140 mg

70 mg duration = minimum (first 140 mg dose date - 1, last 70 mg dose date + 27, EOS date) – first 70mg dose date + 1.

140 mg duration = minimum (last 140 mg dose date + 27, EOS date, date of data cut off) – first 140 mg dose date + 1.

Change from Baseline in Monthly Efficacy Measurement

The change from baseline in monthly efficacy measurement is the monthly efficacy measurement in **between consecutive exposures to IP** prior to the given time point minus the baseline monthly efficacy measurement (see Interval Based on Dose Dates for OLE Phase table presented in [Section 6.4](#)). For example, the change from baseline in monthly migraine days at week 12 will be calculated as:

(Monthly migraine days between week 12 interval start date and week 12 interval end date) – Baseline monthly migraine days

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

Following efficacy endpoints will be calculated as above:

Secondary endpoints

- change from baseline in monthly migraine days
- change from baseline in monthly acute migraine-specific medication treatment in days
- **change from baseline in cumulative monthly headache hours**

Exploratory endpoints

- change from baseline in monthly migraine attacks
- change from baseline in monthly headache (migraine and non-migraine headache) days
- change from baseline in monthly moderate and severe headache (migraine and non-migraine headache) days
- change from baseline in monthly average severity of migraine pain
- change from baseline in monthly average severity of migraine related symptoms (nausea, vomiting, phonophobia, photophobia) for qualified migraine headaches
- **Change from baseline in migraine-specific quality of life, as measured by the MSQ, version 2.1**
- **Change from baseline in migraine-related disability, as measured by the MIDAS**
- **Change from baseline in pain interference with daily activities and migraine-specific impact, as measured by the PROMIS Pain Interference Scale short form and single pain and migraine symptom interference questions**
- **Change in physical impairment over time as measured by the MPFID**

- **Change in impact on everyday activities over time as measured by the MPFID**

Other endpoints

- change from baseline in monthly acute medication treatment in days
- change from baseline in monthly average migraine symptoms interference scale

Percent Change from Baseline

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

$$(\text{post-baseline} - \text{baseline}) * 100 / \text{baseline}$$

If the baseline value is 0, then the percent change from baseline is set to be missing. Percent change from baseline in 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.

Exposure-Adjusted Subject Incidence

The **exposure-adjusted subject incidence in a given period** is defined as the number of subjects with at least one reported occurrence of the event in a given time period of follow-up divided by total subject years of follow-up in that period. **For subjects with events, only the time until the first event contributes to the total subject years of follow-up. This rate will be presented per 100 subject years.** For subjects with multiple occurrences of the same event, the event will be only counted once per subject. Please refer to the table of safety analysis study windows in [Section 6.4](#) to calculate follow-up time in days for each subject.

6.7 Disease Characteristics

Migraine-specific Medication

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

Acute Headache Medication

Acute headache medication includes simple analgesics, combination analgesics, triptans, ergot-derivatives and opioids categories of medications.

Treatment Failure of Prior Migraine Prophylactic Medications

Treatment failure of prior migraine prophylactic medications is determined by “Reason for ending medication” as “Lack of efficacy” or “Adverse Reaction” in the Prior Migraine Prophylactic Medication parent study 20120295 eCRF page.

7. Analysis Subsets

7.1 Full Analysis Set

The full analysis set (FAS) includes all subjects who were enrolled in the study and received at least one dose of investigational product. Enrolled subjects must meet the study inclusion and exclusion. Presentation of disposition and baseline data will utilize this analysis set. **Treatment group identifiers, based on first dose received, will be as follows:**

- **AMG 334 70 mg**
- **AMG 334 140 mg**
- **AMG 334 Total**

7.2 Efficacy Analysis Set

The Efficacy Analysis Set (EAS) includes subjects who were enrolled and received at least one dose of IP and **had at least one change from baseline measurement in monthly migraine day** in study 20130255. **Subjects will be analyzed according to their randomized treatment group in the parent study 20120295 and the first dose received in the 20130255 OLE study, irrespective if a subject received only AMG 334 70 mg, 140 mg or both 70 mg and 140 mg in the 20130255 OLE study.**

Treatment group identifiers will be as follows:

- **Placebo / AMG 334 70 mg**
- **Placebo / AMG 334 140 mg**
- **AMG 334 70 mg / 70 mg**
- **AMG 334 70 mg / 140 mg**
- **AMG 334 140 mg / 70 mg**
- **AMG 334 140 mg / 140 mg**

Analyses for efficacy endpoints and patient reported outcomes (PROs) will utilize this analysis set except C-SSRS and MPFID.

