Statistical Analysis Plan

Protocol Title:	A Phase I, Randomized, Open-label, Multiple-dose Study to Evaluate Safety, Tolerability, and Pharmacokinetics of AMG 334 in Children and Adolescents With Migraine
Short Protocol Title:	Phase I Safety and Pharmacokinetics Study of AMG 334 in Pediatric Subjects With Migraine
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	11SEP2017	Original version
Amendment 1 (v2.0)	27MAR2018	• SAP Amendment 1 was triggered due to Protocol Amendment 1 dated 05 December 2017. • Editorial changes were made throughout the document to improve overall clarity. • Section 3.1 updated to clarify the enrollment of subjects, number of subjects expected in each age group and cohort, and study schema. • Section 3.2 updated to increase the sample size from 45 to 60 and added sample size calculation assumption and reference. • Section 4.2 updated to specify body weight cohort as a sub-group analysis. • Section 6.6 updated to clarify scope of data to be included for the two interim analyses. • Section 7.1 updated to clarify that the second interim analysis will occur, to clarify the criteria of second interim analysis and scope of data to be included for second interim analysis. • Section 7.2 and 7.3 updated to clarify the scope of data to be included for primary and final analysis and to mention that PK and safety data will be summarized by cohort and AMG 334 treatment group. • Section 9.1 updated to clarify that summary results will be presented by body weight cohort and treatment group. • Section 9.4 updated to remove Patient Health Questionnaire (PHQ-9) total score. • Table 9-1 updated to clarify that summary results will be presented by body weight cohort and treatment group. • Section 9.6.2 updated to remove adverse events of interest (EOI) and to update CTCAE version to 4.03. • Section 9.6.3 updated to clarify that summary results will be presented by body weight cohort and treatment

		group and to clarify that shift tables and summary statistics will be presented for all laboratory parameters. • Section 9.6.4 updated to remove respiratory rate from vital signs analysis. • Section 9.7.1 updated to clarify that clearance and central volume of distribution on body weight basis may be summarized. • Section 10 updated to clarify the change from protocol regarding the second interim analysis occurring irrespective of the timing of primary analysis. • Added reference in section 11. [redacted]
Amendment 2 (v3.0)	24AUG2018	• SAP Amendment 2 was triggered due to Protocol Amendment 2 dated 20 June 2018. • Editorial changes were made throughout the document to fix typos and improve overall clarity. “Cohort” is clarified as “body weight cohort” throughout the document. [redacted] • Section 3.1 updated to mention that the enrollment will be staggered by age categories with adolescents (12 to < 18 years of age) starting enrollment first. Children (6 to < 12 years of age) will be enrolled once data from on ongoing juvenile toxicology study in cynomolgus monkeys became available and are considered supportive of dosing in this younger subgroup of subjects. Study schema is also updated. • Section 7.1 updated to clarify the scope of data to be summarized by GBS and CPMS group, status of database at the time of interim analyses and impact of data change during any analysis.

		• Section 7.2 updated to clarify the status of database at the time of primary analysis. [redacted]
Amendment 3 (v4.0)	26JUN2019	• SAP Amendment 3 was triggered due to Protocol Amendment 3 dated 18 April 2019. • Editorial changes were made throughout the document to improve overall clarity. • Included previous SAP version numbers and date on front page. • Included summary of changes from previous SAP versions. • Updated list of sections/ sub-sections/ appendices (including removal of sections/ sub-sections/ appendices which were not applicable in this study). • List of abbreviations updated to include all abbreviations used in this document and to remove abbreviations no longer in use in this document. • Section 3.1 updated to clarify that children enrollment can begin and only adolescents will be given the option to continue in an optional 40-week extension phase. Study schema is also updated along with the timing of safety assessment follow-up visit. • Updated section 5 to improve the treatment-emergent adverse event and treatment-emergent serious adverse event definition to make it align with latest standard. • Section 7.1 updated to align the purpose of second interim analysis with the first one. The role and scope of the DMC in the AMG 334 pediatric program has also been included for consistency with the phase 3 study protocols. • Section 8.3 updated to remove imputation rule for partial or missing stop dates. • Section 9.6.2 updated to mention the latest MedDRA version as 22.0.

