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

AMG 334

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I have read the attached protocol entitled "A Phase I, Randomized, Open-label, Multiple-dose Study to Evaluate Safety, Tolerability, and Pharmacokinetics of AMG 334 in Children and Adolescents with Migraine", dated **03 November 2021**, and agree to abide by all provisions set forth therein. I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.
I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to one year after the study is completed, if there are changes that affect my financial disclosure status.
I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature

Name of Investigator

Date (DD Month YYYY)

Protocol Synopsis

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

Study Phase: 1b

Indication: Migraine prevention

Primary Objectives: To evaluate the safety, tolerability, and pharmacokinetic (PK) profile following multiple subcutaneous (SC) doses of AMG 334 in children and adolescent subjects with migraine, respectively.

Exploratory Objectives:

[redacted]

Hypotheses: Multiple SC 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.

Primary Endpoints:

- Serum PK parameters of AMG 334 (eg, time to maximum concentration [t_{max}]), maximum observed concentration [C_{max}], trough concentration (C_{trough}), area under the concentration time curve (AUC) from 0 to 28 days ($AUC_{0\text{-}28day}$)
- Treatment-emergent adverse events
- Changes in vital signs, 12-lead electrocardiograms (ECGs), clinical laboratory safety tests, and neurological assessments

Exploratory Endpoints:

[redacted]

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 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 including at least **2** subjects aged 6 to < 10 years, 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 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 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 receive a dose of either 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 either 70 mg or 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) as described in the Schedule of Activities (Table 1 and Table 2). 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 against a background of allowed concomitant medications, including agents for migraine prevention (up to 2 treatments on a stable dose) and for acute treatment of migraine.

Sample Size:

A total of at least **52** subjects and up to approximately 60 subjects with migraine will be enrolled in Cohorts 1 and 2. The rate of early discontinuation up to Week 12 assessments is assumed to be 20% and similar across the two cohorts. In Cohort 1, (< 40 kg), at least **12** subjects and up to approximately 22 subjects will be enrolled in order to have at least **12** and up to approximately **15** subjects completing Week 12 assessments. In Cohort 2, (≥ 40 kg), at least 35 subjects and up to approximately 38 subjects will be enrolled in order to have at least 26 and up to approximately 30 subjects completing Week 12 assessments. 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 planned Phase 3 pediatric studies. Assuming clearance (CL) and central volume of distribution (Vc) on mg/kg basis are similar between pediatric and adul**t** subjects, and assuming percent coefficents of variation (%CV) 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.

Summary of Subject Eligibility Criteria:

Male and female subjects ages 6 to < 18 years with a history of migraines at least twelve months prior to screening and with a frequency of ≥ 4 migraine days per month for three months prior to screening. For a full list of eligibility criteria, please refer to Section 4.1 and Section 4.2.

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

Investigational Product

Amgen Investigational Product Dosage and Administration:

Investigational product (IP) (ie, AMG 334) will be dosed subcutaneously. Doses are fixed, based on body weight taken at Day 1, and must not be adjusted for individual subjects during the study; eg due to changes in body weight. Subjects weighing < 40 kg (Cohort 1) will receive a dose of either 35 mg or 70 mg. Subjects weighing ≥ 40 kg (Cohort 2) will receive a dose of either 70 mg or 140 mg.

AMG 334 will be packaged as 70 mg/mL in 1 mL or 140 mg/mL in 1 mL pre-filled syringes and 70 mg/mL vials. Subjects in Cohort 1 (weighing < 40 kg) will be randomized in a 1:2 allocation ratio to low dose (35 mg AMG 334) or high dose (70 mg AMG 334). Subjects in Cohort 2 (weighing ≥ 40 kg) will be randomized in a 1:4 allocation ratio to low dose (70 mg AMG 334), or high dose (140 mg AMG 334). The anatomical sites for administration of Investigational Product are the upper arm, upper thigh, or abdomen.

Procedures:

After written informed consent and assent are obtained, all screening tests and procedures will be performed within 21 days before the administration of the first dose of AMG 334 (Study Day 1), unless otherwise noted.

Following the first AMG 334 dose administration on Day 1, all subjects will be monitored at the facility for at least 2 hours post-dose, at which point they will be discharged with instructions to return to the research facility according to the procedures provided in the Schedule of Activities (Table 1 and Table 2). At the 12 Week visit, adolescent subjects may choose to continue onto the optional 40-week extension phase. All subjects will be followed for 16 weeks after the last administration of AMG 334.

Blood samples for PK[redacted], clinical laboratory safety assessments, and pharmacogenomic assessments will be collected. Vital signs, physical examinations, and ECGs will be performed at predetermined time points throughout the study. All adverse events and use of concomitant medications will be collected for the duration of the study, up to and including the EOS visit. All treatment-emergent adverse events or laboratory abnormalities will be followed until resolution of the abnormality or until it is considered stable in the opinion of the investigator.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Activities (Table 1 and Table 2).

Statistical Considerations:

Descriptive statistics will be provided for selected demographic, safety, and PK data. Descriptive statistics on continuous measurements will include means, medians, standard deviations, first quartile (Q1), third quartile (Q3), minimum, and maximum, while categorical data will be summarized using frequency counts and percentages. For a full description of statistical analysis methods, please refer to Section 10.

The primary analysis of the safety and PK data will occur after all subjects in both body weight cohorts have completed the initial 12 Week treatment phase (ie, Week 12 assessments). 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. The review of the results of this primary analysis will inform further pediatric studies utilizing AMG 334.

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. For both interim analyses, PK data, adverse events, vital sign data, and laboratory data will be summarized. The purpose of the first and second interim analysis is to inform the selection of AMG 334 doses to be evaluated in the Phase 3 pediatric AMG 334 studies.

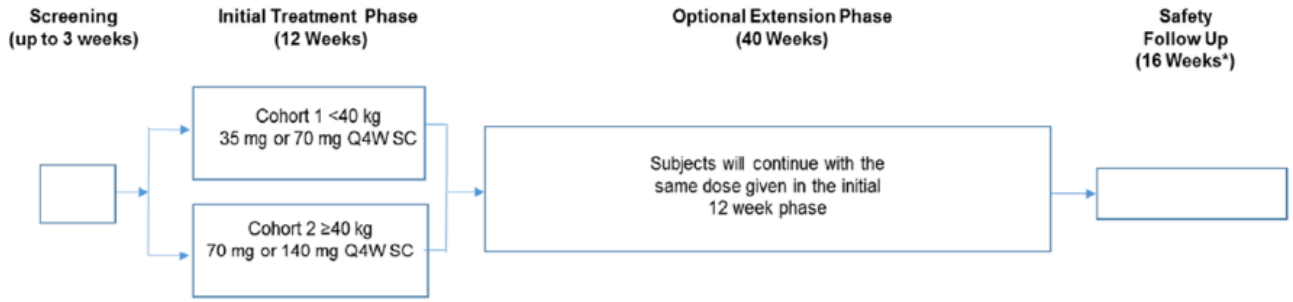
The final safety analysis for the study will be performed at the end of the trial, including the 40-week extension phase and the safety follow-up. No formal hypothesis testing will be performed; all analyses will be descriptive.

Sponsor: Amgen Inc.

Study Design and Treatment Schema

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

Study Glossary

Term/Abbreviation	Explanation/Definition
End of Study	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 16 weeks after the last dose of Investigational Product, or is discontinued from the study for other reasons)
End of Follow-up	defined as when the last subject completes the last protocol-specified assessment in the study
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Treatment	defined as the last assessment for the protocol specified treatment phase of the study for an individual subject
eSAE	electornic serious adverse event
Primary Completion	is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis (ie, when the last subject completes the 12 week assessment or is discontinued from the study)
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies) (ICH Guideline (E6)).
Study Day 1	defined as the first day that protocol specified Investigational Product(s)/protocol-required therapies is/are administered to the subject
Migraine Day	Any calendar day in which the subject experiences a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). A qualified migraine headache is defined as a migraine with or without aura, lasting for ≥ 30 minutes, and meeting at least one of the following criteria (a and/or b) a) ≥ 2 of the following pain features: • Unilateral or bilateral • Throbbing • Moderate to severe • Exacerbated with exercise/physical activity b) ≥ 1 of the following associated symptoms: • Nausea and/or vomiting • Photophobia and phonophobia (in pediatric patients photophobia and phonophobia can be inferred from behavior) If the subject took a migraine-specific medication (ie, triptan or ergotamine) during aura or to treat headache on a calendar day, then it will be counted as a migraine day regardless of the duration and pain features/associated symptoms.
AAP	American Academy of Pediatrics

Term/Abbreviation	Explanation/Definition
AE	Adverse Event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0\text{-}28day}$	Area under the concentration-time from 0 to 28 days after dose
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
CBT	cognitive-behavioral therapy
CI	confidence interval
CL	Clearance
CGRP	Calcitonin gene-related peptide
C_{max}	Maximum concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
C_{trough}	Trough concentration
CTCAE	Common terminology criteria for adverse events
DILI	drug-induced liver injury
DMC	Data Monitoring Comittee
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	electronic data capture
EOS	end-of-study
ePPND	pre-postnatal developmental study
eSAE	electronic serious adverse event
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good laboratory practice
HepBsAg	hepatitis B surface antigen
HepCAb	hepatitis C antibodies
HIV	Immunodeficiency Virus
ICF	informed consent form
IB	Investigator's Brochure
ICH	International Council for Harmonization
ICHD	The International Classification of Headache Disorders
IEC	Independent Ethics Committee

Term/Abbreviation	Explanation/Definition
IgG_2	immunoglobulin G_2
ICMJE	International Committee of Medical Journal Editors
INR	international normalized ratio
IP	investigational product
IPIM	investigational product instruction manual
IRB	Institutional Review Board
IUD	intrauterine device
IV	Intravenous
IVRS	interactive voice response system
K_d	dissociation equilibrium constant
MAD	Multiple Ascending Dose
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no observed adverse effect level
NSAID	non-Steroidal Anit-Inflatory
OTC	Over the Counter
PCR	polymerase chain reaction
[redacted]	
%CV	percent coefficient variation
PFS	pre-filled syringe
PHQ-A	Patient Health Questionnaire for Adolescents (PHQ-A)
PK	pharmacokinetic
Q1	first quartile
Q3	third quartile
QM, Q4W	every 4 weeks
SAD	Single Ascending Dose
SC	subcutaneous
TBIL	total bilirubin
t_{max}	time to maximum concentration
ULN	upper limit of normal
Vc	central volume of distribution

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1. OBJECTIVES

1.1 Primary

To evaluate the safety, tolerability, and pharmacokinetic (PK) profile of multiple subcutaneous (SC) doses of AMG 334 in children and adolescent subjects with migraine, respectively.

1.2 Exploratory

2. BACKGROUND AND RATIONALE

2.1 Disease

2.1.1 Migraines

Migraine is a disabling disorder characterized by primary recurrent headaches lasting 4 to 72 hours (if not treated) with at least two of the following pain characteristics: unilateral, pulsating, moderate or severe intensity, or aggravated by routine physical activity. In addition, migraine attacks are often accompanied by nausea, vomiting, and sensitivity to light (photophobia) and sound (phonophobia) (International Classification of Headache Disorders 3rd edition [ICHD]) (IHS, 2013). Children often have atypical clinical presentations; the younger the child, the more atypical the symptoms tend to be. Childhood migraines tend to be of shorter duration (often less than 4 hours or even 1 hour (Francis, 2013); and are frequently bilateral (bi-temporal or bi-frontal). Furthermore, children may have difficulty describing light and sound sensitivity (Jacobs and Gladstein, 2012). As a result, the current ICHD-III criteria (IHS, 2013) adapted 3 of the adult criteria mentioned above to apply to children: a) by reducing the minimal migraine duration to 2 hours; b) by allowing the migraine headache to be bilateral; and c) by allowing photo- and phono-phobia to be inferred from a young child's behavior.

Migraine affects more than 10% of the world's population (Robbins and Lipton, 2010), and affects approximately 18% of women and 6% of men in the United States and Europe annually (Stovner and Andree, 2010). Prevalence figures for specific age-subgroups reveal a pattern of slowly increasing overall prevalence from childhood

into adolescence, with an overall prevalence of ~4% in the 5-12 year age group and equal prevalence in boys and girls (Arruda et al, 2010). However, during adolescence , women progressively present higher migraine prevalence than men: ~7% and 5% in girls and boys ages 12-17, respectively.

Across the globe, the most frequently used acute migraine medications in adults include paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs; particularly ibuprofen, but children are also responsive to aspirin, naproxen, and diclofenac), and a class of serotonin 5-HT_{1B} and 5-HT_{1D} receptor agonists called triptans. Often, the first prescribed remedies for migraines in children and adolescents are over-the-counter (OTC) analgesics, supplemented by non-pharmacological measures such as changes in lifestyle (good sleep hygiene, diet free of additives, regularity with meals and sleep, limited sun exposure, and regular physical activity, all of which seem particularly efficacious in younger children (Eidlitz-Markus et al, 2010) and complementary therapies such as relaxation, biofeedback, magnesium, or cognitive-behavioral therapy (CBT). Triptans have been used safely for years in pediatrics (Evers, 2013); however, only almotriptan (in US) and sumatriptan (in EU) are approved for use in adolescents (> 12 years of age).