7.3 Safety Analysis Set

The Safety Analysis Set (SAS) includes all enrolled subjects who received at least one dose of investigational product in study 20130255. Analyses for safety endpoints and

summary of IP administration will utilize this analysis set. The SAS and FAS are the same analysis sets.

Treatment group identifiers for non-AE safety data based the duration of AMG 334 70 mg and 140 mg exposure will be as follows (see [Section 6.6](#)):

- **AMG 334 70 mg**
- **AMG 334 140 mg**
- **AMG 334 70 mg / 140 mg**

Treatment group identifiers for AE safety data, based on the occurrence of the event relative to their treatment period, will be as follows:

- **AMG 334 70 mg**
- **AMG 334 140 mg**

7.4 PRO Analysis Set

All subjects participating in the PRO substudy and have at least one monthly score for the MPFID will be included in the PRO analysis set. Treatment group identifiers will be the same as the EAS.

7.5 Pharmacokinetic/Pharmacodynamic Analyses Set

The pharmacokinetic analysis set will include all enrolled subjects in the safety analysis set who have at least one evaluable serum AMG 334 concentration post the first dose of IP. **Treatment group identifiers will be the same as the EAS.**

8. Interim Analysis and Early Stopping Guidelines

On an annual basis or until an administrative decision is made to close the study, descriptive statistics of safety and efficacy will be produced for use in the annual report and/or to support publications, if warranted.

An additional interim analysis may be performed for the purpose of inclusion in a regulatory submission to provide additional long-term safety data. This analysis may take place 4-6 months prior to the planned regulatory submission date (2Q 2017) and will include all safety data collected up to 01 September, 2016. There are no stopping rules applied based on any interim analysis and the outcome of this potential interim analysis will not lead to any changes in the conduct of the study.

Safety monitoring will occur in an ongoing fashion by the safety group.

The following summaries will be included for the interim analysis:

- Disposition, demographic, baseline characteristic and baseline disease characteristics, not including efficacy specific data, medical and surgical history, and important protocol deviations
- Adverse events
- Laboratory, vital signs, ECG, liver, antibody and C-SSRS
- Manufacturing lot numbers

9. Data Screening and Acceptance

9.1 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.

9.2 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. The database will be subject to edit checks outlined in the Data Management Plan (DMP). The eDiary, BSM and ECG data are outside of the RAVE database. All the datasets to be used for planned analyses will be received from **Amgen's Global Study Operations-Data Management (GSO-DM) department**. Additional details will be provided in the DMP and Data Transfer Plan (DTP).

9.3 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 between exposures to IP**. The general procedures outlined below describe what will be done when a data point is missing.

Missing eDiary data in the calculation of monthly measurements about subjects' migraine and non-migraine headaches will be handled **using method below**. Unless otherwise specified, all the final analysis and sensitivity analysis will use monthly measurements calculated as follows:

1. **For monthly intervals with ≥ 14 days of eDiary days (days subjects use eDiary and including retrospective eDiary days) in each interval:**
 - a) Monthly frequency measurements (including migraine days, headache days, migraine attacks, cumulative hours of migraine headaches, cumulative hours of migraine headaches with severe pain, acute medication use, etc.) will be

prorated to 28-day equivalents. **Prorated result does not need to be rounded.**

- b) Monthly average severity of migraine pain, migraine related symptoms, **physical impairment scores and impact on everyday activities scores as measured by MPFID** and monthly average scale of migraine interference with daily activity will be calculated as the average of observed scores.
2. **For monthly intervals with < 14 days of eDiary use (including retrospective eDiary days)**, all monthly measurement will be set as missing and will be handled as described in [Section 9.3.2](#)

An information day is a calendar day which is either an eDiary day or headache day and will be used toward headache day proration. The eDiary days will be used toward migraine day proration and medication use day proration.

