STATISTICAL ANALYSIS PLAN

Phase I, Randomized, Parallel-group, Double-Blind, Placebo-Controlled, Single Dose Study to Evaluate the Blockade of CGRP Receptor by AMG 334 in Preventing PACAP-38 Induced Migraine-like Attacks in Migraine Patients
AMG 334

Protocol Number: **20140207**

Version: ***Version 2.0***

Date: **17 May 2017**

Authors: PPD

NCT Number: 02542605
This NCT number has been applied to the document
for purposes of posting on clinicaltrials.gov

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Table of Abbreviations

Abbreviation/Acronym	Definition
AE	Adverse event
AUC_{84d}	Area under the concentration-time curve from time 0 to 84 Days
BMI	Body Mass Index
BP	Blood pressure
C_{1hour}	Maximum observed concentration from time 0 to 1 hour
CGRP	Calcitonin gene-related peptide
CPMS	Clinical pharmacology modeling and simulation
CRF	Case report form
C-SSRS	Columbia suicide severity rating scale
CTCAE	Common terminology for adverse events
DBP	Diastolic blood pressure
DLRM	Dose level review meeting
DMP	Data management plan
ECG	Electrocardiogram
EOS	End of study
GBS	Global biostatistical science
GSO	Global safety officer
GSO-DM	Global study operations-Data management
HR	Heart Rate
IP	Investigational product
IPD	Important protocol deviation
IV	Intravenous
kg	kilogram
m	meter
MedDRA	Medical dictionary for regulatory activities
Mg	Milligram
MLA	Migraine-like attacks
MM	Medical monitor
NIMP	Non-investigational medicinal product
PACAP	Pituitary adenylate cyclase-activating polypeptides
PI	Principle investigator
PK	Pharmacokinetic(s)

Abbreviation/Acronym	Definition
PKDM	Pharmacokinetics and drug metabolism
pmol	picomole
SAE	Serious adverse events
SBP	Systolic blood pressure
TFL	Tables, Figures, and Listings

1. Introduction

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the AMG 334 Study 20140207 Protocol Amendment 4 (dated 21 Oct 2016), entitled "Phase I, Randomized, Parallel-group, Double-Blind, Placebo-Controlled, Single Dose Study to Evaluate the Blockade of CGRP Receptor by AMG 334 in Preventing PACAP-38 Induced Migraine-like Attacks in Migraine Patients". The scope of this plan includes the interim analysis and the final analyses that are planned and will be executed by the Global Biostatistical Science (GBS) department unless otherwise specified (eg, standard pharmacokinetic (PK) tables will be provided by Clinical Pharmacology Modeling and Simulation [CPMS]).

2. Objectives

2.1 Primary

To evaluate the inhibition of PACAP-38 induced migraine-like attacks by AMG 334

2.2 Secondary

- To evaluate the inhibition of PACAP-38 induced headaches by AMG 334
- To evaluate the safety, tolerability, pharmacokinetics, and immunogenicity of a single intravenous (IV) dose of AMG 334 in migraine patients

2.3 Exploratory

- To evaluate the reduction in severity of PACAP-38 induced migraine-like attacks and headaches by AMG 334
- To evaluate the duration of PACAP-38 induced migraine-like attacks and headaches by AMG 334
- To evaluate the safety and tolerability of a single intravenous (IV) dose of exogenous PACAP-38
- To evaluate CGRP and PACAP-38 levels in migraine patients

3. Study Overview

3.1 Study Design

This is a randomized, double-blind, placebo-controlled, parallel-group study in subjects with episodic migraines. This study will evaluate the efficacy of AMG 334 as measured by inhibition of PACAP-38 induced migraine-like attacks (MLA) after a single dose of AMG 334. MLAs will be defined as attacks fulfilling one of the two criteria:

(1) Headache fulfilling criteria C and D for migraine without aura (IHS 2004)

C. Headache has at least two of the following characteristics:

- unilateral location
- pulsating quality

- moderate or severe pain intensity (≥ 4 on headache questionnaire)
- aggravation by or causing avoidance of routine physical activity

D. During headache at least one of the following:

- nausea and/or vomiting
- photophobia and phonophobia

(2) Headache described as mimicking usual migraine attack treated with triptan.

Part A: PACAP-38 Dose Selection Phase: In order to ensure subject safety and select the lowest PACAP-38 dose that will ideally trigger headache in all subjects within a given cohort and moderate to severe MLA in the majority of the subjects within the same cohort, a dose selection strategy, along with Safety Review Meetings and Dose-Level Review Meetings (DLRM) have been implemented. Dosing of PACAP-38 shall not exceed a total dose of 115 pmol/kg, providing an approximate 10X exposure margin over the non-clinical NOAEL dose. However, the trigger of headaches in the majority of the subjects within a given cohort and mild, moderate or severe MLAs in the majority of the subjects within the same cohort may be considered acceptable to advance to the randomized portion of the study (Part B).

Up to five cohorts consisting of approximately 2 to 5 subjects are planned. Based on emerging safety and tolerability data, as well as the number of subjects experiencing a headache and/or MLA, the voting members of the Safety Review Meetings or DLRM, may decide cohorts should be removed or additional cohorts should be added, with a maximum of 5 total cohorts. Subject numbers within each cohort may also be increased or decreased based on the decision from the Safety Review Meeting or DLRM. Doses to be administered within each cohort may be repeated, higher or lower than the last dosed cohort. Dosing of any subject shall not exceed 115 pmol/kg.