		• Section 10 updated to align with latest protocol version (amendment 3 dated 18 April 2019).
Amendment 4 (v5.0)	12MAY2021	• SAP Amendment 4 was mainly triggered due to Protocol Amendment 4 dated 26 March 2020. Addition of an unplanned interim analysis in the SAP Amendment, as described in section 7.1, is a deviation from the protocol amendment 4. • Administrative updates reflecting protocol amendment 4 were made throughout the document. • Editorial and typographical changes were made throughout the document to improve overall clarity. • Section 3.1 is updated to align with the changes made in recent protocol amendment and to specify: o that age of subjects must be at consent (instead of screening). Note: This update is made throughout the document for consistency. o that concomitant use of up to 2 treatments for migraine prevention and acute treatment of migraine are permitted. o the randomization allocation ratio in the two body weight cohorts (refer to 6th paragraph of section 3.1). • Study Design and Treatment Schema is also updated, in Section 3.1, to align with above changes. • Section 3.2 is updated to replace “weight bands” with “weight cohorts”. • Section 4.2 is updated to remove the general description of analysis by body weight cohort. • Section 5 is updated to add new sub-sections to include more definitions and to update some old definitions. • Section 6.1 is added to define Full Analysis Set. • Section 6.2 is updated to clarify the scope of safety analysis set definition. • Section 6.4 is updated to clarify that requirement for first interim analysis is to include “at least 6 adolescents (12

		to < 18 years of age)" instead of "at least 6 subjects". • Section 6.5 is added to define Extension Analysis Set. • Section 7.1 is updated to include an unplanned interim analysis which will occur when 8 children (aged 6 to < 12 years) have completed study Week 12 assessments. Also added the purpose and scope of this unplanned interim analysis. • Section 9.1 is updated to clarify that analysis will be performed separately for initial treatment phase and optional extension phase. • Section 9.2 is updated to add more milestones for subject accountability and key study dates and to add summary of subjects by study sites. • Section 9.3 is updated to add protocol deviation summary for COVID-19 control measures. [redacted] • Section 9.6.2 is updated to reflect latest MedDRA version of 24.0 and to clarify that summaries of AEs will be provided by treatment phase. • Section 9.6.3 is updated to clarify about the liver function tests. • Section 9.6.6 is updated to include summary of shift in pre- and post-baseline ECG diagnosis. • Section 9.6.9 is updated to clarify that subject listing will be provided for concomitant medication data. [redacted] • Section 9.7.1 is updated to clarify that all PK related analysis will be done by CPMS group. [redacted] • Section 9.7.3 is newly created for Neurological Assessment. Also added that summary of abnormalities will be provided.

		• Section 10 is updated since there is a change to the analyses specified in the study protocol, amendment 4 dated 26 March 2020. Added details about the change.
Amendment 5 (v6.0)	17MAR2022	• SAP Amendment 5 was triggered due to Protocol Amendment 5 dated 3 November 2021. • Administrative updates reflecting protocol amendment 5 were made throughout the document. • Number of subjects, aged 6 to < 12 years old, needed for second interim analysis is updated throughout the document. Also, total number of subjects required to be enrolled in the study, the requirement for number of subjects in 6 to < 10 years age group and the minimum number of subjects needed in different cohorts/ age groups are also updated throughout the document. • Section 5.1 is updated to amend treatment-emergent serious adverse events definition as per DES. • Section 5.4.1 is updated to clarify study periods for ITP, OEP and entire study duration. • Section 5.6 is updated to add the formula for calculation of IP duration. • Section 6.2 is updated to clarify the scope of safety analysis set. • Section 6.4 is updated to remove the unplanned interim analysis set definition. • Section 7.1 is updated to remove the unplanned interim analysis description. • Section 7.2 and 7.3 are updated to clarify that primary analysis will include safety data for ITP and final analysis will include safety data for entire study and separately for OEP. Also, clarified that PK data will be analyzed by CPMS. • Section 9.1 is updated to clarify that safety summaries will be produced for entire study, ITP and OEP, as applicable, and by age group, where appropriate.

		• Section 9.6.2 is updated to reflect the latest MedDRA version of 24.1. Also, AE listing requirement is removed. • Section 9.6.8 is updated to include IP exposure summaries. • Section 10 is updated to clarify that unplanned interim analysis was performed and it fulfilled the requirement for second interim analysis.

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List of Abbreviations

Abbreviation	Explanation
AE	Adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
$AUC_{0\text{-}28day}$	Area under the concentration-time curve from time 0 to 28 Days
BMI	Body Mass Index
CI	Confidence interval
CL	Clearance
C_{max}	maximum concentration
CPMS	Clinical pharmacology modeling and simulation
C-SSRS	Columbia suicide severity rating scale
CTCAE	Common terminology criteria for adverse events
C_{trough}	trough concentration
DARS	Data acquisition requirements specification
DMC	Data Monitoring Committee
DMP	data management plan
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	end of study
GBS	Global Biostatistical Science
GSO-DM	Global study operations-Data management
ITP	Initial Treatment Phase
IP	investigational product
IPD	important protocol deviation
IVRS	Interactive voice response system
kg	Kilogram
m	Meter
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
NCI	National Cancer Institute
OEP	Optional Extension Phase
PD	Pharmacodynamic
[redacted]	
PK	Pharmacokinetic(s)

Abbreviation	Explanation
PT	preferred term
Q4W	every 4 weeks
QTc	QT interval corrected
SAE	serious adverse events
SAP	Statistical Analysis Plan
SC	Subcutaneous
SOC	system organ class
TBL	total bilirubin
TFL	Tables, Figures, and Listings
t_{max}	time to maximum concentration
ULN	Upper limit of normal
Vc	Central volume of distribution
WHO Drug	World Health Organization Drug