Missing PROs (MSQ, MIDAS) collected at office visit at certain assessment will not be imputed.

Missing safety endpoints will not be imputed. **Missing day portion of AE start time will be imputed based on [Section 9.3.1](#).**

Missing pharmacokinetic and antibody data will not be imputed.

9.3.1 Missing and Incomplete Dates

Missing or incomplete date will be listed as it is in any listing. Incomplete start date of an adverse event or concomitant medication taken will be handled by following rule:

	Missing	Imputation	Exception
Start date (AE, 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	01JAN	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	

9.3.2 Missing Baseline Evaluation

Refer to 20120295 study SAP Section 9.3.2 “Missing Baseline Evaluation”, on how to handle missing 20120295 parent study baseline.

For 20130255 study baseline, for variables other than monthly rate or monthly average of migraine and non-migraine headache related efficacy endpoints (**including secondary efficacy endpoints, monthly migraine attacks, monthly headache, monthly moderate and severe headache, monthly average severity of migraine pain and monthly average severity of migraine related symptoms**), unless otherwise defined, baseline value is the last non-missing assessment taken during the last 4 weeks (week 8 through week 12) of the parent study 20120295. If it is still missing following above definition, then baseline evaluations will not be imputed and will be considered as missing. For safety endpoints, 20130255 study baseline is the last non-missing measurement (**including measurements from the 20120295 parent study**) before day 1 IP dose in the study 20130255.

9.3.3 Missing Post-baseline Evaluation in Open-label Treatment Phase

Primary analysis of efficacy endpoints will be conducted on observed data without imputation.

9.4 Detection of Bias

As an open-label extension study, the potential bias introduced by selecting subjects, allocating treatment groups and assessing endpoints is minimal. However, it is recognized that the data of study 20130255 may suffer from a selection bias associated with dropout from the parent study 20120295. Other factors that may bias the results of the study include:

- important protocol deviations
- investigational product dosing non-compliance
- the timing of and reasons for early withdrawal from treatment and from study in 20130255

The incidence of these factors may be assessed. Important protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints will be listed and/or tabulated in the clinical study report (CSR). If necessary, the incidence of other factors will be tabulated.

The timing of and reasons for early withdrawal from treatment and from study will be tabulated and/or listed. Ad-hoc analysis on time to early withdrawal from treatment and

from study may be performed according to the actual treatment received in the parent study 20120295 or the reasons of early withdrawal.

9.5 Outliers

Histograms may be examined to identify outliers in any of the continuous variables used in the analyses. Unexpected or unexplained values in categorical data may 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.

9.6 Distributional Characteristics

Not applicable

9.7 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 9.4 or later and R**.

For the exposure–response analysis, refer to the E-R SSAP for the software used.

10. Statistical Methods of Analysis

10.1 General Principles

The final analysis for the entire study including open-label treatment phase and safety follow-up phase will be performed at the end of study.

All subjects who have enrolled and received at least one dose of AMG 334 in the study will be included in the data analysis.

For the purpose of secondary and exploratory efficacy endpoints in the 20130255 OLE study, the primary baseline is the 20120295 parent study baseline **(from the first day subject used eDiary in baseline at week -4 study visit through the day prior to**

study day 1). However, change from the parent study month 3 data may also be evaluated.

Efficacy endpoints will be summarized based on their randomized treatment group assignment in the parent study 20120295 **and the first dose received in the 20130255 OLE study.**

Summary descriptive statistics by each treatment group will be tabulated at each visit. For continuous endpoints number of observations, mean, median, standard deviation, first and third quartiles, minimum and maximum, and a two-sided 95% confidence intervals of the mean (except for safety laboratory analyses) will be included for descriptive statistics. For categorical and ordinal endpoints, the summaries will contain the number and percentage of subjects falling into each category.

No formal statistical tests will be performed. Missing values for safety endpoints will not be imputed.