On Day 1, approximately 2 subjects in Cohort 1 will receive an infusion of 10 pmol/kg/min over 2.5 minutes (total dose 25 pmol/kg). The Principal Investigator (PI) will be responsible to review heart rate (HR) and blood pressure (BP). The BP assessment is based on a single measurement of systolic blood pressure (SBP) of >150 mm Hg or diastolic blood pressure (DBP) >100 mm Hg. If the mean HR increase of the subjects in Cohort 1 is greater than 50% over baseline during a 2 hour period after dosing and SBP does not increase to >150 mm Hg or DBP to >100 mm Hg, then approximately 3 subjects in Cohort 2 will receive an infusion of 10 pmol/kg/min over 5 minutes (total dose 50 pmol/kg). Written documentation from Amgen of the decision to

proceed with enrollment in Cohort 2 is required. After dosing Cohort 2 and any subsequent cohort, the PI will again be responsible to review HR and BP using previously outlined criteria. These same criteria shall also be assessed for Cohort 3.

After dosing Cohort 3, up to 5 subjects in Cohort 4 will receive 10 pmol/kg/min over 10 minutes (total dose 100 pmol/kg). Following Cohort 4, a DLRM will occur to decide the dose of PACAP-38 to be used in the randomized portion of the study (Part B). This decision will be primarily based on safety and tolerability data, and number of subjects experiencing a headache and/or MLA in Cohort 4, although all of the available data for Cohorts 1 to 4 will be reviewed. The dose-selection for Part B will be based on the goal of ensuring subject safety and ideally triggering headache in all subjects within a given cohort and moderate to severe MLAs in the majority of subjects within the same cohort. However, the trigger of headaches in the majority of subjects within a given cohort and mild, moderate or severe MLAs in the majority of subjects within the same cohort may be considered acceptable to advance to the randomized portion of the study (Part B). If this goal is not achieved, following the DLRM review of the Cohort 4 data, then Cohort 5 dosing of 10pmol/kg/ min over 11.5 minutes (total dose 115 pmol/kg) can commence.

Cohorts 2, 3 and 4 enrollment will occur after a Safety Review Meeting between the principal investigator (PI), medical monitor (MM), and global safety officer (GSO) or designee. At that time, available vital signs and adverse events occurring at least 24 hours following PACAP-38 dosing will be reviewed.

If the PI, MM, and GSO or designee decides not to proceed with enrollment into a subsequent cohort, then a Safety Review Meeting or DLRM will be held after the last dosed cohort. The Safety Review Meeting or DLRM voting members will decide whether or not to proceed with enrollment in Part B Randomization (AMG 334 or Placebo) Phase and if the decision is made to proceed, the Safety Review Meeting or DLRM voting members will select the appropriate PACAP-38 dose from the Dose Selection Phase, Part A. The decision to proceed with Part B of the study will be based on the goal of ensuring subject safety and ideally triggering headache in all subjects within a given cohort and moderate to severe MLAs in the majority of subjects within the same cohort. However, the trigger of headaches in the majority of subjects within a given cohort and mild, moderate or severe MLAs in the majority of subjects within the same cohort may be considered acceptable to advance to Part B of the study.

Part B: Randomization (AMG 334 or Placebo) Phase: PACAP-38 responders from part A, as well as PACAP-38 naïve subjects (those who never received PACAP-38

before) can enter screening in part B. Subjects will be enrolled in Part B following the 21 day screening period. There will be a minimum duration of 2 weeks between the first and second PACAP-38 doses for all subjects enrolling in Part B of the study.

Eligible PACAP-38 responders from Part A will immediately be randomized to receive either AMG 334 or placebo, whereas eligible PACAP-38 naïve subjects will first enter a PACAP-38 challenge phase. Only PACAP-38 responders (those who experienced a MLA within 24 hours after the challenge) will be randomized to receive either AMG 334 or placebo.

A minimum of 16 and a maximum of 36 PACAP-38 responders will be randomized to receive AMG 334 or Placebo.

PACAP-38 Responders from Part A

On Day 1, PACAP-38 responders from Part A will receive 140 mg IV AMG 334 over 30 minutes or placebo, in a one to one allocation ratio. On Day 8, the subjects will be administered the dose of PACAP-38 determined from the PACAP-38 Dose Selection Phase (Part A).