When the response to acute pharmacological treatments is not sufficient, often in combination with non-pharmacological measures and complementary therapies, it is recommended that children and adolescents with persistent disability initiate prophylactic pharmacologic treatment. While no formal treatment guidelines exist for children, generally clinical practice dictates that prophylactic medications are considered when patients have > 3 migraine headaches per month or when migraines are so severe that they interrupt normal activities. [redacted]. Therapy choice is determined on an individual basis, depending on a patient‘s migraine frequency and severity, comorbid conditions, and concomitant medications. Since available treatments used in pediatrics such as propranolol (approved in Finland in children > 7 years of age), topiramate (approved for adolescents in the US), and amitriptyline have adverse events that can negatively affect school and social life, there remains a clear unmet need for new prophylactic treatments for children and adolescents.

2.1.2 Targeting Calcitonin Gene-Related Peptide (CGRP)

Calcitonin gene-related peptide (CGRP) belongs to the calcitonin family of peptides and is widely expressed in the peripheral and central nervous systems including the trigeminal system, which is implicated in the pathophysiology of migraines. CGRP is a nociceptive modulator and potent vasodilator that has been associated with migraine pathophysiology based on several lines of evidence: 1) it is expressed in the trigeminal system (Tajti et al, 1999), 2) CGRP levels are elevated in migraineurs during an attack (Bellamy et al, 2006; Gallai et al, 1995; Goadsby et al, 1988; Goadsby et al, 1990), 3) triptans (approved acute abortive migraine medications) restore CGRP levels to normal after treatment in a time frame that corresponds to significant pain relief and alleviation of accompanying symptoms (Juhasz et al, 2005; Sarchielli et al, 2006), 4) infusion of CGRP into migraine sufferers triggers the onset of a migraine headache (Lassen et al, 2002; Petersen et al, 2005), 5) small molecule CGRP receptor antagonists have demonstrated clinical efficacy in acute migraine reversal (Connor et al, 2009; Hewitt et al, 2009; Ho et al, 2008a; Ho et al, 2008b; Olesen et al, 2004), and 6) small molecule CGRP receptor antagonists and antibody CGRP ligand antagonists have demonstrated clinical efficacy in migraine prevention (Dodick et al, 2014a; Dodick et al, 2014b; Ho et al, 2014). The consistent efficacy data provide strong clinical validation of CGRP as a promising target for treatment of migraine.

2.2 Amgen Investigational Product Background

AMG 334 is a human monoclonal immunoglobulin (IgG_2) against the CGRP receptor. AMG 334 binds to the CGRP receptor complex with high affinity (Kd of ~20 pM) which competitively and reversibly blocks the binding of the native ligand, CGRP. AMG 334 functions as a CGRP receptor antagonist.

2.2.1 Toxicology

The preclinical toxicology data were generated in the cynomolgus monkey, as it was the only laboratory species in which AMG 334 had suitable binding and functional activity. The studies conducted included an exploratory 1-month repeat dose toxicology study (SC, twice weekly), a Good Laboratory Practice (GLP) 1-month repeat dose toxicology study (SC, twice weekly) with a single dose IV arm, a single dose SC cardiovascular, respiratory and neurobehavioral safety pharmacology study in the telemetered monkey, and an enhanced pre-postnatal developmental study with a 6-month postnatal evaluation. In addition, in vitro human and monkey tissue cross-reactivity study with

fluorochrome-labeled AMG 334 was also conducted. There were no significant findings in the toxicology studies that would predict a risk to human subjects.

In the repeat-dose toxicology studies in cynomolgus monkeys, there were no AMG 334-related adverse effects on clinical signs, body weight, food consumption, ophthalmology, electrocardiogram (ECG), body temperature, respiration rate, clinical pathology parameters, macroscopic observations, or on organ weights. [redacted] The no observed adverse effect level (NOAEL) was determined to be the highest evaluated dose of 150 mg/kg administered twice weekly in the 3/6 month repeat-dose study (C_{max} = 2620 μg/mL; AUC = 15300 μg day/mL).

The enhanced pre-postnatal developmental study (ePPND) in cynomolgus monkeys demonstrated that there was no maternal toxicity observed, and there were no effects on fetal or infant losses or on growth and development through 6 months postpartum. The mean maternal AMG 334 exposure values (AUC_{last} and C_{max}) were 4280 μg·day/mL and 422 μg/mL respectively. During the postpartum evaluation phase, the mean maternal/infant serum AMG 334 concentrations on postpartum day or birthday 14, 28, and 91 were 66/117 μg/mL, 23/46 μg/mL, and 0.009/0.188 μg/mL, respectively. The mean infant serum concentrations during the first month after birth were approximately 5- to 12-fold higher than the clinical C_{max} at steady state to the potential adult therapeutic dose of 70 mg and 1.3 – 3.4-fold higher to the clinical dose of 140 mg.

The absence of AMG 334-related findings in the repeated-dose toxicology studies in cynomolgus monkeys (age range of 2.5 years or older) and absence of AMG 334-related effects on infant growth and development through 6 months postpartum when the infants had significant exposure to AMG 334 during the first month after birth suggests that there are no differences in toxicological profiles between younger and older animals and there is no concern of unique age-related developmental toxicities. This study further supports the clinical evaluation of AMG 334 in pediatrics.

A 52–week toxicity study with an 8-week recovery period, (study number 1770628), showed that twice weekly SC administration of 50 mg/kg AMG334 to juvenile cynomolgus monkeys was well tolerated without mortality, clinical signs of toxicity, or abnormalities during neurobehavioral observations, learning ability, cardiovascular investigations, bone mineral content and density, and skeletal development. There were no toxicology findings in preclinical studies that predicted a risk to human subjects.

2.2.2 AMG 334 Clinical Safety Summary

As of the cutoff date for this Investigator's Brochure (IB) (10 February 2020), an estimated **4642** subjects (**4255.37** subject-years [SY]) have been exposed to AMG 334 in Amgen sponsored clinical studies and an estimated **2649** subjects (**1647.74** SY) have been exposed to AMG 334 in Novartis-sponsored clinical studies. In addition, since the international birth date (17 May 2018) of AMG 334 up to the IB cutoff date, the estimated exposure to AMG 334 in the marketed setting has been **405224** patient-years in the Amgen territory and **90161** patient-years in Novartis territories. To date, AMG 334 has demonstrated a safety and tolerability profile that supports further development. Refer to the AMG 334 IB for details.

2.2.3 Pharmacokinetics

AMG 334 exhibited nonlinear PK after single-dose SC administrations over the dose range of 1 to 210 mg (Study 20101267). AMG 334 exposure increased more than dose proportionally from 1 to 70 mg and appeared to increase approximately dose proportionally from 70 to 210 mg after a single SC administration of AMG 334. The mean area under serum concentration time curve from time 0 to the last quantifiable time point (AUC_{last}) increased from 171 to 652 µg•day/mL (3.8-fold) and mean C_{max} increased from 6.25 to 15.2 µg/mL (2.4-fold) following the 3-fold increase in dose from 70 to 210 mg. Following a 140 mg SC dose maximum serum AMG 334 concentrations (C_{max}) were attained at a median time (t_{max}) of 5.5 days (range 4-21 days). The relative exposure as measured by the area under the concentration time curve (AUC) for SC administration compared with IV administration was approximately 54% for the 140 mg AMG 334 dose. There was no apparent difference in PK parameters between the healthy and migraine subjects. It is expected that AMG 334 administered SC every 4 weeks will be effective in migraine prevention in pediatric subjects. The effective half-life is 28 days.

2.3 Risk Assessment

Aimovig is currently approved for the preventive treatment of migraine (episodic or chronic types) in adults in over 40 countries. Doses greater than or equal to 70 mg and 140 mg (the highest dose level in either cohort in this study) have been given to three cohorts of adults in a multiple ascending dose (MAD) Phase 1 study and four cohorts of adults in a single asceding dose (SAD) Phase 1 study; a cohort of healthy subjects and a cohort of migraine subjects received three doses of 140 mg SC every four weeks (QM), and one cohort of healthy subjects received a dose of 280 mg (administered on Day 1) followed by 2 doses of 210 mg SC (administered on Days 29 and 57). In Phase 2, a dose ranging study (20120178) tested 7 mg, 21 mg and 70 mg SC QM vs placebo. In Phase 3, the maximum dose of both pivotal Phase 3 studies in adults with chronic migraine (Study 20120295) and episodic migraine (Study 20120296) was 140 mg SC, QM. In Phase 2 and Phase 3, 2417 subjects have been exposed at least 3 months to either 70 mg or 140 mg. The identified risks for AMG 334 are documented in Appendix A of the currently approved IB (Version 11.0, 10 February 2020). A limited number of adverse drug reactions (injection site reactions, constipation, muscle spasm, and pruritus) have been identified at low frequencies (< 5%) in clinical trials. In post-marketing settings, hypersensitivity reactions (including rash, angioedema and anaphylactoid reactions) and constipation with serious complications have been reported. Available safety data for the clinical trials with AMG 334 are summarized in Section 7.3 of the AMG 334 IB, Annex 2.

Risk mitigation strategies include the monitoring of vital signs, serial ECGs, and adverse events for all subjects at protocol defined time points.

Pediatric Risk Assessment

Beyond the expected relationship between AMG 334 PK and body weight, no additional significant PK covariates (at the dose levels to be tested) are expected in the various populations of migraine subjects, from age 6 years to adult. Based on the known safety profile of AMG 334, it is anticipated that it will be safe and well tolerated in pediatric subjects.

2.4 Rationale

Migraine headaches can have a significant impact on daily functioning, especially in terms of school performance and social life, despite the use of acute (abortive) treatments. With the exception of approved use of propranolol in children > 7 years of age in Finland and the approval of topiramate for adolescents in the United States,

safety and efficacy have not been established definitively for other prophylactic agents in the pediatric population. Moreover, because the side effects of propranolol and topiramate can negatively affect school and social life, there remains an unmet need for new prophylactic treatments. Upon conclusion of these pediatric studies, AMG 334 could provide a new treatment option for migraine prevention in children and adolescents 6 to < 18 years. This study is designed to provide safety, tolerability, and PK data that will support the Phase 3 study in children (6 to < 12 years of age) and adolescents (12 to < 18 years of age).

Four adequately powered and designed placebo-controlled clinical studies providing evidence for the efficacy of AMG 334 in migraine prevention in adults have been conducted. Dose selection in this study is based on the results of these studies in adults, where AMG 334 was evaluated at SC doses of 70 mg QM and 140 mg QM for the treatment of episodic and chronic migraine.

Body weight is the only significant covariate influencing the PK of AMG 334 in adults. This Phase 1 study is meant in part to confirm this finding in the pediatric population. Therefore, dosing in pediatric subjects is planned according to 2 body weight cohorts. Subjects weighing < 40 kg will receive either 35 mg or 70 mg SC AMG 334 and subjects weighing ≥ 40 kg will receive either 70 mg or 140 mg SC AMG 334. Treatments will be allocated to qualifying subjects within either cohort in a randomized fashion using IVRS.

The proposed dosing strategy in this study is expected to confirm that the PK profile of equivalent doses of AMG 334 in either cohort of pediatric subjects of both age categories combined (ie, 35 or 70 mg for subjects weighing < 40 kg, and 70 or 140 mg for those weighing ≥ 40 kg, respectively) is similar to that previously established in adults receiving either 70 mg or 140 mg. Body weights of the younger age group are expected to be roughly 50% of the older age group, the latter of which overlaps with adult body weights according to the US Centers for Disease Control (CDC NHANES 2009-2010). Children with a body weight < 18 kg are excluded from this study. The fifth percentile of body weight in 6-year old males is 19.5 kg and in 6-year old females is 18.4 kg, thus the body weight range in this study encompasses the 6-year old population (Diamond McDowell et al, 2008).

2.5 Clinical Hypotheses

Multiple SC 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.

3. EXPERIMENTAL PLAN

3.1 Study Design

The overall study design is described in the Study Design and Treatment Schema at the end of the protocol synopsis.

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 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 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 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 receive a dose of either 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 either 70 mg or 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) as described in the Schedule of Activities (Table 1 and Table 2). 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.

3.2 Number of Sites

The study will be conducted at approximately 16 sites within the United States. If a site does not enroll subjects within 3 months of site initiation, the site may be closed.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”.
A total of at least **52** subjects and up to approximately 60 subjects with migraine will be enrolled in Cohorts 1 and 2, with at least **12** subjects and up to approximately 22 subjects enrolled into Cohort 1 (< 40 kg) and at least 35 subjects and up to approximately 38 subjects enrolled into Cohort 2 (≥ 40 kg). The number of subjects enrolled into Cohort 1 and Cohort 2 are considered sufficient in order to collect appropriate PK data and preliminary safety data able to support the initiation of the AMG 334 pediatric Phase 3 safety and efficacy studies. This includes an anticipated rate of early discontinuations up to 20% over the first 12 weeks, which is expected to be similar across the two cohorts.

3.4 Replacement of Subjects

Subjects who are withdrawn or removed from treatment or the study may be replaced by another subject in the same body weight cohort at the discretion of the Amgen Medical Monitor in consultation with the Principal Investigator.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

The estimated study duration for subjects completing only the initial 12 week treatment phase is up to 27 weeks, and includes:

- Up to 3 weeks for screening
- 12 week treatment phase
- 12 week safety follow-up phase (16 weeks after the last dose of AMG 334)

The estimated study duration for subjects completing the initial 12 week treatment phase and the optional 40-week extension phase is up to 67 weeks, and includes

- Up to 3 weeks for screening
- 12 week treatment phase
- Optional 40-week extension phase
- 12 week safety follow-up phase (16 weeks after the last dose of AMG 334)

3.5.2 End of Study

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis (ie, when the last subject completes the 12 Week assessment or is discontinued from the study).

End of Study: 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 16 weeks after the last dose of Investigational Product, or is discontinued from the study for other reasons described in Section 8).

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion date will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain pre-screening and screening logs of all potential study candidates which includes limited information about the potential candidate (eg, date of screening).