The full analysis set will be utilized to summarize subject disposition of all enrolled subjects, demographic data, and baseline disease characteristics. The efficacy analysis set will be utilized to analyze efficacy endpoints. The SAS will be used to analyze safety endpoints, **which is the same as the FAS. The PRO analysis set will be used for the PRO substudy (ie evaluation of MPFID).**

10.2 Subject Accountability

The disposition of all enrolled subjects will be tabulated by the treatment group allocated in 20130255 OLE study, **based on the dose into which they entered the study**, including the number of subjects enrolled, who receive the open-label treatment phase IP, successfully completed open-label treatment phase IP administration and completed study. The disposition tables will also include the number of subjects who withdrew from the IP and their reasons for withdrawal.

A footnote on the subject disposition tables will include dates first and last subjects enrolled, the date of study completion (eg, last subject completed the safety follow-up visit or drop out from the study) and corresponding data cutoff date.

10.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, sub-category codes, and

descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol.

10.4 Demographic and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized using descriptive statistics by treatment group into which they entered the 20130255 OLE study and overall using the FAS. If multiple races have been reported for a subject, the subject will be categorized as multiple race.

The following demographic and baseline characteristics will be summarized:

- sex
- ethnicity
- race
- age
- age group
- height (cm)
- **Ever used prophylactic medication topiramate (yes vs. no)**
- **Ever used onabotulinum toxin (yes vs. no)**
- targeted neurological disease diagnosis at 20120295 baseline
- migraine acute headache medications used during 20120295 baseline phase (none, any acute medication)
- prior treatment with migraine prophylactic medication (never failed, failed ≥ 1 , failed ≥ 2 medication classes)
- **prior migraine prophylactic medication (yes vs. no)**
- **prior migraine prophylactic treatment failure (yes vs. no)**
- age at onset of migraine
- disease duration of migraine with or without aura
- class of migraine prophylactic treatments (divalproex sodium, sodium valproate, topiramate, beta blockers, tricyclic antidepressants, flunarizine or verapamil, serotonin-norepinephrine reuptake inhibitors, botulinum toxin, lisinopril or candesartan and other) used and without therapeutic response prior to entry into screening
- **discontinuation reason of prior prophylactic medications**
- region (North America vs. others)
- medication overuse (yes vs. no)

The following 20130255 OLE study demographic, baseline characteristics and monthly endpoints during 20120295 baseline phase and during 20120295 month 3 will be summarized:

- weight (kg)
- body mass index (BMI, kg/m²) - using data from 20120295 baseline phase only
- acute migraine-specific medications used:
 - a. triptans
 - b. ergot-derivatives
- monthly migraine days
- monthly migraine attacks
- monthly headache days
- monthly acute migraine-specific medication use (days)
- monthly acute medication use (days)
- monthly headache days with moderate or severe pain intensity
- monthly average severity of migraine pain
- monthly average severity of migraine related symptoms

10.5 Efficacy Analyses

The analysis for efficacy endpoints will utilize the efficacy analysis set. Subjects will be analyzed according to their randomized treatment groups in the parent study 20120295 **and the first dose received in the 20130255 OLE study.**

For primary analysis of efficacy endpoints summary statistics on observed data are provided by visit and treatment group. Subgroup analysis of the secondary efficacy endpoints on observed data will be provided by sex, race, region and medication overuse, and by visit and treatment group.

PROs include PROMIS Pain interference, migraine symptom interference items, MSQ, **MPFID** and MIDAS. Change from baseline in total score (or subscale if applicable) of each PRO will be summarized descriptively on observed data by visit and treatment group. No sensitivity analysis will be conducted for PROs.

10.6 Safety Analyses

For safety endpoints, including laboratory data, vital signs and other non-AE safety data, all enrolled subjects who received at least one dose of investigational product (ie, utilizing the SAS) will be analyzed based on the treatment received in

the 20130255 OLE study. Three treatment groups will be considered, based on planned dosing:

- 70 mg: including all subjects who receive 70 mg for at least 80% of the time exposed
- 140 mg: including all subjects who receive 140 mg for at least 80% of the time exposed
- 70/140 mg mix: including all subjects who receive any one dose <80% of the time exposed

A total AMG 334 group will also be presented in the tables.

For AE safety data two treatment groups will be considered:

- 70 mg
- 140 mg

A total AMG 334 group will also be presented in the tables.