PACAP-38 Naïve Subjects

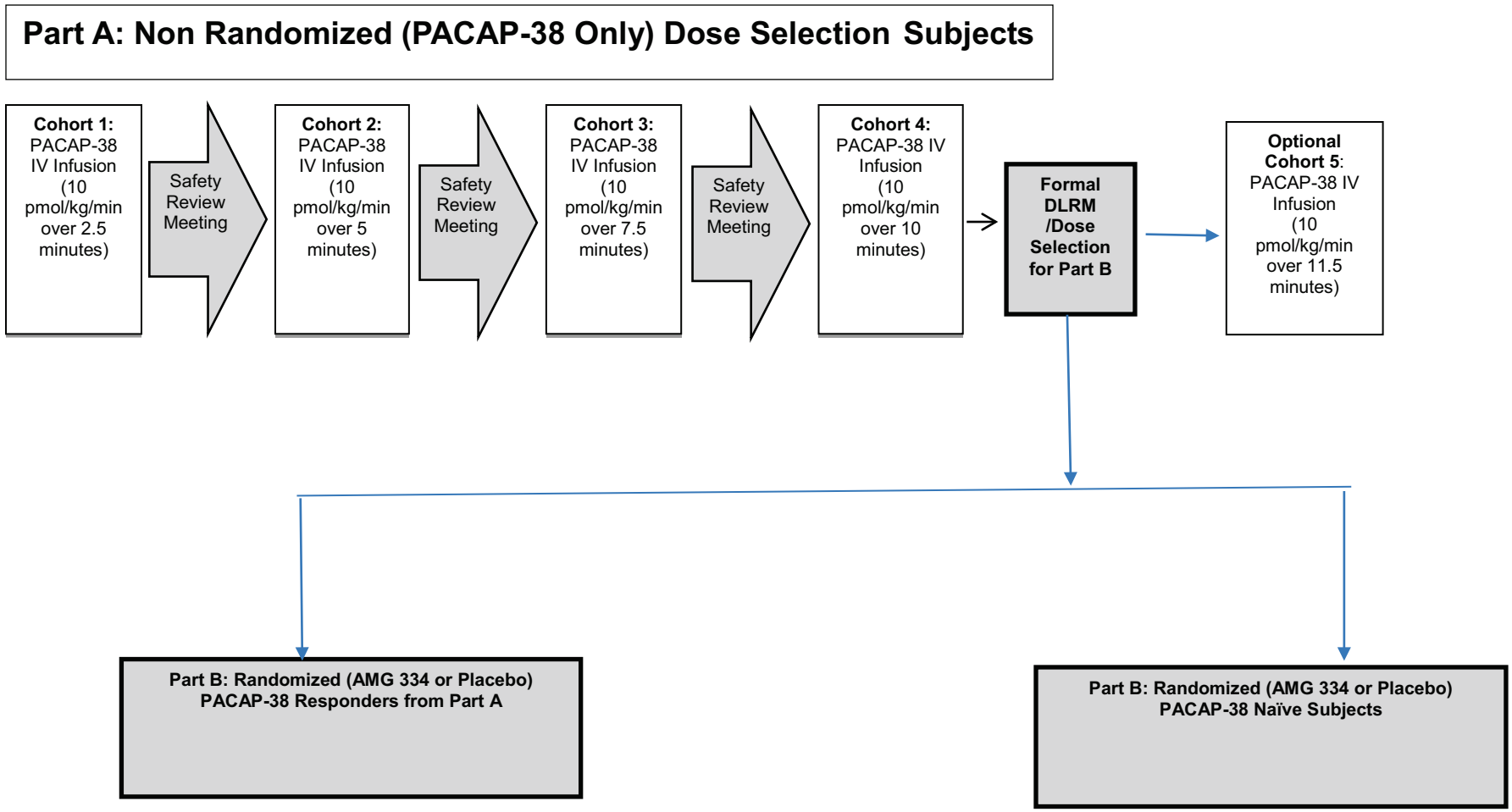
On Phase 1 Day 1 (Challenge Period), PACAP-38 naïve subjects will receive the dose of PACAP-38 determined from the PACAP-38 Dose Selection Phase (part A) and will be followed until Day 8. For subjects that do not experience a MLA within 24 hours following PACAP-38 administration (non-responders), Day 8 will be their End of Study (EOS) visit. Those subjects who experience a MLA within 24 hours following PACAP-38 (responders) will be randomized to receive 140 mg IV AMG 334 over 30 minutes or placebo on Phase 2 Day 1 (Treatment Period), in a one to one allocation ratio. On Day 8, the PACAP-38 responders will be administered the dose of PACAP-38 determined from the PACAP-38 Dose Selection Phase (part A).

All subjects will remain in-house for 24 hours of observation following PACAP-38 infusion. Subjects (respectively PACAP-38 responders from part A and PACAP-naïve subjects) will be followed until Day 85.

Subjects will be monitored and asked questions from the headache questionnaire, as per the Schedule of Assessment in Table 2 of Protocol Amendment 4, to determine if they have experienced a MLA. Previous challenge studies have shown that for migraineurs the median onset of a MLA is within 4 hours with some patients experiencing a MLA as late as 12 hours following PACAP-38 infusion. Therefore, a