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 **5** for study 20160172, AMG 334 dated **03 November 2021**. The scope of this plan includes the interim analyses, the primary analysis and the final analysis that are planned and will be executed by the Amgen Global Biostatistical Science (GBS) department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• T**o e**valuate the safety, tolerability, and pharmacokinetic (PK) profile of multiple subcutaneous (SC) doses of AMG 334 in children and adolescent subjects with migraine, respectively	• Serum PK parameters of AMG 334 (eg, time to maximum concentration [t_{max}], maximum observed concentration [C_{max}], trough concentration [C_{trough}], and area under the concentration time curve [AUC] from 0 to 28 days [$AUC_{0\text{-}28day}$]) • Subject incidence of treatment-emergent adverse events (AEs) • Changes in vital signs, 12-lead electrocardiograms (ECGs), clinical laboratory safety tests, and neurological assessments
Key Secondary	
• Not applicable	• Not applicable
Secondary	
• Not applicable	• Not applicable

Exploratory	
[redacted]	

[redacted]

2.2 Hypotheses and/or Estimations

Multiple subcutaneous doses of AMG 334 will be safe and well-tolerated, and the PK profiles will support further development of AMG 334 in children and adolescents with migraine**,** respectively. There will be no formal hypothesis testing; any comparisons made will be descriptive only.

3. Study Overview

3.1 Study Design

This is a Phase 1b, multicenter, randomized, open-label, multiple-dose study evaluating AMG 334 in male and female children (6 to < 12 years of age) and adolescents (12 to < 18 years of age) with migraine. The study population will consist of 2 cohorts based on body weight at baseline enrolling a total of at least **52** subjects and up to approximately 60 subjects in the study.

Cohort 1 will enroll at least **12** subjects and up to approximately 22 subjects in total with body weight of < 40 kg. At least **9** subjects in Cohort 1 must be aged 6 to < 12 years old including at least **2** subjects aged 6 to < 10 years old, at the time of consent.

Cohort 2 will enroll at least 35 subjects and up to approximately 38 subjects in total with a body weight of ≥ 40 kg at baseline. It is anticipated that most subjects in this cohort will be 12 to < 18 years of age. Enrollment requirements for subjects in Cohort 1 and Cohort 2 will be tracked and administered via Interactive Voice Response System (IVRS) to ensure that the minimum number of subjects in each cohort is achieved. Enrollment will be staggered by age category with adolescents (ie, subjects 12 to < 18 years of age) starting enrollment first.

Children 6 to < 12 years of age at the time of consent will participate in the initial treatment phase, for a total of 12 weeks of treatment. Adolescents 12 to < 18 years of age at the time of consent will participate in the initial treatment phase for a total of 12 weeks of treatment after which they will have the option of continuing treatment in an optional 40-week extension phase, for a total of 52 weeks of treatment. A safety follow-up visit will take place 16 weeks after the last dose to complete end of study (EOS) assessments either (i) after completion of the initial 12-week treatment phase, (ii) after completion of the optional 40-week extension phase for those adolescents who choose

to continue treatment or (iii) after the last dose received before discontinuation of treatment during the study.

Subjects weighing < 40 kg (Cohort 1) will be randomized in a 1:2 allocation ratio to low dose (35 mg) or high dose (70 mg) for a total of at least **12** and up to approximately **15** subjects completing Week 12 assessments. Subjects weighing ≥ 40 kg (Cohort 2) will be randomized in a 1:4 allocation ratio to low dose (70 mg) or high dose (140 mg) for a total of at least 26 and up to approximately 30 subjects completing Week 12 assessments. Treatments will be allocated to qualifying subjects in a randomized order within either cohort through IVRS. Study drug (low-dose or high-dose AMG 334) will be administered in either cohort in an open-label fashion against a background of allowed concomitant medications, including agents for migraine prevention.