Before any study-specific activities/procedure, the appropriate written informed consent and subject assent must be obtained. In addition to written informed consent from a

legally acceptable representative, the assent of the child must also be obtained as appropriate to the age of the subject and/or based on local regulations.
(see Section 11.1).

4.1 Inclusion Criteria

101. Subject's legally acceptable representative has provided informed consent and the subject has provided written assent based on local regulations and/or guidelines prior to any study-specific activities/procedures being initiated.
102. Male and female children and adolescents 6 and < 18 years of age at time of consent
103. Body weight ≥ 18 kg upon entry into screening
104. History of migraines, with or without aura, according to the ICHD-III for at least 12 months prior to the study screening
105. Frequency of ≥ 4 migraine days per month in each of the 3 months prior to the study screening period
106. Physical and neurological examinations, clinical laboratory values, and 12-lead ECGs are clinically acceptable to the investigator and Amgen medical monitor at screening

4.2 Exclusion Criteria

201. Currently receiving treatment in another investigational device or drug study, or less than 30 days (small molecules), 90 days (biologic agents), or 5 half-lives (whichever is longer) since ending treatment on another investigational device or drug study(s). Other investigational procedures while participating in this study are excluded.
202. Use of more than 2 migraine prophylactic medications within 1 month prior to Study Day 1 (see Section 6.4).
203. Taken opioid or butalbital-containing analgesics on ≥ 4 days per month for any indication in either month during the 2 months prior to screening
204. History of migraine with brainstem aura or hemiplegic migraine headache
205. Medical history or other condition that compromises the ability of the subject or legally acceptable representative to give appropriate informed consent and/or assent
206. Malignancy except non-melanoma skin cancers or cervical cancer in situ within the last 5 years.
207. History of hypertension

208. History of chronic or frequent clinically significant painful condition other than migraine
209. History of chronic anemia
210. Uncontrolled asthma or uncontrolled diabetes
211. Vaccinations within 1 month of Study Day 1
212. Major surgery within 6 months of Study Day 1
213. Hospitalization > 24 hours within 28 days of Study Day 1
214. Abnormal hepatic function: ALT or AST ≥ 2.0 times the upper limit of normal (ULN) for the age range, confirmed by repeated measure
215. Abnormal renal function: creatinine ≥ 1.5 times the ULN for the age range, confirmed by repeated measure
216. Known positive results for Human Immunodeficiency Virus (HIV)
217. Positive Hepatitis B Surface Antigen (HepBsAg), Hepatitis B Core Antibody (HepBc Ab) (indicative of chronic Hepatitis B) or detectable hepatitis C virus Ribonucleic acid (RNA) by Polymerase Chain Reaction (PCR) (indicative of active Hepatitis C – screening is generally done by Hepatitis C Antibody (HepCAb), followed by hepatitis C virus RNA by PCR if HepCAb is positive)
218. Subject has known hypersensitivity or known allergy to any of the products to be administered during dosing
219. Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge
220. Subject was previously enrolled in this study
221. Females of reproductive potential who are unwilling to practice an acceptable method(s) of effective birth control while on study through 16 weeks after receiving the last dose of study drug. Acceptable methods of effective birth control includes sexual abstinence (male, female), hormonal birth control, or intrauterine devices (IUDs). Barrier methods are acceptable if a condom with spermicide (male) is used in combination with diaphragm, cervical cap, or cervical sponge (female). Reproductive potential is defined as a female who has had at least one menstrual period, regardless of age
222. Female who is breastfeeding or who plans to breastfeed while on study through 16 weeks after receiving the last dose of study drug

223. Female of reproductive potential with a positive pregnancy test. Reproductive potential is defined as a female who has had at least one menstrual period, regardless of age
224. Female subject planning to become pregnant during study through 16 weeks after receiving the last dose of study drug
225. Male subjects with pregnant partners or whose partners plan to become pregnant during the study
226. Positive illicit drug and/or alcohol test at screening
227. Known substance abuse (eg alcohol, cannabis, illicit drugs) within 12 months of screening
228. Inability, or unwillingness, to refrain from alcohol consumption during study participation
229. Subject has moderate or severe depression based on: a total score of > 11 on the Patient Health Questionnaire modified for adolescents (PHQ-A) or investigator's clinical judgment for children (Refer to Section 7.2.11)
230. Subject has a history or evidence of suicidal ideation (endorsing item 4 or 5) or any suicidal behavior based on an assessment with the Columbia Suicide Severity Rating Scale (C-SSRS) at screening or at baseline
231. History or evidence of any other clinically significant disorder, condition or disease that, in the opinion of the investigator or Amgen medical monitor, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion
232. Subject deemed likely to require modification in migraine prophylactic medication during study participation in the opinion of the investigator or Amgen medical monitor

5. SUBJECT ENROLLMENT

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 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

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.

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, assent, and all other subject information and/or recruitment material, if applicable. All legally acceptable representatives must personally sign and date the informed consent form before commencement of study-specific procedures. All subjects must provide appropriate assent before commencement of study-specific procedures. Subjects are considered enrolled once the investigator has confirmed they meet all eligibility criteria.

The Investigator is to document the enrollment decision and date, in the subject's medical record and in/on the enrollment eCRF.

Each subject and/or legal representative who signs the informed consent and assent enters into the screening period for the study and receives a unique subject identification number before any study procedures are performed. The subject identification number will be assigned manually. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. Re-screening of subjects is acceptable upon discussion with and approval by the Amgen Medical Monitor.

The unique study identification number will consist of 11 digits. The first 3 digits will represent the last 3 digits of the protocol number (eg, 172). The next 5 digits will represent the country code and site number (eg, 66003) and will be identical for all subjects at the site. The last three digits will be assigned in sequential order as subjects are screened (eg, 001, 002, 003). The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

5.1 Allocation to Cohort (Initiation of Screening) and Treatment Assignment (Enrollment)

Subjects will be assigned to one of two cohorts based the subject's body weight on Day 1. Enrollment requirements for subjects in Cohort 1 and Cohort 2 will be tracked and administered via IVRS to ensure that the minimum number of subjects in each

cohort is achieved. Requests for initiation of screening procedures will be administered via IVRS.

Randomization will be based on a schedule generated by Amgen before the start of the study and will be centrally executed using the IVRS. Subjects eligible for randomization on Day 1 will receive a unique randomization number, which will be assigned in sequential order in which a subject met eligibility criteria and study staff dialed into IVRS. At no time will the same randomization number be assigned to more than one subject.

Subjects in Cohort 1 (weighing < 40 kg) will be randomized in a 1:2 allocation ratio to low dose (35 mg AMG 334), or high dose (70 mg AMG 334). Subjects in Cohort 2 (weighing ≥ 40 kg) will be randomized in a 1:4 allocation ratio to low dose (70 mg AMG 334), or high dose (140 mg AMG334). The treatment dose assigned and treatment assignment date are to be documented in the subject's medical record.

The treatment dose assigned (low-dose or high-dose of the body-weight cohort AMG 334) will be administered in either cohort in an open-label fashion.

5.2 Calls to Interactive Voice Response System (IVRS)

Sites are to call the IVRS for the following: to enter the subject into the initial screening phase and to randomize an eligible subject into the treatment phase.

6. TREATMENT PROCEDURES

6.1 Classification of Product(s), Medical Device(s), and/or Combination Product(s)

The Amgen Investigational Product used in this study is AMG 334.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of AMG 334.

6.2 Investigational Product

Investigational Product(s) will be administered at the research facility by a qualified staff member. A physician must be available at the time of administration of Investigational Product.

6.2.1 AMG 334

AMG 334 will be manufactured and packaged by Amgen Inc. The excipients are appropriate for the use in children, thus obviating the need for development of a separate pediatric formulation. AMG 334 will be packaged in prefilled syringes containing either 1 mL of 70 mg/mL AMG 334 or 1 mL of 140 mg/mL AMG 334.

AMG 334 will also be packaged in 3 mL clear glass vials containing 1 mL of 70 mg/mL AMG 334.

6.2.1.1 Dosage, Administration, and Schedule

A qualified staff member will administer the appropriate dose and number of AMG 334 injections into the abdomen, the upper arm or the upper thigh, the 3 anatomical sites for administration of Investigational Product. For subjects weighing < 40 kg at baseline (Cohort 1), one injection of either 35 mg (0.5 mL) or 70 mg (1 mL) will be administered. For subjects weighing ≥ 40 kg at baseline (Cohort 2) one injection of either 70 mg (1 mL) or 140 mg (1 mL) will be administered.

Subjects in either cohort will be randomly assigned to one of two Investigational Product dose levels; doses are fixed and will not be adjusted for individual subjects during the study. The anatomical sites for administration of Investigational Product are the upper arm, upper thigh, or abdomen.

All subjects in this study will be administered AMG 334 against a background of allowed concomitant medications, including agents for migraine prevention.

AMG 334 will be administered Q4W on Study Day 1, and on Study Days 29 (± 3 days) and 57 (± 3 days). Adolescent subjects will have the option to participate in the optional 40-week extension phase, receiving IP as noted in the Schedule of Activities (Table 1 and Table 2), at the dose they received during the initial 12 Week treatment phase regardless of any changes in weight that might occur during the study. All subjects will be monitored on site 2 hours post-dose on Day 1 for any acute reactions that might occur. All subjects will be monitored on site for 30 minutes post-dose on Days 29 and 57. The post-dose safety monitoring will be extended for 2 hours if the subject shows any safety concerns post-dose during the last dosing visit. The date, time, injection location, volume (full, partial, or none), and lot number of each treatment will be recorded in the subject's source documents and on the appropriate eCRF. The effects of overdose of AMG 334 are not known. All overdose occurrences must be documented and corresponding adverse events must be recorded on the appropriate eCRF and in the source documents.

The study may be terminated at any point in time at the discretion of the sponsor. Subjects who permanently discontinue IP during the initial 12 week treatment phase will have the EOS/Week 12 visit assessments performed and will then return for the safety follow-up visit 16 weeks after the last dose of Investigational Product. Subjects who

permanently discontinue IP during the 40-week extension phase will have the EOS/Week 52 visit assessments performed and then will return for the safety follow-up visit 16 weeks after the last dose of Investigational Product.

6.2.2 Medical Devices

The following investigational combination product or medical device provided by Amgen for use in this study is the pre-filled syringe.

The AMG 334 pre-filled syringe is a single-use, disposable, handheld manual injection device for fixed dose SC injection of [1 mL of 70 mg/mL] deliverable volume.

Additional details are provided in the IPIM.

Other non-investigational medical devices may be used in the conduct of this study as part of standard care.

Non-investigational Non-Amgen medical devices (eg, syringes, sterile needles), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

6.3 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (eg, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBIL]) or international normalized ratio [INR]) or signs/symptoms of hepatitis may meet the criteria for discontinuation of Investigational Product depending upon the clinical circumstances discussed below (as specified in the FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009).

6.3.1 Criteria for Permanent Withholding of AMG 334 due to Potential Hepatotoxicity

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR, and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or TBIL values include, but are not limited to:

- Hepatobiliary tract disease
- Viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, toxoplasmosis, and Parvovirus)

- Right-sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic Fatty Liver Disease including Steatohepatitis
- Non-hepatic causes (eg, rhabdomylosis, hemolysis)

Amgen Investigational Product and other protocol-required therapies, as appropriate, should be withheld pending investigation into alternative causes of Drug Induced Liver Injury (DILI). If Investigational Product(s) is/are withheld, the subject is to be followed for possible DILI. Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBIL, is discovered and the laboratory abnormalities resolve to normal or baseline. Permanent discontinuation of Investigational Product is recommended if all of the following apply:

- TBL > 2 x ULN or INR > 1.5
- AND increased AST or ALT from the relevant baseline value as specified below:

Baseline AST or ALT value	AST or ALT elevation
< ULN	> 3 x ULN

- AND no other cause for the combination of the above laboratory abnormalities is immediately apparent (eg, hepatobiliary tract disease, viral hepatitis, right-sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia, etc.)

Conditional withholding of investigational medicinal product or other protocol-required therapies is recommended if all of the following apply:

- Elevation of either AST or ALT according to the following schedule:

Baseline AST or ALT value	AST or ALT elevation
Any	> 8 x ULN at any time
Any	> 5 x ULN but < 8 x ULN for ≥ 2 weeks
Any	> 5 x ULN but < 8 x ULN and unable to adhere to enhanced monitoring schedule
Any	> 3 x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice).

- OR: TBIL > 3 x ULN at any time
- OR: ALP > 8 x ULN at any time

6.4 Concomitant Therapy

Throughout the study, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.7.

All appropriate concomitant medications taken by a subject while on study are to be collected (therapy name, indication, dose, unit, frequency, start and stop dates).

The subject may use up to 2 of the following medications with possible migraine prophylactic effects. Doses must be stable within 1 month prior to the Day 1 visit and throughout the study. Use of more than 2 of the following medications is prohibited within 1 month prior to the Day 1 visit and throughout the study.

- Divalproex sodium, sodium valproate, topiramate, carbamazepine, gabapentin
- Beta blockers (for example: atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol)
- Tricyclic antidepressants (for example: amitriptyline, nortriptyline, protriptyline)
- Venlafaxine, desvenlafaxine, duloxetine, milnacipran
- Flunarizine, verapamil, lomerizine
- Lisinopril, candesartan
- Clonidine, guanfacine
- Cyproheptadine

- Methysergide
- Pizotifen
- Butterbur, feverfew, magnesium (≥ 9 mg/kg/day), riboflavin (≥ 25 mg/day)
- Botulinum toxin

6.5 Alcohol and Drug Restrictions

Subject must refrain from alcohol consumption and cannabis use throughout the study.