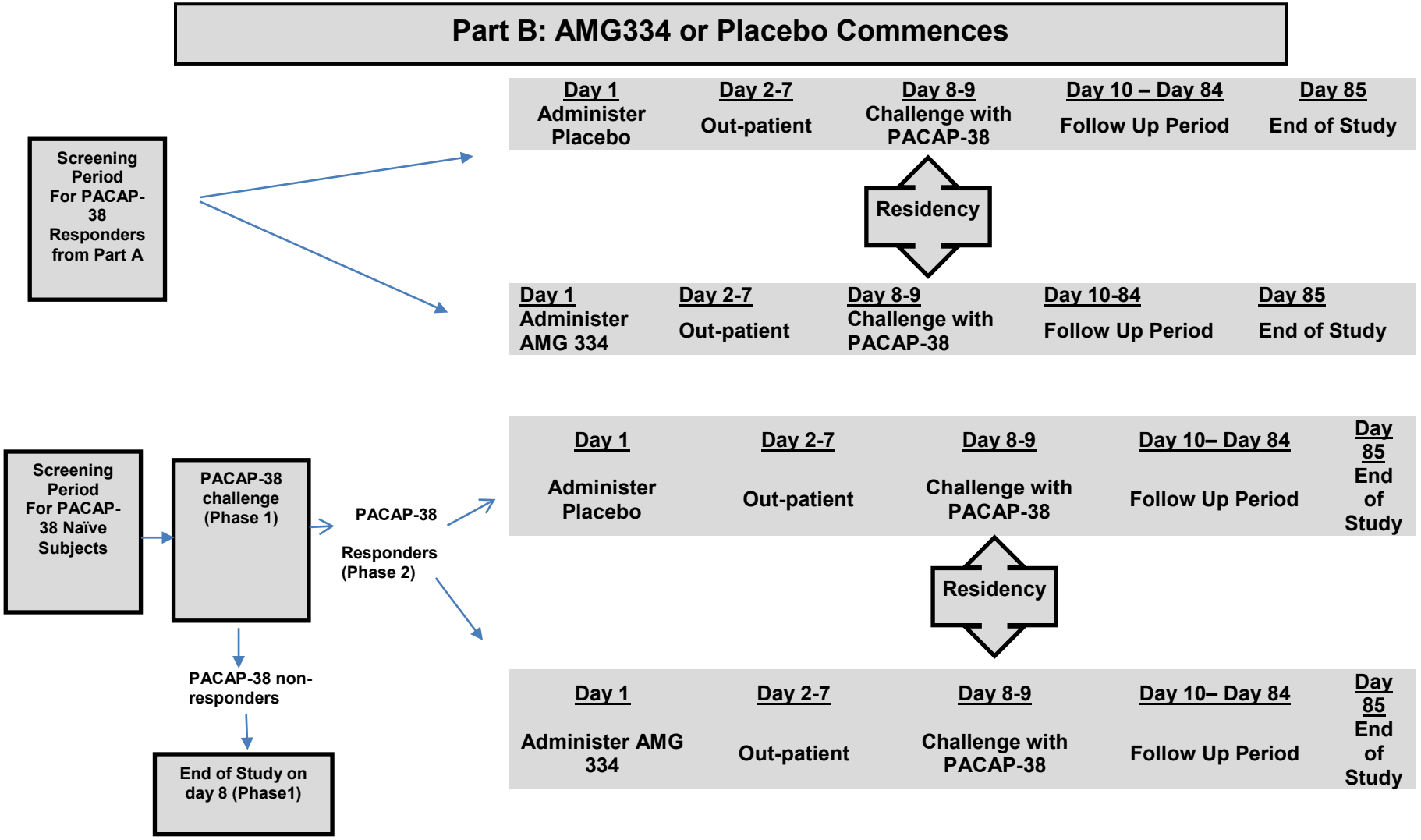
headache questionnaire covering the 24 hours after infusion will ensure capture of all the PACAP-38 induced MLAs. After 24 hours of data from the first 16 randomized (AMG 334 or Placebo) subjects challenged with PACAP-38 is available, an interim analysis will be conducted to determine if challenge rates are comparable to historical rates (~66%) and if AMG 334 has greater efficacy than placebo. If AMG 334 is found to completely block PACAP-38 induced migraines, or have the same efficacy as placebo, the study will be terminated. Otherwise, approximately 20 randomized (AMG 334 or Placebo) subjects will be added.

The overall study design is described in the study schema below:



Abbreviations:

DLRM = Dose Level Review Meeting
IV = Intravenous


Part B: AMG334 or Placebo Commences
Screening Period For PACAP-38 Responders from Part A
Day 1 Administer Placebo
Day 2-7 Out-patient
Day 8-9 Challenge with PACAP-38
Day 10 – Day 84 Follow Up Period
Day 85 End of Study
Residency
Day 1 Administer AMG 334
Day 2-7 Out-patient
Day 8-9 Challenge with PACAP-38
Day 10-84 Follow Up Period
Day 85 End of Study
Screening Period For PACAP-38 Naïve Subjects
PACAP-38 challenge (Phase 1)
PACAP-38 Responders (Phase 2)
PACAP-38 non-responders
End of Study on day 8 (Phase1)
Day 1 Administer Placebo
Day 2-7 Out-patient
Day 8-9 Challenge with PACAP-38
Day 10– Day 84 Follow Up Period
Day 85 End of Study
Residency
Day 1 Administer AMG 334
Day 2-7 Out-patient
Day 8-9 Challenge with PACAP-38
Day 10– Day 84 Follow Up Period
Day 85 End of Study

3.2 Sample Size

Up to 25 subjects may participate in Part A. An adequate number of migraine subjects are planned to be randomized and enrolled into Part B of the study, in order to obtain 16 PACAP-38 responders to participate in the interim analysis and depending on those results an additional 20 PACAP-38 responders to complete the study. If ambiguous results in Part A occur regarding the ability of PACAP-38 to ideally safely trigger a headache in all subjects within a given cohort (although, safely triggering headaches in the majority of subjects within a given cohort may be considered acceptable to advance to Part B of the study) and mild, moderate or severe MLAs in the majority of subjects within the same cohort, then a previously dosed cohort sample size may be expanded to up to 5 subjects per cohort. Once the PACAP-38 dose has been selected, enrollment in part B can start. The data collected for the 16 subjects that received AMG 334 or Placebo will be included in the interim analysis. Following the interim analysis, if the decision is to continue enrollment for the study, an additional 10 subjects will be planned to receive placebo, and another 10 subjects to receive AMG 334.