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

10.6.1 Adverse Events and Disease Related Events

The Medical Dictionary for Regulatory Activities (MedDRA) version **18.0** or later will be used to code all events categorized as adverse events (AEs) to a system organ class and a preferred term (PT). **All adverse events will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.** Refer to [Section 6.1](#) for the definition of treatment-emergent adverse event.

Exposure-adjusted subject incidence of AEs will be summarized for all treatment-emergent AEs (TEAEs), serious AEs, AEs leading to withdrawal of investigational product, fatal AEs and treatment-related adverse events.

Exposure-adjusted subject incidence of all TEAEs, serious AEs, AEs leading to withdrawal of investigational product, serious AEs leading to withdrawal of investigational product and fatal AEs will be tabulated by system organ class and preferred term in alphabetical order.

In addition, exposure-adjusted subject incidence of all TEAEs and serious AEs will be tabulated by system organ class, preferred term and CTCAE grade in alphabetical order. Exposure-adjusted subject incidence of all TE AEs and serious AEs will also be tabulated by preferred term in descending order of frequency.

10.6.1.1 Relationship of AEs to Dose During the OLE Phase

The exposure-adjusted subject incidence of TEAEs (defined in [Section 6.3](#)) will be tabulated by the dose level of AMG 334 that the subject was receiving on the onset date for a specific TEAE. If a subject had his/her dose withheld or didn't receive IP at that dose level on the date of onset for a specific AE, the planned dose level will be assigned. The time of the first occurrence of the TEAE within each dose will determine the dose level. If a subject had multiple occurrences of the same AE both within a dose level, or at different dose levels, only the first occurrence within each dose level will be presented. Incomplete AE start dates will be imputed according to the algorithm defined in [Section 9.3.1](#).

Exposure-adjusted subject incidence of TEAE at a dose level = $(100 * \text{total number of subjects with the TEAE at the dose level}) / \text{total time (years) at risk for reporting the TEAE for subjects exposed at the dose level}$.

Total time (years) at risk for reporting a specific TEAE at a dose level = $\text{sum of all subjects' time (days) at risk for the TEAE at the dose level} / 365.25$.

For those who have experienced the TEAE, the time (days) at risk for reporting the TEAE at the respective dose level = time (days) at the respective dose level before the occurrence of the TEAE. The exposure-adjusted subject incidence of TEAEs will also be tabulated by the combined dose levels of AMG 334 by ignoring the dose level in which the TEAE occurred.

10.6.2 Laboratory Test Results

Shifts tables of the most extreme post-baseline (after the first IP in 20130255 study) laboratory toxicity based on CTCAE grade relative to 20130255 study baseline will be tabulated by treatment group. Laboratory values and changes from 20130255 study baseline for selected panels may be summarized descriptively by visit and treatment group. In the cases when CTCAE grading scales include numeric ranges 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.

Shifts tables of the laboratory toxicity for **absolute neutrophil count (ANC)** based on CTCAE grade relative to baseline will be tabulated by treatment group.

Summary of change from baseline for ANC, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) will also be provided by visit.

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

10.6.3 Vital Signs

The analyses of vital signs (systolic and diastolic blood pressure and heart 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: ≥ 10 , < 20 mmHg and ≥ 20 mmHg and analyzed for SBP >140 mmHg (Yes vs. No) and DBP > 90 mmHg (Yes vs. No) at each time point.

10.6.4 Columbia-Suicide Severity Rating Scale (C-SSRS)

No statistical testing will be performed on C-SSRS. The number and percentage of subjects reporting any suicidal ideation and any suicidal behavior will be summarized descriptively by treatment group and visit. **Shift table of C-SSRS maximum severity of suicidal ideation/behavior compared to baseline will be provided by treatment group.**

10.6.5 Electrocardiogram (ECG)

The ECG measurements from this clinical study were performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QTc effect. Because these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; neither summaries nor statistical analyses will be provided, and these data would not be expected to be useful for meta-analysis with data from other trials. **A summary of ECG diagnoses will be tabulated.**

10.6.6 Antibody Formation

The number and percentage of subjects who develop anti-AMG 334 antibodies (binding and, if positive, neutralizing) for baseline and post-baseline will be tabulated by treatment group. **The list of subjects testing positive for antibodies at any time will be provided.**

10.6.7 Exposure to Investigational Product

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 investigational product in days will be summarized by treatment group.