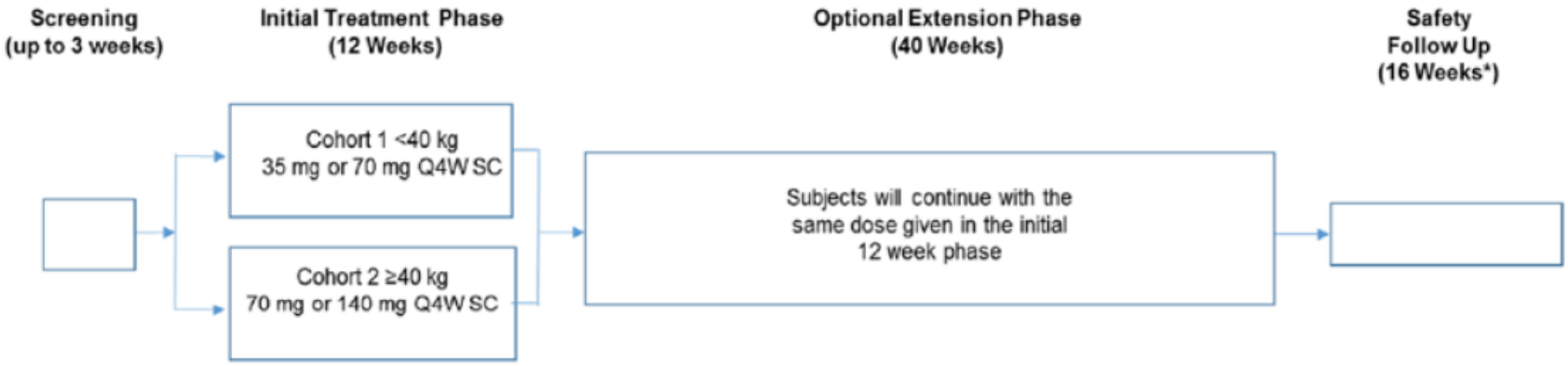
It is anticipated that at least **52** and up to approximately 60 subjects will be enrolled in the study to ensure that at least **38** and up to approximately **45** subjects complete Week 12 assessments.

During the initial treatment phase, each subject will receive a total of 3 SC doses of AMG 334 administered every 4 weeks (Q4W) on Days 1, 29 (± 3 days), and 57 (± 3 days), respectively. The study is expected to confirm a PK profile in pediatric subjects that is similar to that in adults, based on population PK analysis, and to provide preliminary safety data in each body weight cohort supportive of the initiation of the AMG 334 Phase 3 studies in the pediatric population. All subjects will be administered AMG 334. Concomitant use of agents for migraine prevention (up to 2 treatments on a stable dose) and for the acute treatment of migraine are permitted during the study. All subjects will be followed for 16 weeks following the last dose of AMG 334.

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

Study Design and Treatment Schema

AMG 334 Pediatric, PK / Safety, Open-Label Phase 1 Study Schema
N ≈ 60 subjects



Q4W – Every 4 weeks; SC – Subcutaneous

Cohorts assigned by Day 1 body weight

Children 6 to < 12 years of age at the time of consent, will only participate in the initial treatment phase, for a total of 12 weeks of treatment.

Adolescents 12 to < 18 years of age at time of consent will participate in the initial treatment phase after which they will have the option of continuing treatment in an optional 40-week extension phase.

Subjects completing the initial 12 Week treatment phase and not participating in the optional 40-week extension phase will proceed directly to the Safety Follow-Up Visit.

* Safety Follow-Up Visit will take place 16 weeks after last dose of IP

3.2 Sample Size

The study population will consist of 2 cohorts based on body weight enrolling a total of at least **52** subjects up to approximately 60 subjects in the study. Cohort 1 will enroll at least **12** subjects and up to approximately 22 subjects in total with body weight of < 40 kg at baseline. It is anticipated that most subjects in this cohort will be 6 to < 12 years of age. Cohort 2 will enrol at least 35 subjects and up to approximately 38 subjects with a body weight of ≥ 40 kg at baseline. It is anticipated that most subjects in this cohort will be 12 to < 18 years of age.

Subjects weighing < 40 kg (Cohort 1) will receive a dose of 35 mg or 70 mg for a total of at least **12** and up to approximately **15** subjects completing Week 12 assessments.

Subjects weighing ≥ 40 kg (Cohort 2) will receive a dose of 70 mg or 140 mg for a total of at least 26 and up to approximately 30 subjects completing Week 12 assessments.

The rate of early discontinuation up to Week 12 assessments is assumed to be 20% and similar across the two cohorts.

All subjects in this study will be administered AMG 334. The sample size for this study is based on clinical and practical considerations to adequately fulfil its objectives and to inform on planned phase 3 pediatric studies. Assuming clearance (CL) and central volume of distribution (Vc) on body weight basis is similar between pediatric subjects and adults, and assuming the percentage coefficient of variation for CL and Vc are 43% and 53%, respectively (based on total between-subject-variability from adult population PK), the proposed sample size provides > 80% power to estimate 95% confidence interval (CI) of CL and Vc within 60-140% of the true parameters for both weight cohorts combined and across the two age categories (Wang Y et al, 2012).

3.3 Adaptive Design

Not applicable.

4. Covariates and Subgroups

4.1 Planned Covariates

Covariates are not applicable in this study as no formal statistical modeling will be performed.

4.2 Subgroups

Selected safety analyses based on age group (6 to < 12 years and 12 to < 18 years) may be performed.

5. Definitions

5.1 Definition of Terms Included in Study Endpoints

Treatment-emergent AE

Events categorized as Adverse Events (AEs) starting on or after first dose of investigational product as determined by "Did event start before first dose of investigational product" equal to "No" or missing on the Events electronic case report form (eCRF) and up to the End of Study date.

Treatment-emergent Serious Adverse Events (SAEs)

Treatment-emergent adverse events indicated as serious on the Events eCRF.