The sample size is not based on any power calculations; it is based on practical considerations and is consistent with this type of study. The results from 10,000 simulated trials demonstrate that, if, PACAP-38 produces MLA in 70% of placebo treated PACAP-38 responders, and AMG 334 is effective in blocking MLA such that only 20% of AMG 334 treated subjects have a headache, then there is approximately a 91% chance of overall trial success (see Section 8 for more details).

4. Study Endpoints and Covariates

4.1 Study Endpoints

Primary Endpoints:

- Occurrence of a MLA within 24 hours of challenge-agent infusion

Secondary Endpoint(s):

- Occurrence of a headache within 24 hours of challenge-agent infusion
- Treatment-emergent AE
- Clinical significant changes in vital signs, ECGs, physical examinations, laboratory safety tests, and neurological assessments
- AMG 334 PK parameters, including $C_{1\ hour}$ and AUC_{84d}
- Anti-AMG 334 antibodies

Exploratory Endpoint(s):

- Severity of PACAP-38 induced MLA and headaches
- Duration of PACAP-38 induced MLA and headaches
- Migraine characteristics: localization, accompanying symptoms and pre-monitory symptoms.
- PACAP-38 related treatment-emergent AE
- Evaluate the concentration of PACAP-38 and CGRP following administration of AMG 334

4.2 Planned Covariates and Subgroups

Planned covariates consist of baseline measures. No subgroup analysis is planned.

5. Hypotheses and/or Estimations

A single dose of 140 mg IV of AMG 334 will inhibit MLAs in subjects challenged with PACAP-38.

6. Definitions

Adverse Event (AE)

Serious Adverse Event (SAE):

SAE determined by the flag indicating if the adverse events is serious on the AE eCRF page will include these that occur after signing the informed consent and up to and including end of study (EOS).

Treatment-Emergent AE:

A treatment-emergent AE is that occurs on or after the initial dose of investigational product (IP) as determined by the flag indicating if the AE started prior to the first dose on the AE eCRF and up to and including end of study.

Disease-Related AE:

Migraine will be considered a disease related event; however, worsening of migraines (ie. increased frequency and/or intensity) should be reported as an AE.

Baseline

Unless otherwise stated, baseline will be defined as the last assessment taken prior to the first IP (AMG 334 or placebo) administration (ie, Day 1 pre-dose or Screening if Day 1 pre-dose is not available).

Change from Baseline:

The arithmetic difference between a post-baseline value and the baseline value:

Change (absolute) from Baseline = (Post-baseline Value – Baseline Value)

Change (percent) from Baseline = [(Post-baseline Value – Baseline Value) / Baseline Value] x 100

Body Mass Index (BMI)

BMI will be calculated as {weight (kg)/ [height (m)]^2} in the clinical database.

Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a clinical rating of suicidal ideation and behavior. Refer to Appendix E and Appendix F in the protocol for complete details on the C-SSRS. The Baseline/Screening version of the C-SSRS will be administered at screening (Day -21 to -2), while the Since Last Visit version of the C-SSRS will be administered at the other time point(s) on the Schedule of Assessments. Reports of suicidal ideation with intent to act (endorse item 4 or 5) and reports of actual, aborted, or interrupted suicide attempts or a behavior preparatory for making an attempt indicate subjects at high risk for suicide. If such reports are identified, the investigator is to appropriately manage the subject in accordance with standard of care.

End-of-Study (EOS)

The EOS is the last planned clinical visit for each subject enrolled in this study.

Primary Completion:

Defined as the time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis (ie., when the last subject completes the migraine questionnaire 24 hours after challenge agent (PACAP-38) administration or is discontinued from the study).

End of Trial:

Defined as the time 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 11 weeks after the challenge agent (PACAP-38) administration, or is discontinued from the study).

Subject-level EOS Date

EOS for each subject is defined as the date the subject last participated in the study. The date will be recorded on the EOS case report form (CRF) page.

Enrollment

A subject will be considered enrolled when the investigator decides that the subject has met all eligibility criteria. Enrollment Date is defined as the date collected on the CRF.

Investigational Product (IP)

The term IP is used in reference to AMG 334 or placebo.

PACAP-38

Pituitary adenylate cyclase-activating polypeptides-38 is a neuropeptide belonging to the VIP/secretin/glucagon superfamily. PACAP-38 is a non-investigational medicinal product (NIMP) and used as a challenge agent.

Randomization Date

The day the subject was assigned a randomization number.

Study Day 1

Day 1 is defined as the first day that IP is administered to the subject. The day before Day 1 is referenced as Day-1.

Study Day

Post day of dose: study day= (study date - date of study Day 1) +1

Pre day of dose: study day= (study date - date of study Day 1)

The day prior to the first IP dosing is Day –1 while the day of the first IP dose is Day 1.

7. Analysis Subsets

7.1 Safety Analysis Set

The safety analysis set will consist of all subjects who receive IP (AMG 334 or placebo). Subjects will be analyzed according to the IP received (AMG 334 or Placebo).

7.2 Pharmacokinetic (PK) Analysis Set

The PK analysis set will contain all subjects who receive IP and have at least one PK concentration result.