6.6 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug**, combination product,** or device after it is released for distribution to market or clinic by either **(1)** Amgen or **(2)** distributors **or** partners for whom Amgen manufactures the material. **This includes all components distributed with the drug, such as packaging drug containers, delivery systems, labeling, and inserts.**

This includes any **investigational/non-investigational product(s),** device(s) or combination product(s) provisioned and/or repackaged/modified by Amgen: **AMG 334.**

Any product complaint(s) associated with an **investigational product(s),** non-investigational **products(s), devices(s), or combination** product(s) supplied by Amgen are to be reported.

6.7 Excluded Treatments, Medical Device Use, and/or Procedures During Study Period

Medication excluded in the eligibility criteria (Section 4) are excluded for the duration of the study with the exception of vaccinations which are allowed after the completion of Day 85 assessments. Any other exceptions (eg, medication given for the treatment of an adverse event) should be first discussed with Amgen.

7. STUDY PROCEDURES

7.1 Schedule of Activities

For Schedule of Activities refer to (Table 1 and Table 2). Refer to the applicable supplemental laboratory and electrocardiogram manuals for detailed collection and handling procedures.

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 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 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.

Table 1. Schedule of Activities

Study Day[g]	**-21 to -2**	**1**				**8**	**15**	**29**			**57**			**64**	**71**	**85**	**169**
Time (in hours)[a]		Pre-Dose	0	0.5	2			Pre-Dose	0	0.5[j]	Pre-Dose	0	0.5[j]				
General & Safety Assessments																	
Informed Consent	X																
Medical History	X																
Body Weight[i]	X	X						X			X					X	X
Height[c]	X																X
Vital Signs (BP, HR, TEMP)	X	X		X	X	X		X		X	X		X	X		X	X
Physical Examination	X	X			X	X		X		X	X		X	X		X	X
Neurological Examination	X	X				X		X			X			X		X	
12-Lead Electrocardiogram	X	X			X	X		X		X	X		X	X		X	
Serious Adverse Event Assessment: Collection/Recording/Reporting	X	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Adverse Event Assessment: Collection/Recording/Reporting			←	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Adverse Device Effect Assessment: Collection/Recording/Reporting			←	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Concomitant Medications	X	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Laboratory Assessments																	
Clinical Chemistry	X						X				X					X	X
Clinical Hematology	X						X				X					X	X
Estimated Creatinine Clearance	X																
Urinalysis	X						X				X					X	X
Drug and Alcohol Screening[k]	X	X															X
Hep C Ab, HepBc Ab, HbsAg	X																
Pregnancy Test[b]	X	X						X			X					X	X

Footnotes defined on next page of the table

Table 1. Schedule of Activities

Study Day[g]	**-21 to -2**	**1**				**8**	**15**	**29**			**57**			**64**	**71**	**85**	**169**
Time (in hours)[a]		Pre-Dose	0	0.5	2			Pre-Dose	0	0.5[j]	Pre-Dose	0	0.5[j]				
Questionairres																	
Pediatric PHQ-A[l]	X																
[redacted]																	
Dosing																	
Study Drug Administration[c h]			X						X			X					
Collect blood for biomarker development		X															X
Other																	
Pharmacogenetics (optional)[d]		X															
[redacted]																	
AMG 334 Serum PK Collection [e f]		X				X	X	X			X			X	X	X	X

Footnotes defined on next page of the table

Abbreviations: BP = blood pressure; ECG = electrocardiogram; ET = Early Termination; HepBc Ab = hepatitis B core antibody; HBSAg – hepatitis B surface antigen; HepC Ab = hepatitis C antibody; HR = heart rate; PK = pharmacokinetic; Pre = pre-dose

[a] All time in hours are relative to AMG 334 administration

[b] Females of reproductive potential only. A serum pregnancy test will be performed at screening At all other time points a urine pregnancy test will be performed, all performed pre-dose. Female subjects who experience menarche while they are followed in the study will be subject to the pregnancy test as specified in the Schedule of Activities starting with the next scheduled assessment following their first menstrual period.

[c] Allowable injection sites: upper arm, thigh, abdomen (See Investigational Product Instruction Manual)

[d] For subjects who provided informed consent/assent for the pharmacogenetic studies, DNA will be obtained from the cell pellet collected in the plasma tube used for the biomarker development sample. Therefore, additional sampling is not required.

[e] Samples for PK assessment will be serum

[f] PK samples must be collected prior to administering AMG 334

[g] A subject who discontinues the study during the initial 12 Week treatment phase, or chooses not to continue with the optional 40-week extension, will complete the Week 12 visit outlined in Table 1 and the safety follow-up visit 16 weeks after the last dose of IP as outlined in Table 1. A subject who continues with the optional 40- week extension will complete the Week 12 visit outlined in Table 2. A subject who discontinues IP or the study during the optional 40-week extension will complete the Week 52 visit and the safety follow-up visit 16 weeks after the last dose of Investigational Product as outlined in Table 2.

[h] Dose will be based on body weight collected pre-dose on Day 1.

[i] Weight measured in kilograms to the nearest decimal fraction.

[j] The post dose safety monitoring will be extended to 2 hours if they subject showed any safety concerns post-dose during the last dosing visit

[k] Drug and alcohol testing will occur based on the Investigator's discretion for children in Cohort 1 (See Section 7.2.15)

[l] Pediatric PHQ-A for adolescent subjects only ((See Section 7.2.11 and Section 7.2.15)

Table 2. Schedule of Activities

Activity	Optional 40-Week Open-Label Extension Phase (40 Weeks)											Safety F/U
Study Week	12	16	20	24	28	32	36	40	44	48	52 or ET[f]	16 Weeks after last Dose of IP[f]
Study Day[a]	85	113	141	169	197	225	253	281	309	337	365	449
General & Safety Assessments												
Informed Consent	X											
Body Weight[g]	X			X			X			X		X
Height												X
Vital Signs (BP, HR, TEMP)	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X
Neurological Examination											X	
Serious Adverse Event Assessment: Collection/Recording/Reporting	←	—	—	—	—	—	—	—	—	—	—	→
Adverse Event Assessment: Collection/Recording/Recording	←	—	—	—	—	—	—	—	—	—	—	→
Adverse Device Effect Assessment: Collection/Recording/Reporting	←	—	—	—	—	—	—	—	—	—	—	→
Concomitant Medications	←	—	—	—	—	—	—	—	—	—	—	→
Laboratory Assessments												
Clinical Chemistry	X						X					X
Clinical Hematology	X						X					X
Urinalysis	X						X					X
Drug and Alcohol Screening												X
Pregnancy Test[b]	X	X	X	X	X	X	X	X	X	X	X	X
Questionairres												
[redacted]												
Dosing												
Study Drug Administration[c]	X	X	X	X	X	X	X	X	X	X		
Collect blood for biomarker development												X

Footnotes defined on last page of the table

Table 2. Schedule of Activities

Activity	Optional 40-Week Open-Label Extension Phase (40 Weeks)											Safety F/U
Study Week	12	16	20	24	28	32	36	40	44	48	52 or ET[f]	16 Weeks after last Dose of IP[f]
Study Day[a]	85	113	141	169	197	225	253	281	309	337	365	449
Other												
AMG 334 Serum PK Collection[d e]	X	X		X			X				X	X

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Abbreviations: BP = blood pressure; ECG = electrocardiogram; ET = Early Termination; HepBc Ab = hepatitis B core antibody; HBSAg – hepatitis B surface antigen; HepC Ab = hepatitis C antibody; HR = heart rate; PK = pharmacokinetic; Pre = pre-dose

[a] Each dosing visit during the optional 40-week extension has a visit window of ± 4 days.

[b] Females of reproductive potential only. A serum pregnancy test will be performed at screening At all other time points a urine pregnancy test will be performed, all performed pre-dose. Female subjects who experience menarche while they are followed in the study will be subject to the pregnancy test as specified in the Schedule of Activities starting with the next scheduled assessment following their first menstrual period.

[c] Allowable injection sites: upper arm, thigh, abdomen (See Investigational Product Instruction Manual)

[d] Samples for PK assessment will be serum

[e] PK samples must be collected prior to administering AMG 334.

[f] A subject who discontinues the study during the initial 12 Week treatment phase, or chooses not to continue with the optional 40-week extension, will complete the Week 12 visit outlined in Table 1 and the safety follow-up visit 16 weeks after the last dose of IP as outlined in Table 1. A subject who continues with the optional 40- week extension will complete the Week 12 visit outlined in Table 2. A subject who discontinues IP or the study during the optional 40-week extension will complete the Week 52 visit and the safety follow-up visit 16 weeks after the last dose of Investigational Product as outlined in Table 2.

[g] Weight measured in kilograms to the nearest decimal fraction

7.2 General Study Procedures

A signed and dated IRB/IEC-approved informed consent and appropriate subject assent must be obtained before any study-specific procedures are performed. All subjects will be screened for eligibility before enrollment. Only eligible subjects will be enrolled into the study.

During the study, every effort should be made to perform study procedures as indicated in Schedule of Activities (Table 1 and Table 2). Additional procedures deemed necessary as part of standard of care or as required by local laws and regulations may be performed at the investigator's discretion. Throughout the study, with the exception of the PK sample collections, the permitted time windows for scheduled assessments will be as follows:

- ± 12 hours for Day 1 visit
- Each study visit during the initial 12 week treatment phase and safety follow-up (except Day 1) has a window ± 3 days
- Each study visit during the optional 40-week extension phase has a window of ± 4 days

Laboratory Assessments

For a complete listing of laboratory test panels and analytes collected, please refer to Section 7.2.4.

Repeat Assessments and Rescreening.

Vital signs, ECGs, laboratory assessments, as well as drug and alcohol testing can be repeated during screening. Whether a subject has failed screening after repeat assessment will be decided on a case-by-case basis at the discretion of the Principal Investigator.

Investigators may re-screen a subject if the investigator is reasonably certain that reasons for screen failure will be resolved prior to or during a repeat screening attempt. Reasons to re-screen may include but are not limited to the following:

- Laboratory value(s) out of range due to sampling error or that might be within range after medically-appropriate supplementation.
- The subject has a medical condition that can be stabilized or resolved prior to the repeat screening attempt.
- Additional time is required following the subject's last dose of an excluded medication.

The decision to rescreen a subject will be made on a case-by-case basis at the discretion of the Amgen Medical Monitor in consultation with the Principal Investigator.

7.2.1 Informed Consent

A signed informed consent and appropriate subject assent must be obtained from each subject prior to any study mandated procedures.

7.2.2 Medical History

The Investigator or designee will collect a complete medical, psychiatric and surgical history that started within 21 days prior to enrollment through enrollment. Medical history will include information on the subject's concurrent medical conditions. A detailed history of prior and/or concurrent use of alcohol, tobacco, and other drug use will be obtained. All findings will be reported on the medical history eCRF.

7.2.3 Height and Weight Measurements

Height in centimeters should be measured without shoes. Weight in kilograms, to the nearest decimal fraction should be measured without shoes.

7.2.4 Vital Signs

The following measurements must be performed: Systolic/Diastolic Blood Pressure, Heart Rate, and Temperature. Subject must be in a supine position in a rested and calm state, back supported, and arm at heart level for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign eCRF. In children, blood pressure should be taken in the right arm, as normative values are obtained in the right arm. Finally, the cuff size should be appropriate for the subject's arm. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs eCRF. Record all measurements on the vital signs eCRF.

7.2.5 Physical Examination

Physical examination will be completed as per standard of care. The Investigator or qualified designee will perform a complete physical examination (excluding breast, genital, and rectal examination) at time points specified in the Schedule of Assessment (Table 1 and Table 2). Abnormal measurements may be repeated at the discretion of the Investigator.

7.2.6 Neurological Examination

Neurological examination will be completed as per standard of care. Neurological examination findings should be recorded on the appropriate eCRF.

7.2.7 Electrocardiogram

Subject must be in supine position in a rested and calm state for at least 5 minutes before 12-lead ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible.
A single 12-lead ECG will be performed at time points designated in the Schedule of Activities (Table 1 and Table 2). Data will be reported on the CRF. The ECG must include the following measurements: Heart Rate, QRS, QTc, and PR intervals.
Standard ECG machines should be used for all study-related ECG requirements. The PI or designated site physician will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen.

7.2.8 Drug and Alcohol Screening

A urine screen for drugs with a high potential of abuse will be performed at time points specified in the Schedule of Activities (Table 1 and Table 2). Breath ethanol screens will be performed at time points specified in the Schedule of Activities (Table 1 and Table 2). Subjects with a positive drug test at screening may be retested once at the discretion of the investigator. Subjects with a positive test for alcohol at screening will be asked to refrain from drinking alcohol for 24 hours prior to dosing on Day 1. Subjects who test positive at Day 1 for drugs and alcohol, will not qualify for Investigational Product administration and will be withdrawn from study participation. Drug and alcohol testing will occur based on the Investigator's discretion for children in Cohort 1 (See Section 7.2.15).