Device-related Treatment-emergent Adverse Event

A treatment-emergent adverse event with the indicator flag "Is there a reasonable possibility that the event may have been caused by the investigational device" equal to "Yes" on the Events eCRF.

5.2 Study Dates

Enrollment Date

Enrollment Date is defined as the date collected on the eCRF.

Randomization Date

Randomization Date is defined as the date subject was allocated to a treatment group.

First Investigational Product (IP) Dose Date

First IP Dose Date is the date on which a subject is administered the first dose of IP following randomization, which may be the same day or after the randomization date**, as recorded on IP Administration eCRF**. For subjects who are randomized but not dosed with IP after randomization, First IP Dose Date is considered missing.

First Initial Treatment Phase (ITP) IP Dose Date

First ITP IP Dose Date is the date on which a subject is administered the first dose of IP in the initial treatment phase, as recorded on IP Administration eCRF.

First Optional Extension Phase (OEP) IP Dose Date

First OEP IP Dose Date is the date on which a subject is administered the first dose of IP in the optional extension phase following completion of initial treatment phase**, as recorded on IP Administration eCRF**.

Last IP Dose Date

Last IP Dose Date for each subject is defined as the latest date IP is administered**, as recorded on IP Administration eCRF**.

Last ITP IP Dose Date

Last ITP IP Dose Date for each subject is defined as the latest date IP is administered during the initial treatment phase, as recorded on IP Administration eCRF.

Last OEP IP Dose Date

Last OEP IP Dose Date for each subject is defined as the latest date IP is administered during the optional extension phase, as recorded on IP Administration eCRF.

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 eCRF.

End of ITP Date

End of ITP date for each subject is defined as the date recorded on the End of Initial Treatment Phase eCRF.

End of OEP Date

End of OEP date for each subject is defined as the date recorded on the End of Optional Extension Treatment Phase eCRF.

Subject-level End of Study (EOS) Date

EOS for each subject is defined as the date the subject last completed a protocol-specified procedure, as recorded on the EOS eCRF page.

5.3 Study Points of Reference

Baseline

Unless otherwise stated, baseline will be defined as the last assessment taken prior to the first AMG 334 administration (ie, Day 1 pre-dose or Screening if Day 1 pre-dose is not available) of the ITP. For subjects continuing treatment in an OEP after completion of the ITP, their baseline will be the same as the ITP.

[redacted]

For ECG and Neurological Evaluation, the entire set of data from the Day 1 visit will be used as baseline. If the data is missing on Day 1, the entire set of data from the Screening visit will be used as baseline.

Study Day 1

Day 1 is defined as the first day that IP is administered to the subject. For subjects who are randomized but not dosed after randomization, the Study Day 1 is defined as the date of randomization. The day before Day 1 is referenced as Day -1.

Study Day

- On or after Study Day 1: Study Day = (Study Date - Date of Study Day 1) + 1
- Before Study Day 1: Study Day = (Study Date - Date of Study Day 1)

5.4 Study Time Interval

5.4.1 Study Periods

The following data will be categorized into treatment periods, if applicable. Any data occurred after EOS date will not be included in the analysis [redacted]

Study Phase	Start Time Point	End Time Point
Initial Treatment Phase	Study Day 1	For Treatment-emergent Adverse Event: • Min (First OEP Dose Date – 1, **EOS date**) for subjects who received OEP dose; • EOS Date, for subjects who did not receive any OEP dose For lab, ECG, [redacted], Neurological Evaluation and Vital Signs: • Min (First OEP Dose Date, EOS date) for subjects who received OEP dose; • EOS Date, for subjects who did not receive any OEP dose [redacted]

Study Phase	Start Time Point	End Time Point
		[redacted]
Optional Extension Phase	For Treatment-emergent Adverse Event: • First OEP Dose Date For [redacted] lab, ECG, [redacted] Neurological Evaluation and Vital Signs: • First OEP Dose Date + 1	For Treatment-emergent Adverse Event, lab, ECG, [redacted] Neurological Evaluation and Vital Signs: • EOS Date [redacted]
Entire Study	Study day **1**	**EOS**

5.5 Subject Disposition

Randomized

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

Exposed to Investigational Product

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

Completing the Initial Treatment Phase

Subjects are defined as completing the ITP if they complete the Week 12 assessment. It will be derived from the End of Initial Treatment Phase eCRF with “Completed” as the primary reason for ending study phase.

Completing the Optional Extension Phase

Subjects are defined as completing the OEP if they complete the Week 52 assessment. It will be derived from the End of Optional Extension Treatment Phase eCRF with “Completed” as the primary reason for ending study phase.

Completing Study

Subjects are defined as completing study if they complete the entire study **duration, as applicable**. It will be derived from the End of Study eCRF with "Completed" as the primary reason for ending study.