10.6.8 Exposure to Concomitant Medication

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

10.7 Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Analysis

The pharmacokinetic concentration will be summarized with descriptive statistics by visit and treatment group using PK analyses set. Treatment group assignments will follow those specified for the efficacy analysis.

11. Changes From Protocol-specified Analyses

Since most subjects are likely to receive both 70 mg and 140 mg in this study, descriptive summaries on efficacy endpoints will be presented by randomized treatment group in the 20120295 parent study and first dose received in this study, and not by maximum dose as described in the protocol.

Bed days and missed work/school days due to migraine symptoms not summarized since they were not summarized in 20120295 parent study.

12. Literature Citations / References

Fairclough DL1, Cella DF. Functional Assessment of Cancer Therapy (FACT G): non-response to individual questions. Qual Life Res. 1996 Jun;5(3):321-9.

13. Prioritization of Analyses

Summary tables of safety and efficacy will be produced for the use of the annual report and to support publications, if warranted. Therefore, they might be prepared earlier than others.

14. Data Not Covered by This Plan

There are no plans to specifically analyze or summarize the following data points. However, a listing of these data may be presented and/or additional exploratory analyses may be performed should inspection of the data warrant.

- ECG data
- general comments
- population pharmacokinetics
- biomarker

15. Appendices

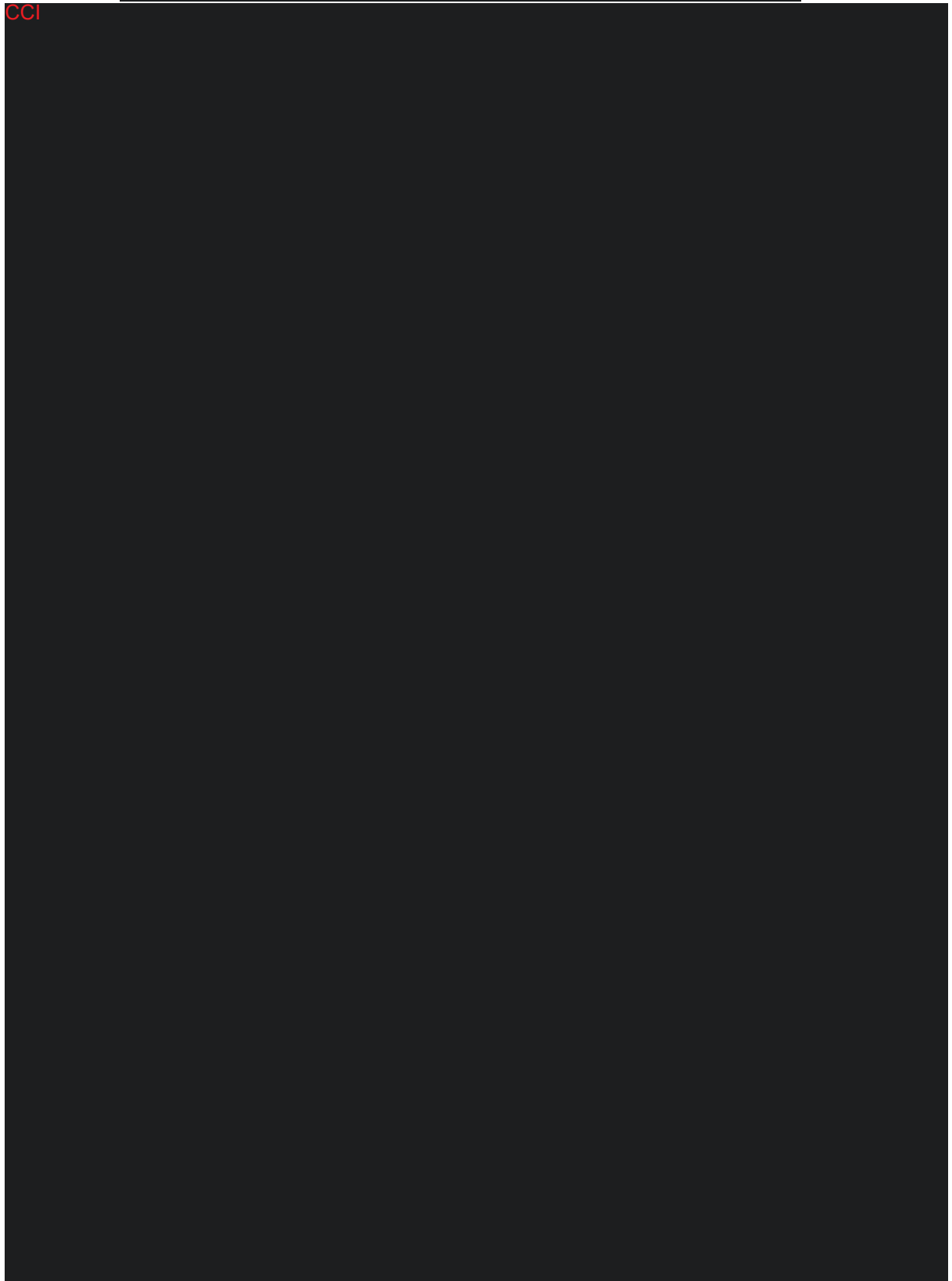
Appendix A. Reference Values/Toxicity Grades