8. Interim Analysis and Early Stopping Guidelines

8.1 Dose Level Review Meetings and Safety Review Meetings

The DLRM members will be composed of the PI, Amgen MM, Amgen GSO or designee, Early Development Leader or designee, Clinical Study Manager or designee, and Biostatistics representative or designee. Additional members may be added as needed (eg, PK Scientist). The Safety Review Meeting members include the PI, Amgen MM, and Amgen GSO or designee. The DLRM and Safety Review Meeting voting members will include the PI, Amgen MM, and Amgen GSO or designee.

A Safety Review Meeting will be held after PACAP-38 dosing has been completed in each cohort in Part A. Available vital signs and AE occurring at least 24 hours following PACAP-38 dosing for each cohort will be reviewed by the Safety Review Meeting members to decide enrollment in subsequent cohort. If the Safety Review Meeting members decide not to proceed with enrollment in subsequent cohort, then a Safety Review Meeting or DLRM will be held after the last dosed cohort. Unscheduled DLRMs can be called at any time by any of the DLRM voting members.

The Safety Review Meeting and DLRM voting members will decide whether or not to proceed with enrollment in the Randomization (AMG 334 or Placebo) Phase and if the decision is to proceed with enrollment in the Randomization (AMG 334 or Placebo) Phase, the Safety Review Meeting and DLRM voting members will select a PACAP-38 dose. The maximum dose of PACAP-38 will not exceed 115 pmol/kg. At any time the Safety Review Meeting members may decide to add additional Non Randomized (PACAP-38 Only) Dose Selection Subjects pending review of emerging safety, and/or tolerability data. A future modification of the PACAP-38 dose may occur based on emerging safety, and/or tolerability findings.

All available study data, including the headache questionnaires, demographics, IP administration, medical history, concomitant medications, AE (including MLA), ECGs, vital signs, and laboratory results will be reviewed. Data to be reviewed at the Safety Review Meeting and DLRMs during the PACAP-38 Dose Selection Phase will not be blinded. Data to be reviewed for any unscheduled DLRM post the PACAP-38 Dose Selection Phase will be reviewed blinded (ie., treatment assignment will not be revealed) unless unblinding is deemed necessary for the review team to make dosing decisions. If deemed necessary, unblinding will be performed to assist dose decisions in accordance with Amgen standard procedures.

8.2 Interim Analysis

Once 24 hours of data is collected from 16 PACAP-38 responders dosed with AMG 334 or Placebo (8 per group) after PACAP-38 infusion on Day 8, an interim analysis will be performed to determine if the challenge-agent, PACAP-38, invokes historical rates of MLA (~66%) and if AMG 334 has greater efficacy than placebo. If the number of MLAs does not meet historical rates, AMG 334 does not appear to be better at blocking PACAP-38 induced migraines compared with placebo, or AMG 334 appears to be sufficiently better at blocking PACAP-38 induced migraines compared with placebo, the study will be terminated (see below for more details). Otherwise, another 20 PACAP-38 responders will be randomized. Appropriate decision rules, outlined below were developed to determine whether to increase the sample size (another 20 responders dosed with AMG 334 or Placebo, 10 per treatment group) or to stop, either due to demonstration of treatment effect or treatment utility.

Decision rules to be applied during the trial are:

1. At the interim analysis, if 3 or less of the 8 placebo subjects have a MLA, randomization will be stopped and it will be concluded that PACAP-38 does not induce a sufficient proportion of MLA for the study to test the hypothesis.
2. At the interim analysis, if 4 or more placebo subjects have a MLA, yet more subjects receiving AMG 334 have MLA than placebo subjects, then randomization will be stopped and it will be concluded that AMG 334 is ineffective in blocking PACAP-38 induced MLA.
3. If the difference at the interim analysis in the proportion of subjects with MLA (placebo-AMG 334) is greater than or equal to 75% then randomization will be stopped and it will be concluded that AMG 334 is effective in blocking PACAP-38 induced MLA.
4. If none of the first 3 decision rules apply at the interim analysis, an additional 20 subjects will be randomized in the trial. At the end of trial, if the p-value from the one-sided Fisher's Exact test is less than 0.1, it will be concluded that AMG 334 is effective in blocking MLA (TRIAL SUCCESS –LATE), or if the p-value from the one-sided Fishers Exact test is greater than or equal to 0.1, it will be concluded that AMG 334 is ineffective at blocking MLA.

The results from 10,000 simulated trials demonstrating the probability of failing at the interim analysis, as well as the probability of overall trial result, for different potential scenarios of the proportion of subjects with MLA in each treatment group are shown below:

Probability of Fail at the Interim Analysis:

Placebo subjects with MLA

20%	35%	50%	70%		
95%	**72%**	36%	6%	20%	AMG 334 subjects with MLA
	73%	40%	8%	35%	
		50%	15%	50%	
			40%	70%	

Probability of Overall Trial Success:

Placebo subjects with MLA

20%	35%	50%	70%		
1%	14%	48%	91%	20%	AMG 334 subjects with MLA
	4%	23%	72%	35%	
		6%	38%	50%	
			5%	70%	

From the above, it can be seen that, if PACAP-38 does not induce MLA in a sufficient proportion of subjects for the study to test the hypothesis, or AMG 334 appears to be ineffective in blocking PACAP-38 induced MLA, the trial is more likely to fail at the interim analysis stage (the bold and underlined in the results with respect to the probability of fail at the interim analysis). However, should the study continue from the interim analysis stage, even by chance, the overall type I error is controlled such that the study is highly unlikely to conclude AMG 334 is effective in blocking PACAP-38 induced MLA (overall trial success) when it is not (the bold and underlined in the results with respect to the probability of overall trial success).