5.6 Arithmetic Calculations

Change from Baseline:

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

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

Duration of IP Exposure During ITP

If subject enters into OEP,

Minimum (Last ITP IP Dose Date + 27, First OEP Dose Date - 1, EOS Date) – First ITP IP Dose Date + 1

Otherwise,

Minimum (Last ITP IP Dose Date + 27, EOS Date) – First ITP IP Dose Date + 1

Duration of IP Exposure During OEP

Minimum (Last OEP IP Dose Date + 27, EOS Date) – First OEP IP Dose Date + 1

Duration of IP Exposure During Entire Study

Minimum (Last IP Dose Date + 27, EOS Date) – First IP Dose Date + 1

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 enter that period (ie, number of at-risk subjects). For subjects with multiple occurrences of the same event in a given period, the event will only be counted once per subject in that period.

Exposure-adjusted Incidence Rate

The exposure-adjusted incidence rate for a given event in a given period is defined as the number of subjects with at least one reported occurrence of the event in a given period divided by total exposure time of all subjects who are at risk for the event. For subjects with a given event, only the time until the onset of each subject's first event contributes to the exposure time. For subjects without a given event, the exposure time

is the entire duration of the period. This incidence rate will be presented as number of subjects per 100 subject-years.

6. Analysis Sets

The following subsections define the analysis sets for this study.

6.1 Full Analysis Set

The Full Analysis Set (FAS) includes all randomized subjects. Subjects will be analyzed according to their randomized treatment, regardless of the treatment received. Tabulations of demographic and baseline characteristics, disposition, important protocol deviations (IPD) and protocol deviations related to COVID-19 control measures will utilize this analysis set.

6.2 Safety Analysis Set

The safety analysis set will consist of all randomized subjects who received at least one dose of AMG 334 during ITP. Subjects will be analyzed according to the randomized treatment unless a subject has received the incorrect dose during the entire ITP. Analyses for safety endpoints **and summary of IP administration** in ITP **and for entire study duration** will utilize this analysis set.

6.3 Pharmacokinetic/Pharmacodynamic Analyses Set(s)

The Pharmacokinetic (PK) analysis set will contain all randomized subjects who receive at least one dose of AMG 334 and have at least one PK concentration result. Pharmacodynamic (PD) analysis set is not applicable for this study.

6.4 Interim Analyses Set(s)

The interim analysis set will be defined separately for each interim analysis. For the first interim analysis, the analysis set will include a subset of the safety analysis set consisting of at least 6 adolescents (12 to < 18 years of age) who have completed study Week 8 assessments and all available data collected for all subjects up to and including the corresponding data cutoff date. For the second interim analysis, the analysis set will include a subset of the safety analysis set consisting of at least **8** children (6 to < 12 years of age) who have completed study Week 12 assessments and will include all available data collected for all children up to and including the corresponding data cutoff date.

6.5 Extension Analysis Set

The Extension Analysis Set will consist of all adolescent subjects receiving at least one dose of AMG 334 in the OEP. This analysis set will be used when summarizing data collected during the OEP.

7. Planned Analyses

There are two planned interim analyses, one primary analysis, and one final safety analysis.

7.1 Interim Analysis and Early Stopping Guidelines

There are 2 interim analyses of PK and safety planned for this study. The first interim analysis will occur when at least 6 adolescents (12 to < 18 years of age) have completed study Week 8 assessments. The second interim analysis will occur when at least **8** children (6 to < 12 years of age) have completed study Week 12 assessments. All data collected up to and including the corresponding data cutoff date will be available but only AEs, vital sign data and laboratory data will be summarized by GBS group, and PK data will be analyzed by Clinical Pharmacology Modeling and Simulation (CPMS) group. The purpose of the first and second interim analyses is to inform the selection of AMG 334 doses to be evaluated in the AMG 334 Phase 3 pediatric studies.

Results from the interim analyses will be presented to the independent Data Monitoring Committee (DMC) responsible for reviewing and making recommendations regarding the AMG 334 Phase 3 pediatric studies. The DMC will not review individual patient level data from this study or make recommendations regarding this study.

Impact of any changes in data during any analysis as compared to previous analysis will be assessed separately.

Interim Data Review Team

The interim data review team will consist of the Sponsor study team, including at least one medical monitor, safety representative, PK representative, biostatistician, and one representative from Novartis, which is partner in the development of AMG 334. At each interim analysis, this team will review the PK and safety data.

Early Stopping Guidelines

No early stopping rules are planned

7.2 Primary Analysis

The primary analysis for the study will be performed at the End of the Study milestone described in the protocol Section 3.5.2. All data will be cleaned and a database lock will occur.

No formal hypothesis testing will be performed; all analyses will be descriptive. PK and safety data will include summaries by body weight cohort and AMG 334 treatment dosage group. **Primary analysis will include safety summaries for ITP only. Safety data will be analyzed by GBS and PK data will be analyzed by CPMS.** The review of the results of this primary analysis will inform on further pediatric studies utilizing AMG 334.