7.2.9 Hepatitis B Surface Antigen, Hepatitis C Antibody Status

HBs Ag, and HepC Ab titers will be assessed as specified in the Schedule of Activities (Table 1 and Table 2). The result must be negative and will be documented in the source document but will not be recorded on the eCRF. If Hepatitis B and/or Hepatitis C status is not known to be positive by serology,the following laboratory testing is required:

- Hepatitis B Surface Antigen (HepBsAg) and total Hepatitis B Core Antibody (HepBcAb)
    - If results are HepBcAb positive or HepBsAg positive, no additional testing is necessary as subject meets exclusion criteria.
- Hepatitis C virus antibody
    - If results are Hepatitis C virus antibody positive, no additional testing is necessary as subject meets exclusion criteria

7.2.10 Pregnancy Test

All female subjects of reproductive potential will have a serum pregnancy test performed at screening and a urine pregnancy test performed pre-dose at all dosing visits as specified in the Schedule of Activities (Table 1 and Table 2). Subjects of reproductive potential with a positive result at screening or Day 1 will be excluded from the study. Female subjects who experience menarche while they are followed in the study will be subject to the pregnancy testing as specified in the Schedule of Activities (Table 1 and Table 2) starting with the next scheduled assessment following their first menstrual period.

7.2.11 Patient Health Questionnaire– Adolescents (PHQ-A)

The PHQ-A is a 9-item questionnaire that assesses the severity of depression by evaluating each of the 9 DSM-IV criteria for depression validated in adolescent patients. Each item is scored as “0” (not at all) to “3” (nearly every day). The total score is categorized into 4 severity grades: none (0-4), mild depression (5-9), moderate depression (10-14), moderately severe depression (15-19), and severe depression (20-27). The PHQ-A is intended to be self-administered by the subject and their parent. It can be completed in collaboration, but the answers need to be confirmed with the subject. The PHQ-A should be administered to adolescent subjects only.

[redacted]

7.2.14 Blood and Urine Assessments

Table 3. Approximate Blood Volumes for Cohorts 1-2 in Initial 12 Week Treatment Phase

Test	Volume (mL) per Collection	Approximate Number of Collections	Approximate Total Volume (mL)
Chemistry and Hematology	8	5	40
Hep C Ab, HepBc Ab, HBsAg	3.5	1	3.5
Serum Pregnancy (female subjects of reproductive potential only)	5	1	5
Blood sample for PK	0.5	8	4
[redacted]			
Optional Blood sample for pharmacogenetics	Cell Pellet from Biomarker Plasma	1	0
Biomarker Development			
Serum	5	2	10
Plasma	5	2	10
Plasma CGRP	6	2	12
Total blood volume collected during the initial 12 week treatment phase (does not include safety follow-up)			87

Table 4. Approximate Blood Volumes for Optional 40-Week Extension Phase

Test	Volume (mL) per Collection	Approximate Number of Collections	Approximate Total Volume (mL)
Chemistry and Hematology	8	3	24
Blood sample for PK	0.5	6	3
[redacted]			
Total blood volume collected during the optional 40-week extension phase			30
Total blood volume collected during the initial 12 week treatment phase			79
Total blood volume collected during both the initial 12 week treatment phase and the optional 40-week extension phase (includes safety follow-up)			109

7.2.14.1 Pharmacokinetic Blood Sampling

Blood samples for PK testing are to be collected for the measurement of pharmacokinetic concentrations as stated in the Schedule of Activities (Table 1 and Table 2.).

For PK serum collection, the permitted window for scheduled collection time points will be as follows:

- Pre-Dose samples on Day 1, Day 29, and Day 57 must be taken within 1 hour prior to dosing
- ± 3 days for Days 8, 15, 64, 71, and 85 (initial 12 week treatment phase)
- ± 4 days for Days 85, 113, 169, 253, 365, and 449 (optional 40-week extension phase)

7.2.14.2 Clinical Laboratory Assessments

The laboratory analytes listed in (Table 5) will be assessed at time points designated in Schedule of Activities (Table 1 and Table 2.).

Table 5. List of Analytes

Local Laboratory Chemistry	Local Laboratory Hematology	Local Laboratory Urinalysis	Other
Sodium Potassium Chloride Bicarbonate (CO2 or HCO3) Total protein Albumin Glucose Blood urea nitrogen Creatinine** Total creatine kinase Total bilirubin Direct bilirubin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase	Hemoglobin Hematocrit Mean corpuscular volume Platelets White blood cell Differential • Total neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes	Specific gravity pH Blood Protein Glucose Bilirubin Microscopic exam (performed at the discretion of the Investigator)	Local Laboratory: • Serum Pregnancy* • Urine Pregnancy* • Urine Drug • Breath Alcohol • Hepatitis B surface antigen • Hepatitis B total core antibody • Hepatitis C antibody Central Laboratory: • Pharmacokinetics [redacted] • Pharmacogenetics (optional)

* Serum and urine pregnancy testing only for female subjects of reproductive potential
** Estimated creatinine clearance derived from serum creatinine, age, weight and gender of subject.

Additional procedures deemed necessary as part of standard of care or as required by local laws and regulations may be performed at the Investigator's discretion.

7.2.15 Screening and Enrollment

The following procedures are to be completed during the screening period at time points designated in the Schedule of Activities (Table 1 and Table 2.).

- Confirmation that the Informed Consent Form and Assent form have been signed
- Demographic data including sex, age, race, and ethnicity will be collected in order to explore their possible association with subject safety and treatment effectiveness. Additionally demographic data will be used to study the impact pharmacokinetics of the protocol-required therapies
- Physical Examination as per standard of care
- Neurological Examination
- Medical and Surgical History
- Single 12-Lead ECG
- Height and Weight
- Vital signs (eg, blood pressure, heart rate temperature)

- Laboratory Assessments:
  - Chemistry Panel
  - Hematology Panel
  - Urinalysis
  - Estimated Creatinine Clearance
  - Serum Pregnancy Test (female subjects of reproductive potential)
  - Drug and Alcohol screen (adolescents only; at Investigator's discretion for children)
  - Hepatitis serology testing
- Serious Adverse Event reporting
- Documentation of concomitant and rescue medications
- Patient Health Questionnaire (PHQ-A) (adolescents only)

[redacted]

Subjects who fail screening may be re-screened upon discussion with and approval by the Amgen Medical Monitor. A new informed consent and assent form must be signed unless it has been < 21 days since the previous ICF and assent signature was obtained.

7.2.16 Initial 12 Week Treatment Phase Visits

The following procedures will be completed during the 12 week treatment phase at the times designated in the Schedule of Activities (Table 1 and Table 2.). All visits during this phase, except Day 1 are ± 3 days.

- Body weight pre-dose
- Neurological exam pre-dose
- Vital signs (eg, blood pressure, heart rate, temperature) pre-dose and 30 minutes post-dose; also 2 hours post-dose on Day 1 only.
- Physical examination pre-dose and 30 minutes post-dose.; also 2 hours post-dose on Day 1 only.
- Single 12-Lead ECG pre-dose and 2 hours post-dose on Day 1 only.
- Laboratory Assessments:
  - Chemistry Panel
  - Hematology Panel
  - Urinalysis
  - Urine Pregnancy Test (female subjects of reproductive potential)
  - Drug and Alcohol Screen

- Serious Adverse Event reporting
- Adverse Event reporting

[redacted]

- Modified PedMIDAS pre-dose
- Documentation of concomitant and headache rescue medications.
- Collect blood for biomarker development pre-dose
- Pharmacogenetics (optional) pre-dose

[redacted]

- AMG 334 serum PK collection pre-dose
- Study drug administration (dose will be based on pre-dose body weight collected on Day 1)
- Following the AMG 334 dose administration at Day 1, all subjects will be monitored at the facility for at least 2 hours post-dose, at which point they will be discharged with instructions to return to the research facility according to the procedures provided in the Schedule of Activities (Table 1 and Table 2.). Following the AMG 334 dose administration on Days 29 and 57, all subjects will be monitored at the facility for at least 30 minutes post-dose. The post dose safety monitoring will be extended to 2 hours if the subject showed any safety concerns post-dose during the last dosing visit.

7.2.17 Optional 40-Week Extension Phase

The following procedures will be completed during the optional 40-week extension phase, for adolescents who choose to continue treatment, at the times designated in the Schedule of Activities (Table 1 and Table 2.). All visits during this phase are ± 4 days of the scheduled time point. Children 6 to < 12 years of age will not be offered the option to enter the optional 40-week extension phase.

- Confirmation that the Informed Consent Form Appendix A has been signed
- Body weight (pre-dose)
- Vital signs (eg, blood pressure, heart rate, temperature) (pre-dose)
- Physical examination (pre-dose)
- Laboratory Assessments:
  - Chemistry Panel
  - Hematology Panel
  - Urinalysis
  - Urine Pregnancy Test pre-dose (female subjects of reproductive potential)
- Serious Adverse Event reporting
- Adverse Event reporting

- Adverse Device Effect reporting

[redacted]

- Documentation of concomitant and headache rescue medications

[redacted]

- AMG 334 serum PK Sample (pre-dose)

7.2.18 End of Study Visit

All Subjects will be followed for 16 weeks after the last administration of AMG 334.

The following procedures will be completed during the final visit (Study Day 169, early termination or Day 449, if subject continued in the optional 40-week extension phase).

- Physical Examination as per standard of care
- Single 12-Lead ECG
- Height and Weight Measurements
- Vital signs (eg, blood pressure, heart rate, temperature)
- Laboratory Assessments:
  - Chemistry Panel
  - Hematology Panel
  - Urinalysis
  - Urine Pregnancy Test (female subjects of reproductive potential)
  - Drug and Alcohol Screen

[redacted]

- AMG 334 serum PK Sample
- Serious Adverse Event reporting
- Adverse Event reporting
- Adverse Device Effect reporting
- Documentation of concomitant and rescue medications

[redacted]

7.4 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Biomarker development can be useful in developing markers to identify disease subtypes, guide therapy, and/or predict disease severity. Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to AMG 334.

Blood (plasma and serum) samples will be collected for biomarker development on Day 1 and at the EOS visit (Day 169 or Day 449 if completing the optional 40-week extension) or Early Termination. Amgen may attempt to develop blood tests designed to identify subjects most likely to respond positively or negatively to AMG 334.

Biomarker development may be pursued by use of advanced biochemical analyses such as proteomic methods. Refer to the laboratory manual for detailed collection and handling procedures for all biomarker development samples.

7.5 Pharmacogenetic Studies

If the subject (or legally acceptable representative) consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of migraine and/or to identify subjects who may have positive or negative response to AMG 334. No additional samples are collected for this part of the study. For subjects who consent to this/these analysis/analyses, DNA may be extracted.

7.6 Sample Storage and Destruction

Any blood or PK samples collected according to the Schedule of Activities (Table 1 and Table 2.) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject (or legally acceptable representative), Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand migraine prevention the dose response and/or prediction of response to AMG 334 and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetics or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject (or legally acceptable representative) retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject (or legally acceptable representative), the Investigator is to provide the

sponsor with the required study and subject number so that any remaining blood samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The Sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the Investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the Sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.

See Section 11.4 for subject confidentiality.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution. Subjects (or a legally acceptable representative) can decline to continue receiving Investigational Product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the Investigator is to discuss with the subject the appropriate processes for discontinuation from Investigational Product, device or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Activities (Table 1 and Table 2.) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events. Subjects who have discontinued Investigational Product and/or protocol required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data. The Investigator must document the level of follow-up that is agreed to by the subject. Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent

will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent. The Investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

8.2 Reasons for Removal From Treatment

Reasons for removal from protocol-required Investigational Product(s) or procedural assessments include any of the following:

- subject request
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy, protocol-specified criteria
- pregnancy
- death
- lost to follow-up
- decision by sponsor (other than subject request, safety concern, lost to follow-up)

8.3 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

The Investigator and/or Sponsor can decide to withdraw a subject(s) from Investigational Product, medical device(s), and/or other protocol required therapies, protocol procedures, or the study as a whole at any time prior to study completion.
Subjects may be eligible for continued treatment with Amgen Investigational Product(s) and/or other protocol required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.1.

8.4 Reasons for Removal From Study

- Reasons for removal of a subject from the study are:
- decision by Sponsor
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy, pregnancy)
- withdrawal of consent from study
- death
- lost to follow-up

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The Investigator is responsible for ensuring that any adverse events observed by the Investigator or reported by the subject are recorded in the subject's medical record.
The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration more than would be expected and/or has an association with a significantly worse outcome than expected. A pre-existing condition that has not worsened more than anticipated (eg, more than usual fluctuation of disease) during the study, or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.
The Investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

Adverse Device Effect Definition

An adverse device effect is any adverse event related to the use of a combination product or a medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

9.1.2 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria

- Results in death (fatal)
- life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity

- congenital anomaly/birth defect
- other medically important serious event

An adverse event would meet the criterion of "requires hospitalization", if the event necessitated an admission to a health care facility (eg, overnight stay).
If an Investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event". Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug induced liver injury (DILI) (see Appendix A for DILI reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention

9.2 Safety Event Reporting Procedures

9.2.1 Adverse Events

9.2.1.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

The Investigator is responsible for ensuring that all adverse events observed by the Investigator or reported by the subject that occur after the first dose of investigational product through the end of the safety follow-up visit (16 weeks after the last dose of investigational product) or EOS, whichever occurs **later**, are reported using the Event eCRF.
The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Severity [and/or toxicity per protocol],
- Assessment of relatedness to AMG 334 and/or the Amgen medical device (pre-filled syringe) and/or other protocol-required therapies and/or study mandated procedure/activity], and
- Action taken

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE). The grading scale used in this study is described in Appendix A.

Since the criteria the CTCAE grading scale differs from the regulatory **criteria** for serious adverse events**, if adverse events correspond to grade 4 CTCAE toxicity grading scale criteria (eg, laboratory abnormality reported as grade 4 without manifestation of life-threatening status), it will be** left to the investigator's judgment to **also** report these abnormalities as serious adverse events. **For any adverse event**

that applies to this situation, comprehensive documentation of the event's severity must be recorded in the subject medical records.