Designated personnel from Biostatistics will be unblinded for the interim analysis. After interim analysis, the designated unblinded Biostatistics personnel will recommend to the study team whether the sample size remains at 8 per group or needs to be increased to 18 per group.

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.

Details of PK, Antibody, and external lab data transfer to the data base is provided in the corresponding study data transfer plans. See Data Management Plan (DMP).

9.3 Handling of Missing and Incomplete Data

Imputation Rules for Partial or Missing Start Dates

	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	

Imputation Rules for Partial or Missing Stop Dates

If the month and year are present, impute the last day of the month. If only the year is present, impute December 31 of that year. If the stop date is entirely missing, assume

the event or medication is ongoing. If a partial or complete stop date is present and the 'ongoing' or 'continuing' box is checked, then it will be assumed that the AE or conmed stopped and the stop date will be imputed, if partial. Ensure the imputed stop date is on or after the complete or imputed start date.

9.4 Detection of Bias

Lack of protocol compliance and the potential for biased statistical analyses will be examined by assessing the incidence of important protocol deviations (IPD) in each treatment group. The clinical study team will identify and document the criteria for IPD.

9.5 Outliers

All confirmed outlier data will be included in the analyses presented in this SAP unless there is sufficient scientific justification (eg, IPD leading to invalid data) to exclude them.

PK concentration data will be evaluated for outliers by visual inspection and decisions to re-assay individual samples will be made in accordance with standard Pharmacokinetics and Drug Metabolism (PKDM) practice. All excluded observations will be detailed by PKDM along with reasons for exclusion, in accordance with standard PKDM practices.

9.6 Distributional Characteristics

Where appropriate, the assumptions underlying the proposed statistical methodologies will be assessed. If required data transformations or alternative non-parametric methods of analyses will be utilized.

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 (TFL) 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.

Additional statistical software may be used to perform exploratory/ad-hoc analyses.

10. Statistical Methods of Analysis

10.1 General Principles

Unless otherwise stated, data from PACAP-38 responders who go on to be randomized and receive IP will be summarized. Data from PACAP-38 non-responders, and data from

PACAP-38 responders that do not receive IP, will not be included in the summaries, but will be reviewed.

Unless otherwise specified, data will be summarized using the safety analysis set, by actual treatment group (AMG 334 or Placebo).

Descriptive statistics will be provided for selected demographics, safety and PK data. Descriptive statistics on continuous measurements will include means, medians, standard deviations (and standard errors for post-baseline data), quartiles, and ranges, while categorical data will be summarized using frequency counts and percentages. Where statistical models are applied to the data, estimates of the differences/ratios, confidence intervals and corresponding p-values will be presented, as applicable. However, these are for descriptive and illustrative purposes only and to aid interpretation of the data; no formal statistical hypothesis testing will be performed.

When data are summarized by time, the values recorded against the scheduled time points, including any time windows specified in the protocol will be used.

When assessing minimum/maximum increases or decreases over the study, all assessments, including unscheduled assessments will be used.

10.2 Subject Accountability

The number and percent of subjects who received IP (AMG 334 or placebo), completed study and discontinued the study (including reasons for discontinuing) will be summarized. A list of subjects who withdraw early will be reviewed. It will include the reason and timing of the withdrawal. Similarly, the reason any subject is excluded from an analysis set will also be reviewed.

10.3 Important Protocol Deviations

IPD 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.

The final IPD list will be used to produce the Summary of IPDs table and the list of subjects with IPDs. In addition, a separate listing of all inclusion and exclusion deviations will be provided.

10.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized.

Demographics:

- Age (years) at enrollment (continuous summary statistics)
- Age groups (years) [18-64, 65-74, 75-84, >=85] at enrollment (number and percentage of subjects in each age group category)
- Sex (number and percentage of males and females)
- Ethnicity (number and percentage in each ethnicity category)
- Race (number and percentage of subjects in each race, or mixed race combination)

Baseline Characteristics:

- Height, Weight and BMI (continuous summary statistics)

10.5 Primary Endpoint Planned Analysis

The number and percent of subjects experiencing a MLA within 24 hours after PACAP-38 infusion will be summarized for each treatment group. Comparison of PACAP-38 ability to produce MLA between AMG 334 and placebo will be done using the Fisher's Exact test.

10.6 Secondary Endpoint(s)

10.6.1 Number of Headaches

The number and percent of subjects experiencing a headache within 24 hours after PACAP-38 infusion will be summarized for each treatment group. Comparison of PACAP-38 ability to produce headaches between AMG 334 and placebo will be done using the Fisher's Exact test.

10.6.2 Safety Endpoints

10.6.2.1 Adverse Events (AEs)

The Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 or later will be used to code all AE to a system organ class and a preferred term. The subject incidence of AEs will be summarized for all treatment-emergent, serious treatment-emergent, those leading to withdrawal of IP, fatal, and events of interest (EOI), where treatment refers to IP. The identification of EOI is a continuous process. Events may be identified and documented as the safety profile of the drug is characterized. The severity of each AE will be graded using common terminology for AE (CTCAE) version 4.0 criteria.

Subject incidence of all treatment-emergent, serious treatment-emergent, those leading to withdrawal of IP, and fatal AE will be tabulated by system organ class and preferred term, where treatment refers to IP. Where appropriate, the tables will also be presented by worst grade. The above AE tables will not be created if two or fewer subjects experience the AE. The above AE tables will be summarized separately for events occurring between Day 1 and Day 7 following administration of IP and events occurring from Day 8 onwards following administration of IP and the second dose of PACAP-38.