7.3 Final Analysis

The final analysis will **utilize** the **same database as** the **primary analysis**.

No formal hypothesis testing will be performed; all analyses will be descriptive. PK and safety data will include summaries by body weight cohort and AMG 334 treatment dosage group. **Final analysis will include safety summaries for the entire study and separately for OEP only, as appropriate. Safety data will be analyzed by GBS and PK data will be analyzed by CPMS.**

8. Data Screening and Acceptance

8.1 General Principles

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

8.2 Data Handling and Electronic Transfer of Data

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

Details of PK, [redacted], and external lab data transfer to the database is provided in the corresponding study data transfer plans. See Data Management Plan (DMP) and Data Acquisition Requirements Specification (DARS).

8.3 Handling of Missing and Incomplete Data

In general, missing data will not be imputed. However, missing and incomplete dates for AEs and concomitant medications will be handled using the methods described below.

Imputation Rules for Partial or Missing Start Dates

	Missing	Imputation	Exception on Adverse Event Start Date
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 Events eCRF
	Day/Month	01JAN	Default to Study Day 1 if an adverse 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 Events eCRF
	Day/Month/Year	No imputation	

8.4 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 age group. The clinical study team will identify and document the criteria for IPD.

8.5 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 CPMS evaluation practice. All excluded observations will be detailed by CPMS along with reasons for exclusion, in accordance with standard CPMS practices.

8.6 Distributional Characteristics

Not applicable for this study.

8.7 Validation of Statistical Analyses

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

Tables, Figures and Listings (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.

9. Statistical Methods of Analysis

9.1 General Considerations

Unless otherwise stated, descriptive statistics will be provided for demographic and baseline characteristic by body weight cohort (< 40 kg and ≥ 40 kg), treatment dosage (35 mg, 70 mg and 140 mg), and all subjects combined.

Safety summaries during the **entire study,** ITP **or OEP, as applicable,** will be provided by body weight cohort (< 40 kg and ≥ 40 kg), treatment dosage (35 mg, 70 mg and 140 mg), and all subjects combined.

Where appropriate, **safety** summaries **will be provided by** each age group (adolescents and children) separately**.**

PK data will be summarized by body weight cohort and treatment dosage.

Descriptive statistics on continuous measurements will include **number of subjects (n),** means, medians, standard deviations (and standard errors for post-baseline data), first and third quartiles, and minimum and maximum, while categorical data will be summarized using frequency counts and percentages. No formal statistical hypothesis testing will be performed.

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

When assessing post-baseline minimum/ maximum increases or decreases over the study **(eg, shift in lab toxicity grade),** all assessments, including unscheduled assessments will be used.

9.2 Subject Accountability

The number and percent of subjects randomized, those who received AMG 334, completed ITP, discontinued the ITP (including reasons for discontinuing), entered the OEP, completed OEP, discontinued the OEP (including reasons for discontinuing), completed investigational product and discontinued investigational product (including reasons for discontinuation) will be summarized. Subjects who withdraw early, reason for withdrawal, and timing of the withdrawal will be reviewed.

Key study dates for the first subject enrolled, last subject enrolled, last subject's end of investigational product and last subject's end of study will be presented.

The number and percent of subjects randomized will be tabulated by study site.

The number and percent of subjects for each analysis set will also be summarized.

9.3 Important Protocol Deviations

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

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.

Protocol deviations related to COVID-19 controlled measures will be summarized.

9.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized.

Demographics:

- Age (years) at consent (continuous summary statistics)
- 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). If multiple races have been reported for a subject, the subject will be categorized as multiple race (as well as by combination of races).

Baseline Characteristics:

- Height, weight and BMI (continuous summary statistics)

9.5 Efficacy Analyses

Not applicable for this study.

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

Primary and exploratory safety endpoints are summarized in the table below.

Table 9-1. Safety Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method
Primary Safety Endpoint • Subject incidence of treatment-emergent adverse events (AEs) • Changes in vital signs, 12-lead electrocardiograms (ECGs), clinical laboratory safety tests, and neurological assessments Exploratory Safety Endpoint [redacted]	Summary statistics will be provided by body weight cohort and treatment dosage group

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 24.**1** or later will be used to code all events categorized as adverse events to a system organ class and a preferred term.

The subject incidence and exposure-adjusted subject incidence of all treatment-emergent adverse events, treatment-emergent serious adverse events, device-related treatment-emergent adverse events, treatment-emergent adverse events leading to discontinuation of **investigational product**, and fatal adverse events **will be summarized**.

Treatment-emergent adverse events, treatment-emergent serious adverse events, device-related treatment-emergent adverse events, treatment-emergent adverse events leading to discontinuation of AMG 334, and fatal adverse events will be tabulated by system organ class (SOC) in alphabetical order and preferred term (PT) in descending order of frequency. Summaries of treatment-emergent AEs and treatment-emergent serious adverse events will be tabulated by system organ class, preferred term, and

grade. The severity of each AE will be graded using Common Terminology Criteria for AE (CTCAE) version 4.03 criteria.