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

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Appendix C. Calculation of eDiary Efficacy Endpoints

Calendar-Day-Headache

Every headache (HA) event reported is identified by a unique headache event number.

If a patient responds NO to the question “HA ended while sleeping” in their eDiary then the HA end date-time is defined as the HA end date-time. If a patient responds YES to the question “HA ended while sleeping” in their eDiary then HA end date-time is defined as the wake up date-time.

For each HA whose start and end date-times are not on the same calendar day, so there are one or more midnights (00:00 AM) between the HA start and end date-times, the headache will be split into a consecutive sequence of calendar-day-headaches using the intervening midnights as end and start date-times. For example, if a head starts on May 5 at 08:00 and ends May 7th 13:00 then this headache will be split into 3 consecutive calendar-day-headaches using midnights of May 6th and May 7th, namely from 05May 08:00 to 06May 00:00, 06May 00:00 to 07May 00:00 and 07 May 00:00 to 07May 13:00, respectively.

For the headache whose start and end date-times are on the same calendar day the corresponding calendar-day-headache is that calendar day.

Each calendar-day-headache has a corresponding duration given by:

- calendar-day-headache duration = HA end date-time – HA start date-time.

The calendar-day-headaches will be sorted by headache start date-time in ascending order.

Calendar-Day-Migraine-Headache

A calendar-day-headache is a calendar-day-migraine-headache, if

- it is a migraine without aura, ie, the calendar-day-headache duration is ≥ 4 hours and meet the following criteria a and/or b:
 - a) ≥ 2 of the following pain features:
 - Unilateral
 - Throbbing
 - Moderate to severe
 - Exacerbated with exercise/physical activity

b) ≥ 1 of the associated symptoms:

- Nausea and/or vomiting
- Photophobia and phonophobia

OR

➤ It is a migraine with aura, ie, meet the following criteria c and d:

c) Meeting ≥ 1 of the following fully reversible aura symptoms:

- Visual
- Sensory
- Speech and/or language
- Retinal
- Brainstem

d) Aura is accompanied or followed within 60 minutes by a calendar-day-headache duration ≥ 4 hours.

OR

➤ If a migraine specific medication (triptan or ergot-derivatives) is taken on the same calendar day (date) as a calendar-day-headache start date and the time in which this migraine specific medication is taken is less than or equal to the calendar-day-headache start time, regardless of calendar-day-headache duration.

Migraine Day

A calendar day is called a migraine day if

➤ there is at least one calendar-day-migraine-headache on that day

OR

➤ the subject took a migraine specific medication (triptan or ergot-derivatives) on that calendar day regardless of

- whether the subject had or not had a calendar-day-headache
- the duration and pain features or associated symptoms, if the medication was used to treat headache pain

“Aura is accompanied” means either aura start or end date-time is between the start date-time and end date-time of a calendar-day-headache, or aura start date time is before calendar-day-headache start date time and aura end date time is after calendar-day-headache end date time. “Aura is followed within 60 minutes” means the difference of a calendar-day-headache start date time minus aura end date time is between 0 and 60 minutes.