For PACAP-38 related treatment-emergent AEs, all treatment-emergent AEs where the question “Is there a reasonable possibility that the event may have been caused by PACAP-38?” is ticked “yes” will be summarized by treatment group.

Details of each AE will be listed.

10.6.2.2 Vital Signs

Vital signs will be reviewed for each subject. Summaries of HR and BP data over time and change from baseline will be provided. Depending on the size and scope of change in other vital signs, summaries may be provided.

10.6.2.3 Electrocardiogram (ECG)

All on-study ECG data will be reviewed for each subject.

10.6.2.4 Physical Examination

Physical examination results will be reviewed for each subject. Depending on the size and scope of change in weight and BMI, summaries may be provided.

10.6.2.5 Laboratory Test Results

Hematology, chemistry and urinalysis data will be reviewed for each subject. Depending on the size and scope of changes in laboratory data, summaries of laboratory data over time and/or changes from baseline over time may be provided. Liver function abnormalities will be summarized.

10.6.2.6 Neurologic Assessment

Neurological assessment data will be reviewed for each subject.

10.6.3 Pharmacokinetic Endpoints

Serum AMG 334 concentrations will be determined using a validated assay. Individual serum concentration-time plots for AMG 334 will be presented for each subject as well as mean concentration-time plots for each treatment group. PK parameters $C_{1\ hour}$, and AUC_{84d} will be estimated using either compartmental (eg, PK modeling) or non-compartmental methods. Actual dosing and sampling times will be used for

calculation of PK parameters. Summary statistics will be generated for each PK parameter for each treatment group and provided by CPMS. The PK analysis set will be used for these analyses.

10.6.4 AMG 334 Antibody Assessment

Binding antibody and neutralizing antibody formation will be assessed at predose and at various time points throughout the study including EOS. Antibody data will be listed for each subject. The incidence and percentage of subjects who develop anti-AMG 334 antibodies (binding and if positive, neutralizing) at any time will be tabulated by treatment group.

10.7 Exploratory Endpoint(s)

10.7.1 Migraine-like Attacks (MLA) and Headaches

The reduction in severity of MLA and headaches by AMG 334 within 24 hours after infusion of PACAP-38 on day 8 will be assessed and summarised based on a severity score (0-10; 0=pain free; 10=extreme pain). Severity of MLA and headaches will be analysed separately using a repeated measure analysis of variance model. Independent variables will be treatment, hour, and treatment by hour interaction. Subject will serve as a random effect. For each treatment by hour combination, least square means, ratio to placebo, 95% confidence intervals and corresponding nominal p-values for the null hypothesis of no difference from placebo will be presented. Graphical summaries of severity scores will also be provided. For SAS code, see Appendix A1.

10.7.2 Duration of Migraine-like Attacks (MLA) and Headaches

Descriptive statistics will be provided for the duration of MLA and headaches by treatment group.

10.7.3 Migraine Characteristics

Descriptive summaries of measured characteristics of MLA and headaches, such as localization and accompanying symptoms and pre-monitory symptoms, within 24 hours after infusion with PACAP-38 will be presented for each treatment group.

10.7.4 Plasma Concentration of PACAP-38 and CGRP

Summary statistics will be generated for plasma PACAP-38 and CGRP levels pre/post dosing with PACAP-38. Summaries will be produced by treatment group for the second dose of PACAP-38 (ie., the dose administered after administration of IP).

10.8 Columbia Suicide Severity Rating Scale (C-SSRS)

Subject incidence of treatment-emergent suicidal ideation and behavior as assessed by C-SSRS will be reviewed and may be summarized.

10.9 Exposure to Investigational Product (IP)

Subject listings of manufacturing lot numbers and a separate listing of unique manufacturing lot numbers used in this study will be provided. Details for each AMG 334 administration will be listed for every subject.

10.10 Exposure to Non-Investigational Medicinal Product (NIMP)

Subject listings of PACAP-38 used in this study will be provided. Details for PACAP-38 administration will be listed for every subject.

10.11 Exposure to Concomitant Medication

All medication will be coded using the World Health Organization Drug (WHO DRUG) dictionary. All prior and concomitant medications will be reviewed.

11. Changes From Protocol-specified Analyses

Minor changes to the protocol-specified analyses have been made and clarified in this SAP.

The safety analysis set has been modified slightly to include all subjects who receive IP (AMG 334 or placebo), but excludes any reference to whether the subject receives PACAP-38 or not. This is to take into account any subjects that receive IP, but do not receive PACAP-38 (eg, subject withdrew from the study before PACAP-38 could be administered). In these cases, the subject's data will be reviewed, but will not be included in any data summaries.

ECG data will not be summarized as specified in the protocol, as the data was collected as part of the standard of care and not in a thorough manner.

12. Literature Citations / References

Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders, 2nd edition. *Cephalalgia*. 2004; 24(Suppl. 1):8-160.

13. Data Not Covered by This Plan

The following analyses will be analyzed outside of this SAP:

- The changes in plasma PACAP-38 and CGRP concentrations pre- and post-dosing with AMG 334
- Blood samples collected for biomarker development

14. Appendices

Appendix A. Code Fragments

CCI

[redacted]