9.6.3 Laboratory Test Results

The following analyses will be provided for chemistry, hematology and urinalysis laboratory data:

- Shifts tables of the laboratory toxicity for all laboratory parameters based on CTCAE grade (version 4.03) relative to baseline will be tabulated by body weight cohort 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.
- Descriptive statistics of change from baseline by visit for all laboratory parameters
- Subject listing of grades ≥ 3 laboratory toxicities for all laboratory parameters as applicable
- Subject incidence of suspected Hy's Law cases
- Summary of liver function abnormalities for alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin (TBL) or the following categories:
  - ALT (> 3x upper limit of normal (ULN); > 5x ULN; > 10x ULN; > 20x ULN respectively)
  - AST (> 3x ULN; > 5x ULN; > 10x ULN; > 20x ULN respectively)
  - AST or ALT (> 3x ULN; > 5x ULN; > 10x ULN; > 20x ULN respectively)
  - Total Bilirubin (> 1x ULN; > 1.5x ULN; > 2x ULN respectively) and ALP (> 1.5 ULN)

Unscheduled assessments will be incorporated in the laboratory analyses where possible.

9.6.4 Vital Signs

Vital signs will be reviewed for each subject. Summaries of heart rate, temperature, and blood pressure (systolic and diastolic) data over time and change from baseline will be provided.

9.6.5 Physical Measurements

Height, weight, and BMI will be summarized by visit and change from baseline will be provided, as applicable.

9.6.6 Electrocardiogram

The electrocardiogram (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 QT interval corrected (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 for QTc data, and these data would not be expected to be useful for meta-analysis with data from other studies.

Shift in pre- and post-baseline ECG diagnosis will be summarized.

[redacted]

9.6.8 Exposure to Investigational Product

Number of IP doses received and duration of exposure to IP will be summarized. Subject listings of manufacturing lot numbers and a separate listing of unique manufacturing lot numbers used in this study will be provided.

9.6.9 Exposure to Concomitant Medication

All medication will be coded using the World Health Organization Drug (WHO DRUG) dictionary and a subject listing will be provided.

[redacted]

9.7 Other Analyses

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic 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 dose. PK parameters 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 (eg, time to maximum concentration [t_{max}],

maximum observed concentration [C_{max}], trough concentration [C_{trough}], and area under the concentration time curve [AUC] from 0 to 28 days [$AUC_{0\text{-}28day}$]).

Clearance (CL) and central volume of distribution (Vc) on body weight basis may be summarized.

Summary statistics will be generated for each PK parameter for each treatment group. All PK-related tables, figures, listings and other deliverables will be generated by CPMS.

9.7.2 Analyses of Clinical Outcome Assessments

[redacted]

9.7.3 Neurological Assessment

Neurological assessment will be completed as per standard of care and subject incidence of abnormalities will be summarized.

10. Changes From Protocol-specified Analyses

As a change from protocol-specified analysis per protocol amendment 4 dated 20 March 2020, an unplanned interim analysis was conducted in May 2021, when at least 8 children (aged 6 to < 12 years) had completed study Week 12 assessments, to facilitate engagement with health authorities regarding modifications to the AMG 334 Pediatric Investigational Plan (PIP) and commencement of enrollment of children in AMG 334 Pediatric Phase 3 studies. An as-is database snapshot occurred and included all data up to and including corresponding data cutoff date. Safety analyses including AEs, vital sign, laboratory, ECG, [redacted] was summarized by GBS group. PK data was analyzed by CPMS group based on all available PK data including all adolescent and children subjects from both Cohort 1 (< 40 kg) and Cohort 2 (≥ 40 kg).

The unplanned interim analysis fulfilled the requirement of second interim analysis (as described in Section 7.1), as reflected in Protocol Amendment 5 dated 03 November 2021. All TFLs generated during the unplanned interim analysis will be considered as second interim analysis outputs for the purpose of study documentation.

There is a change in timing of the primary analysis (as described in Section 7.2) compared to the Protocol Amendment 5 dated 03 November 2021.

11. Literature Citations / References

Wang Y, Jadhav PR, Lala M, Gobburu JV. Clarification on precision criteria to derive sample size when designing pediatric pharmacokinetic studies. J Clin Pharmacol. 2012;52(10):1601-6.

12. Prioritization of Analyses

Prioritization of analyses has not been identified at this time.

13. Data Not Covered by This Plan

There are no plans to specifically analyze or summarize the following data:

- ECG QTc data
- Data for biomarker development
- Pharmacogenetic data

14. Appendices

Appendix A. Reference Values/Toxicity Grades

Adverse event severity and laboratory toxicity are graded based on National Cancer Institute (NCI) Common Toxicity Criteria version 4.03 or higher, which is available at the following: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Appendix B. Clinical Outcome Assessment Forms/Instruments