The Investigator must assess whether the adverse event is possibly related to the Investigational Product. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product and/or medical device (pre-filled syringe [PFS])?

The investigator must assess whether the adverse event is possibly related to any study-mandated activity (eg, administration of investigational product, protocol-required therapies, device(s) and/or procedure (including any screening procedure(s)). This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity (eg, administration of Investigational Product, protocol-required therapies, device(s)), and/or procedure?"

The Investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

The Investigator is expected to follow reported adverse events until stabilization or reversibility.

9.2.1.2 Reporting Procedures for Serious Adverse Events

The Investigator is responsible for ensuring that all serious adverse events observed by the Investigator or reported by the subject that occur after signing of the informed consent through the end of safety follow-up visit (16 weeks after the last dose of Investigational Product) or EOS, whichever occurs **later**, are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the Investigator's knowledge of the event via the Event eCRF.

If the electronic data capture (EDC) system is unavailable to the site staff to report the serious adverse event, the information is to be reported to Amgen via an electronic

Serious Adverse Event (eSAE) Contingency Report Form within 24 hours of the Investigator's knowledge of the event. See Appendix B for a sample of the Serious Adverse Event Form/electronic Serious Adverse Event Contingency Report Form (which is a paper-based form). For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen via the **electronic** Serious Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

The Investigator must assess whether the serious adverse event is possibly related to the Investigational Product. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the Investigational Product and/or medical device (pre-filled syringe [PFS])? Relatedness means that there are facts or reasons to support a relationship between Investigational Product and the event.

The Investigator must assess whether the serious adverse event is possibly related to any study-mandated activity or procedure. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity/procedure?"

The Investigator is expected to follow reported serious adverse events until stabilization or reversibility.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. The investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the applicable CRF (eg, Event CRF).

If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and institutional review boards (IRBs) / independent ethics committees (IECs) in compliance with all reporting requirements according to local regulations and good clinical practice.

The investigator is to notify the appropriate IRB/IEC of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures and statutes.

9.2.2 Reporting Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to Amgen. In some countries (eg, European Union [EU] member states), Investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the Investigator is to report them to Amgen within 24 hours following the Investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

If further safety-related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study.

9.2.2.1 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

9.2.2.2 Adverse Device Effects: Recording, Evaluating, Reporting

In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of any adverse device effects that occur during the study with such devices (Amgen pre-filled syringe).

All adverse device effects are to be reported as adverse events following the same reporting periods and procedures. The Investigator is responsible for ensuring that all adverse device efforts observed by the Investigator or reported by the subject that occur after first dose of Investigational Product through the end of the safety follow-up visit (16 weeks after the last dose of Investigational Product) or end of study, whichever occurs **later**, are reported using the Event CRF.

Any adverse event resulting from an adverse device effect that occur during the study will be documented in the subject's medical records, in accordance with the Investigator's normal clinical practice, and on the Event CRF page.

It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by Amgen) at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident.

Product complaints are described in Section 6.6 Product Complaints.

9.3 Pregnancy and Lactation Reporting

If a female subject becomes pregnant, or a male subject fathers a child, while the subject is taking AMG 334, report the pregnancy to Amgen Global Patient Safety as specified below.

In addition to reporting any pregnancies occurring during the study, Investigators should report pregnancies that occur through 16 weeks after the last dose of AMG 334.

The pregnancy should be reported to Amgen Global Patient Safety within 24 hours of the Investigator's knowledge of the pregnancy. Report a pregnancy on the Pregnancy Notification Form (Appendix C). Amgen Global Patient Safety will follow-up with the Investigator regarding additional information that may be requested.

If a female subject becomes pregnant during the study, the Investigator should attempt to obtain information regarding the birth outcome and health of the infant.

If the outcome of the pregnancy meets a criterion for immediate classification as a Serious Adverse Event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the Investigator will report the event as a Serious Adverse Event.

If a female breastfeeds while taking protocol-required therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, Investigators should report lactation cases that occur through 16 weeks after the last dose of protocol-required therapies.

Any lactation case should be reported to Amgen Global Patient Safety within 24 hours of the Investigator's knowledge of event. Report a lactation case on the Lactation Notification Form (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a male subject's female partner becomes pregnant, the Investigator should discuss information regarding the birth outcome and health of the infant from the pregnant partner.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

Primary Endpoints:

- 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 ($AUC_{0\text{-}28day}$)
- Treatment-emergent adverse events (AEs)
- Changes in vital signs, 12-lead electrocardiograms (ECGs), clinical laboratory safety tests, and neurological assessments

Exploratory Endpoints:

[redacted]

10.1.2 Analysis Sets

The safety analysis set will consist of all randomized subjects who receive at least one dose of Investigational Product.

10.1.3 Covariates and Subgroups

No subgroup analyses are planned.

10.1.4 Handling of Missing and Incomplete Data

Data will be analyzed as is; no imputation of missing data is planned.

10.2 Sample Size Considerations

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 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 enroll 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 mg/kg basis is similar between pediatric subjects and adults, and assuming %CV 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% 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).

10.3 Planned Analyses

10.3.1 Interim Analyses

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. For both interim analyses, all available data will be cleaned and a database snapshot will occur. PK data, AEs, vital sign data, and laboratory data will be summarized. The purpose of the first and second interim analysis is to inform the selection of AMG 334 doses to be evaluated in the Phase 3 pediatric AMG 334 studies. Results from the interim analyses will be presented to the independent Data Monitoring Committee (DMC) responsible for reviewing and making recommendations regarding the Phase 3 pediatric AMG 334 studies. The DMC will not review individual patient level data from this study or make recommendations regarding this study.

10.3.2 Primary Analysis

The primary analysis of the safety and PK data will occur after all subjects in both body weight cohorts have completed the initial 12 week treatment phase. All available data up to and including the data cutoff date will be cleaned and a database snapshot will occur. No formal hypothesis testing will be performed; all analyses will be descriptive. The review of the results of this primary analysis will inform on further pediatric studies utilizing AMG 334.

10.3.3 Final Safety Analysis

The final safety analysis for the study will be performed at the end of the trial. All data will be cleaned and a database lock will occur. No formal hypothesis testing will be performed; all analyses will be descriptive. Safety data will include summaries by body weight and AMG 334 treatment dosage group. Final Safety Analysis activities are commenced based on achieving the End of Trial milestone described in Section 3.5.2.

10.4 Planned Methods of Analysis

10.4.1 General Considerations

No formal hypothesis testing will be performed. Descriptive statistics will be provided for selected demographic, safety, and PK data for the safety analysis set. Descriptive statistics on continuous measurements will include means, medians, standard

deviations, first quartile (Q1), third quartile (Q3), minimum, and maximum, while categorical data will be summarized using frequency counts and percentages.

10.4.2 Primary Endpoints

10.4.2.1 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 dose. PK parameters will be estimated using either compartmental (eg PK modelling) 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}), area under the concentration time curve (AUC) from 0 to 28 days ($AUC_{0\text{-}28day}$).

10.4.2.2 Treatment-Emergent Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term according to the medical dictionary for regulatory activities (MedDRA) terminology. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from IP or other protocol-required therapies, and significant treatment emergent adverse events will also be provided. Adverse events resulting in treatment discontinuation will be identified.

10.4.2.3 Safety Endpoints

10.4.2.3.1 Vital Signs

Vital signs will be reviewed for each subject. Summaries of heart rate and blood pressure data over time and change from baseline will be provided. Depending on the extent and scope of change in other vital signs, summaries of other vital signs may be provided.

10.4.2.3.2 Electrocardiograms

ECG data will be reviewed for each subject as per the standard of care for routine safety monitoring.

10.4.2.3.3 Clinical Laboratory Tests

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.

10.4.2.3.4 Neurological Assessments

Neurological assessment data will be reviewed for each subject.

10.5 Exploratory Endpoint

[redacted]

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Study Manager to the Investigator. The written informed consent form is to be prepared in the language(s) of the potential subject population.

Before a subject's participation in the clinical study, the Investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specific screening procedures or any Investigational Product(s) is/ are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.

The investigator is also responsible for asking the subject (or legally acceptable representative) if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the

informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject or legally acceptable representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

In this study, obtaining assent from the child and consent from the parents or legally authorized representative, except if the child is very young, as defined by local law. A child is defined as a person who has not attained the legal age for consent for treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will take place. The local IRB/IEC will determine the process for obtaining and documenting the assent process for pediatric subject, but should follow the guidelines established by the Department of Health and Human Services Office of Human Research Protections guidelines, which state an explanation of the procedures involved in the study should be made in a language appropriate to the child's age, experience, maturity, and condition.

11.2 Institutional Review Board/Independent Ethic Committee

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen Investigational Product.

The Investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The Investigator is to notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The Investigator is responsible for obtaining annual IRB/IEC approval throughout the duration of the study. Copies of the Investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen.

11.3 Subject Confidentiality

The Investigator must ensure that the subject's confidentiality is maintained:

- Subjects are to be identified by a unique subject identification number
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations
- On the demographics page, in addition to the unique subject identification number, include the age at the time of enrollment
- For Serious Adverse Events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations)
- Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in strict confidence by the investigator, except as described below

In compliance with governmental/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the subject to permit named such individuals to have access to his/her study related records, including personal information.

11.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the Investigator or, in the case of multi-center studies, the coordinating Investigator.

The coordinating Investigator, identified by Amgen, will be any or all of the following: a recognized expert in the therapeutic area an Investigator who provided significant contributions to either the design or interpretation of the study an Investigator contributing a high number of eligible subjects

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. After Amgen amends the protocol, the Investigator is to return the signed Investigator's Signature page confirming agreement to continue participation in the study according to the amendment. The IRB/IEC must be informed of all amendments and give approval. The Investigator must send a copy of

the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.
Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.
Subjects may be eligible for continued treatment with Amgen Investigational Product by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen Investigational Product(s), and by what mechanism, after termination of the study and before it is available commercially.

12.2 Study Documentation and Archive

The Investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on eCRFs will be included on the Amgen Delegation of Authority Form.
Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.
The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.
Elements to include:

- Subject files containing completed informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

Retention of study documents will be governed by the Clinical Trial Agreement.

12.3 Study Monitoring and Data Collection

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, eCRFs and other pertinent data) provided that subject confidentiality is respected.

The Clinical Monitor is responsible for verifying the eCRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Clinical Monitor is to have access to subject medical records and other study related records needed to verify the entries on the eCRFs.

The Investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, are resolved.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the electronic eCRFs must be maintained and readily available
- Updates to electronic eCRFs will be automatically documented through the software's "audit trail"
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer
- The Investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that the Investigator inspected or reviewed the data on the eCRF, the data queries, and agrees with the content

12.4 Investigator Responsibilities for Data Collection

The Investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as

stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Activities (Table 1 and Table 2.), the Investigator can search publically available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

12.6 Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other Investigators and to collaborate with authors and Amgen staff as appropriate as defined in the Publication Charter. Membership on the committee (both for Investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

12.7 Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The Common Terminology Criteria for Adverse Events Version 4 (CTCAE v4.03) is available at the following location:
http://ctep.cancer.gov/protocolDevelopment/electronicapplications/ctc.htm.

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation according to the criteria specified in Section 6.3 require the following:

The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)

The appropriate eCRF (eg, Event eCRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.2.1.2.

Additional Clinical Assessments and Observation

All subjects in whom Investigational Product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Section 6.3.1 or who experience AST or ALT elevations > 3 x ULN or 2-fold increase above baseline values for subjects with evaluated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels. Assessments that are to be performed during this period include:

Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours

In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the Investigational Product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL.

The following are to be considered depending on the clinical situation:

- Complete blood count (CBC) with differential to assess for eosinophilia
- Serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels
- A more detailed history of:
  - Prior and/or concurrent diseases or illness
  - Exposure to environmental and/or industrial chemical agents
  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - Prior and/or concurrent use of alcohol, recreational drugs and special diets
  - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- Viral serologies
- CPK, haptoglobin, LDH, and peripheral blood smear
- Appropriate liver imaging if clinically indicated

Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected

Hepatology consult (liver biopsy may be considered in consultation with an hepatologist)

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all Investigational Product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in corresponding eCRFs.