Or use the following algorithm:

The calendar-day-headache start date time is before the aura start date time and the calendar-day-headache end date time is after the aura start date time, or the calendar-day-headache start date time is between the aura start date time and ≤ 0 minutes after the aura end date time.

The calendar-day-headaches and the symptoms are matched by headache event number ID first, then by date (to match calendar-day-headaches, from a long headache spans several calendar days with same ID, with daily symptom records).

If there are two sets of symptoms associated with one headache that begin and end on the same day, the set of symptoms whose eDiary date matches the headache's beginning date will be used.

Headache Day

Any calendar day in which the subject experiences a qualified migraine or non-migraine headache (initial onset, continuation or recurrence of the headache).

A calendar day is a headache day if

- there is at least one calendar-day-headache on that calendar day
 - with calendar-day-headache duration ≥ 4 hours

OR

- with any duration for which acute medication (simple analgesics, combination analgesics, triptans, ergot-derivatives, opiates) was administered for treatment of headache pain

OR

- The calendar day is a migraine day (to cover the additional case: the subject took a migraine specific medication (triptan or ergot-derivatives) on that calendar day even without any calendar-day-headache).

Qualified Headache

- 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 continuously for ≥ 4 hours and is not a qualified migraine headache, or
- a headache of any duration for which acute headache treatment is administered

Acute Medication Use Day

An acute medication use day is any calendar day on which a subject uses acute medications. Medications for acute treatment of migraine pain include simple analgesics, combination analgesics, triptans, ergot derivatives and opiates. More specifically, acute medications include triptan-based migraine medications, non-opioid acute headache medications, ergotamine-based migraine medications, opioid-containing acute headache medications, opioid-containing butalbital containing medications and non-opioid butalbital containing medications (medication code is not missing nor equal to “999999”).

Migraine Specific Medication Use Day

A migraine specific medication use day is any calendar day on which a subject uses migraine-specific medication (triptan or ergot-derivatives). Migraine specific medication use day is based on the date-time migraine-specific medication is taken.

eDiary Day

An eDiary day is any calendar day on which a subject has recorded eDiary data. An eDiary day can be identified by the availability of eDiary date-time information for that day such as whether a headache starts and/or ends on that day, the subject woke up on that day while a headache ends during sleep or aura start. An eDiary is also any day on which medication use start date-time is recorded even if no headache is recorded on that day.

Information Day (used for Headache Day calculations)

An information day is any calendar day which is either an eDiary or headache day.

Migraine Attack

A migraine attack is an episode of any qualified migraine headache or episode for which the subject took a triptan or ergot-derivative to treat headache or aura. The following rules will be used for distinguishing an attack of long duration from two attacks, or for distinguishing between attacks and relapses:

- A migraine attack which is interrupted by sleep or temporarily remits, and then recurs within 48 hours after onset of the attack will be considered as one attack, and not two.
- An attack primarily treated successfully with medication but with relapse within 48 hours will be considered as one attack.

Monthly Cumulative Migraine Headache Duration (in hour)

Repeat the step for baseline phase and each 28-day interval:

Add up durations for all calendar-day-migraine-headaches in baseline phase or each 28-day interval after Day 1.

Extent of Exposure and Exposure Adjusted Data Presentation

Subjects are allocated into three groups for non-AE safety data presentation:

- 80% of time exposed to 70 mg
- 80% of time exposed to 140 mg
- remaining subjects

Subjects are allocated to treatment groups based on the relative timing a subject increases dose to 140 mg based on when 20130255 Protocol Amendment 3 was implemented with respect to the subjects study start date (see [Section 6.6](#)).

The calculation is reasonable given low incidence of dose withholding and dose administration error.

In the extent of exposure summary table

- Total number of injection is calculated based on actual dose administered. Dose withholding is counted. Dose administration error is not counted. For example, during the 140 mg treatment period, if a subject only received 70 mg for one visit, this administration is still counted in 140 mg dose group.
- Exposure duration is calculated based on total duration, as discussed above.