Appendix B. Sample electronic Serious Adverse Event Contingency Report Form

AMGEN
Study # 20160172
Erenumab (AMG 334)

Electronic Serious Adverse Event Contingency Report Form
For Restricted Use

Reason for reporting this event via fax
The Clinical Trial Database (eg. Rave):
☐ Is not available due to internet outage at my site
☐ Is not yet available for this study
☐ Has been closed for this study

AMGEN SAFETY US FAX NUMBER: +888 814 8653

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____
and start date: Day ____ Month _____ Year _____

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day___ Month___ Year___

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	If serious enter Serious Criteria code (see codes below)	Relationship: Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? Erenumab (AMG334) No✓	Erenumab (AMG334) Yes✓	Pre-filled Syringe No✓	Pre-filled Syringe Yes✓	Outcome of Event •Resolved •Not resolved •Fatal •Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No							
				☐Yes ☐No							
				☐Yes ☐No							

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly / birth defect; 06 Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event: Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
Erenumab (AMG 334)	☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Amgen Pre-filled Syringe (PFS)	☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

FORM-050000 *Version 7.0 Effective Date: 1 February 2018*

AMGEN Study # 20160172 Erenumab (AMG 334)	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

	Site Number	Subject ID Number	

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY *(include dates, allergies and any relevant prior therapy)*

8. RELEVANT LABORATORY VALUES *(include baseline values)* Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Test											
	Unit											

9. OTHER RELEVANT TESTS *(diagnostics and procedures)* Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study # 20160172 Erenumab (AMG 334)	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

	Site Number	Subject ID Number	

10. CASE DESCRIPTION *(Provide narrative details of events listed in section 3)* Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee –	Title	Date
_____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*		

Appendix C. Pregnancy and Lactation Notification Forms

Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: Erenumab (AMG 334) - 20160172

Study Design: ☑ **Interventional** ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
AMG 334				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐ N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd__/ yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: Erenumab (AMG 334) - 20160172

Study Design: ☑ **Interventional** ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
AMG 334				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

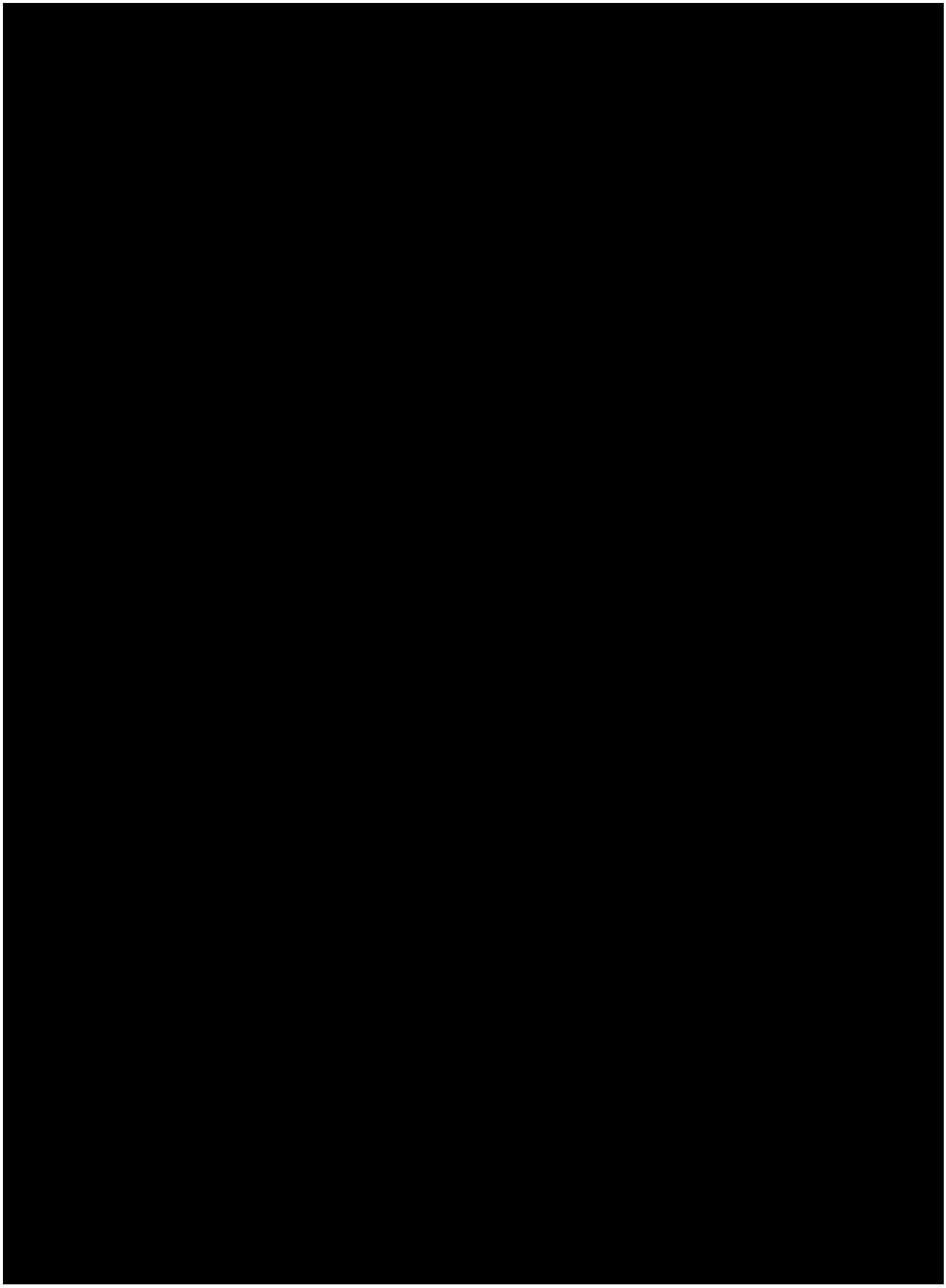
_____

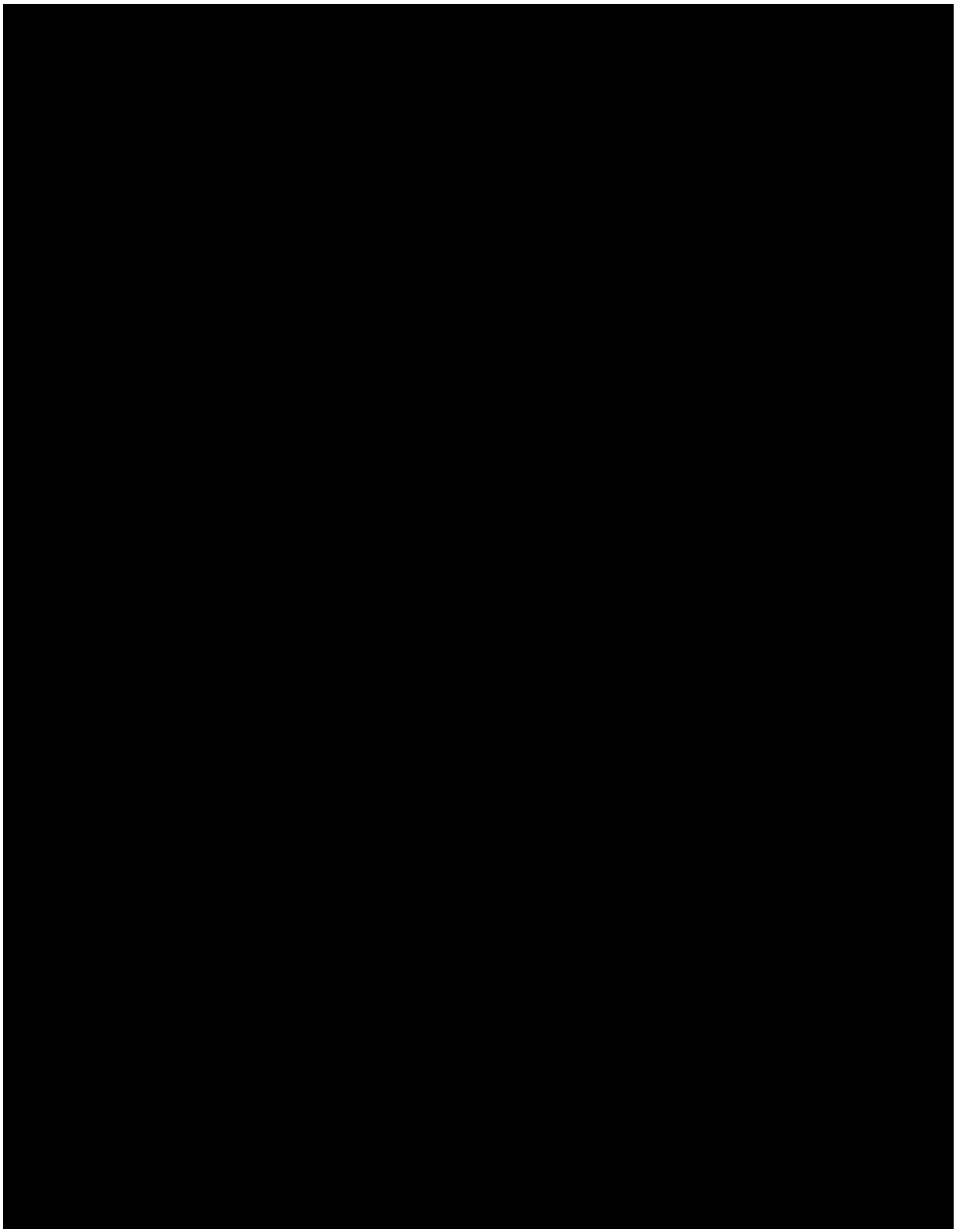
_____

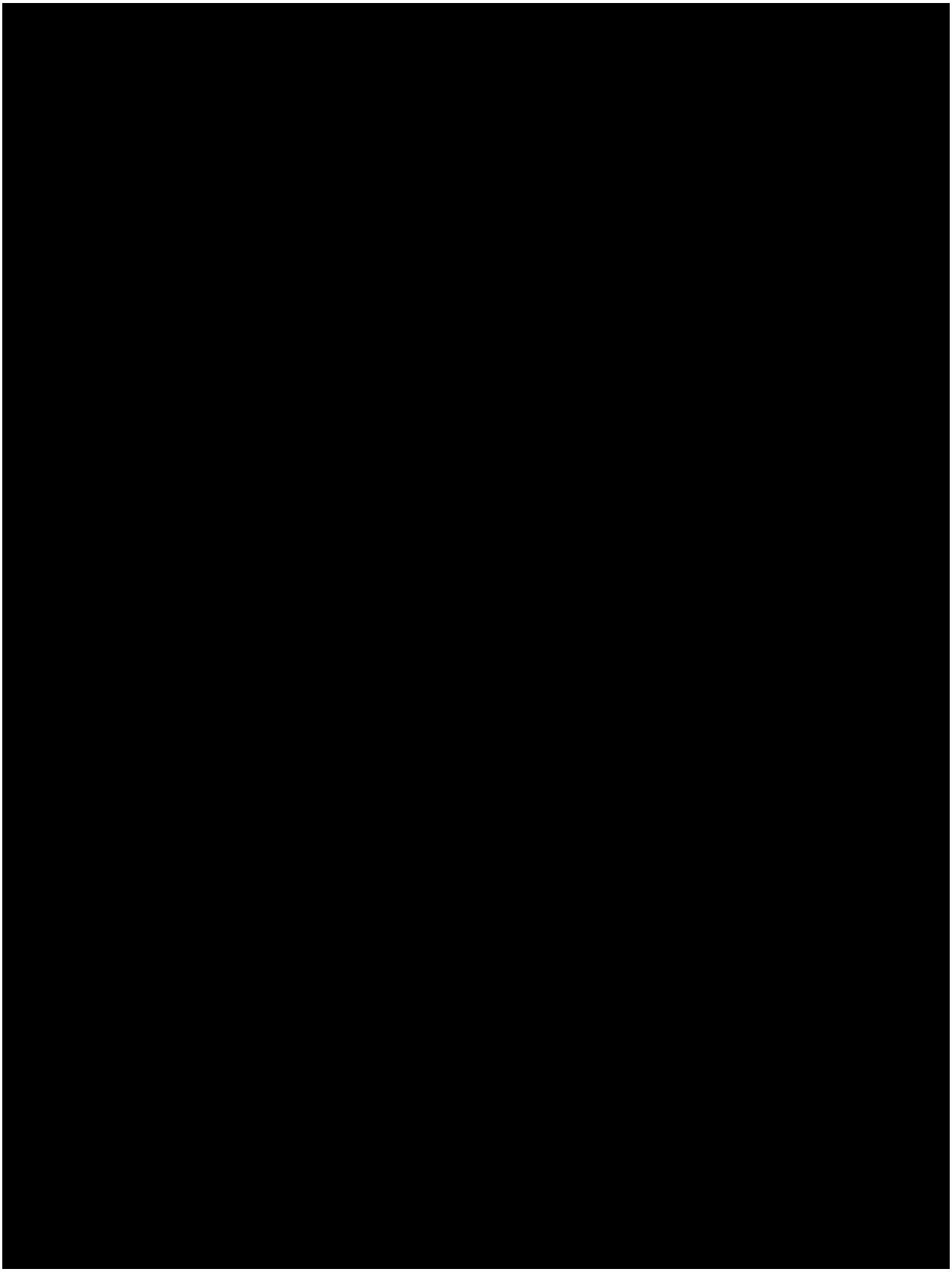
Form Completed by:

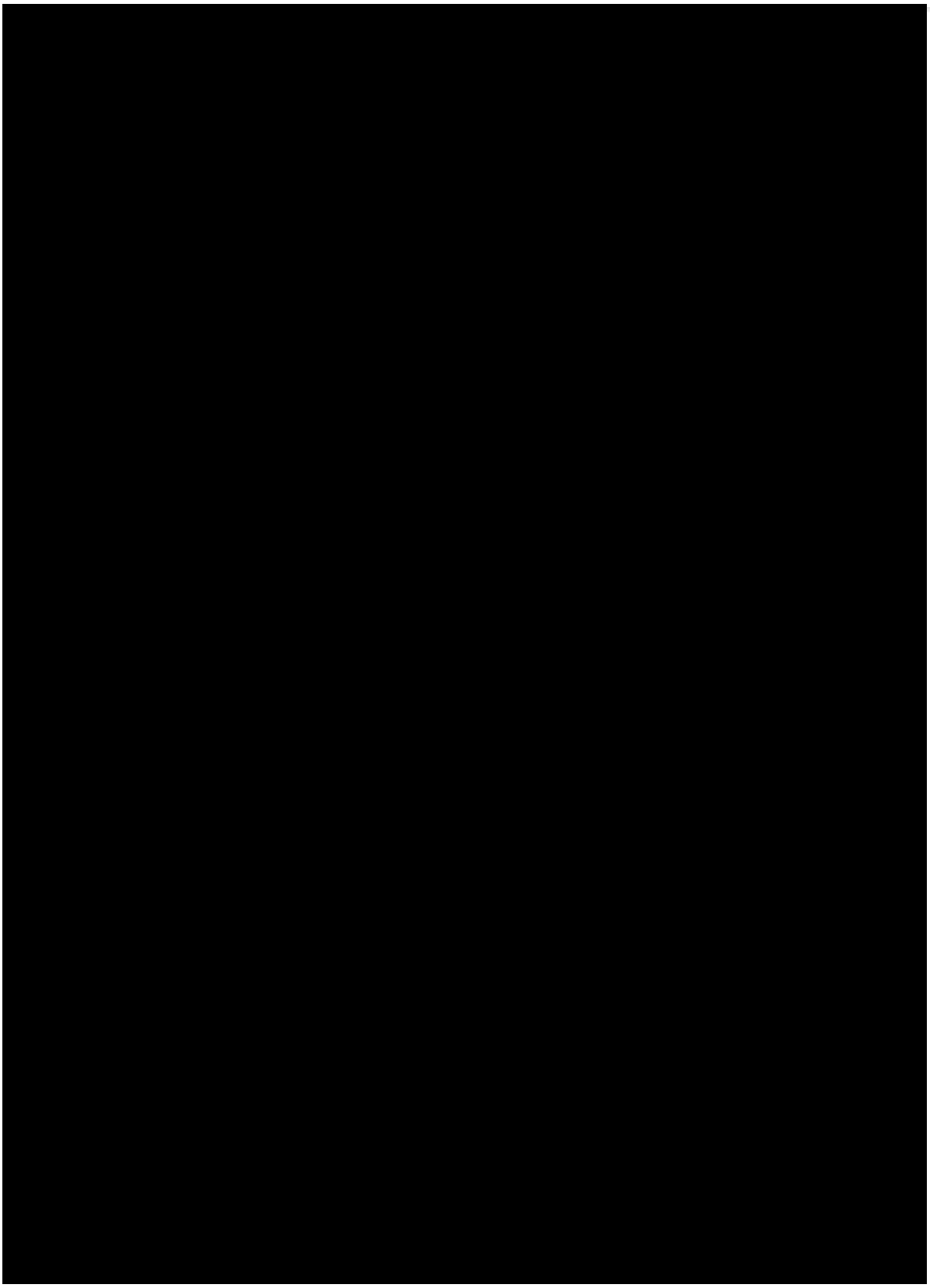
Print Name: _____ **Title:** _____

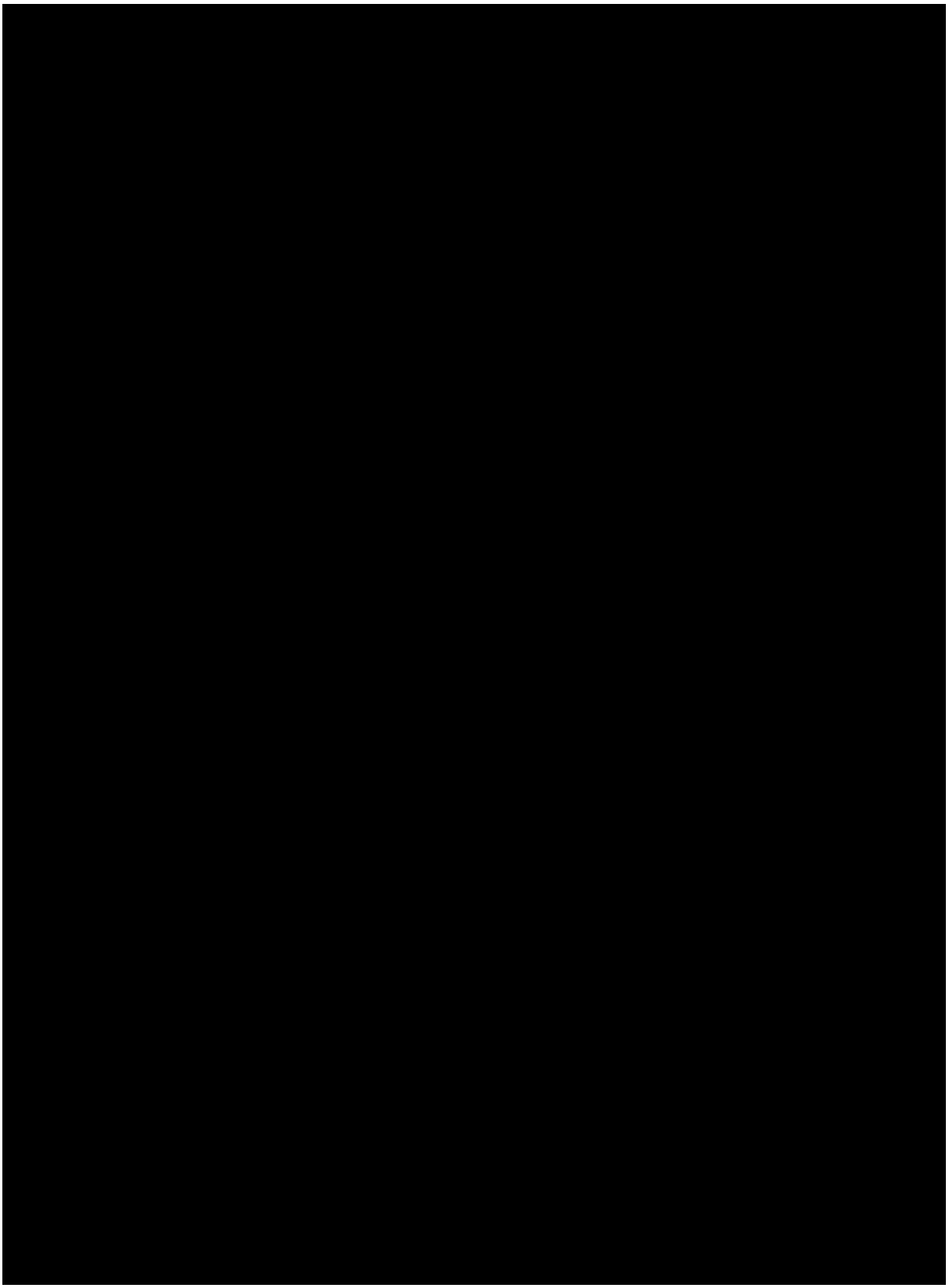
Signature: _____ **Date:** _____

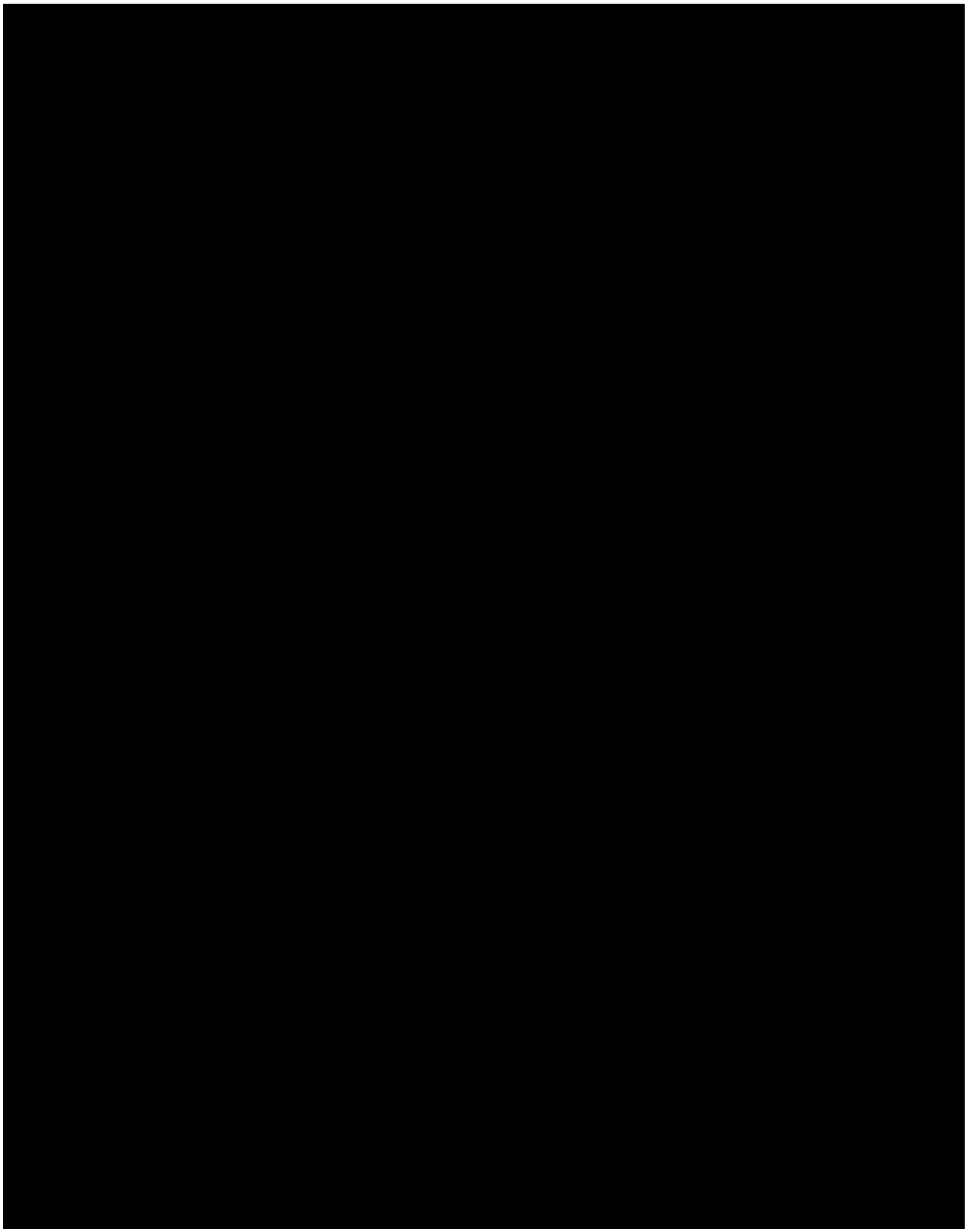


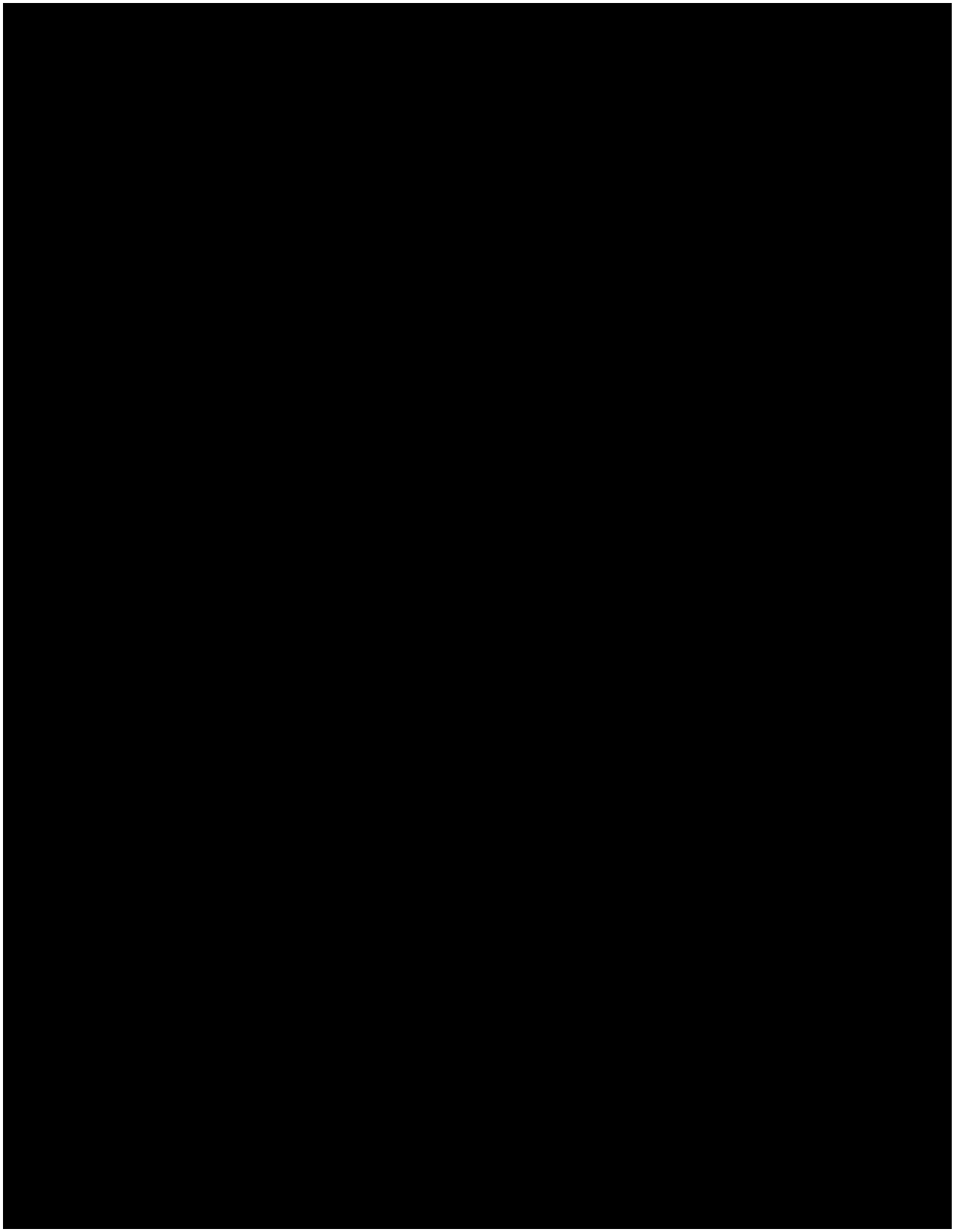


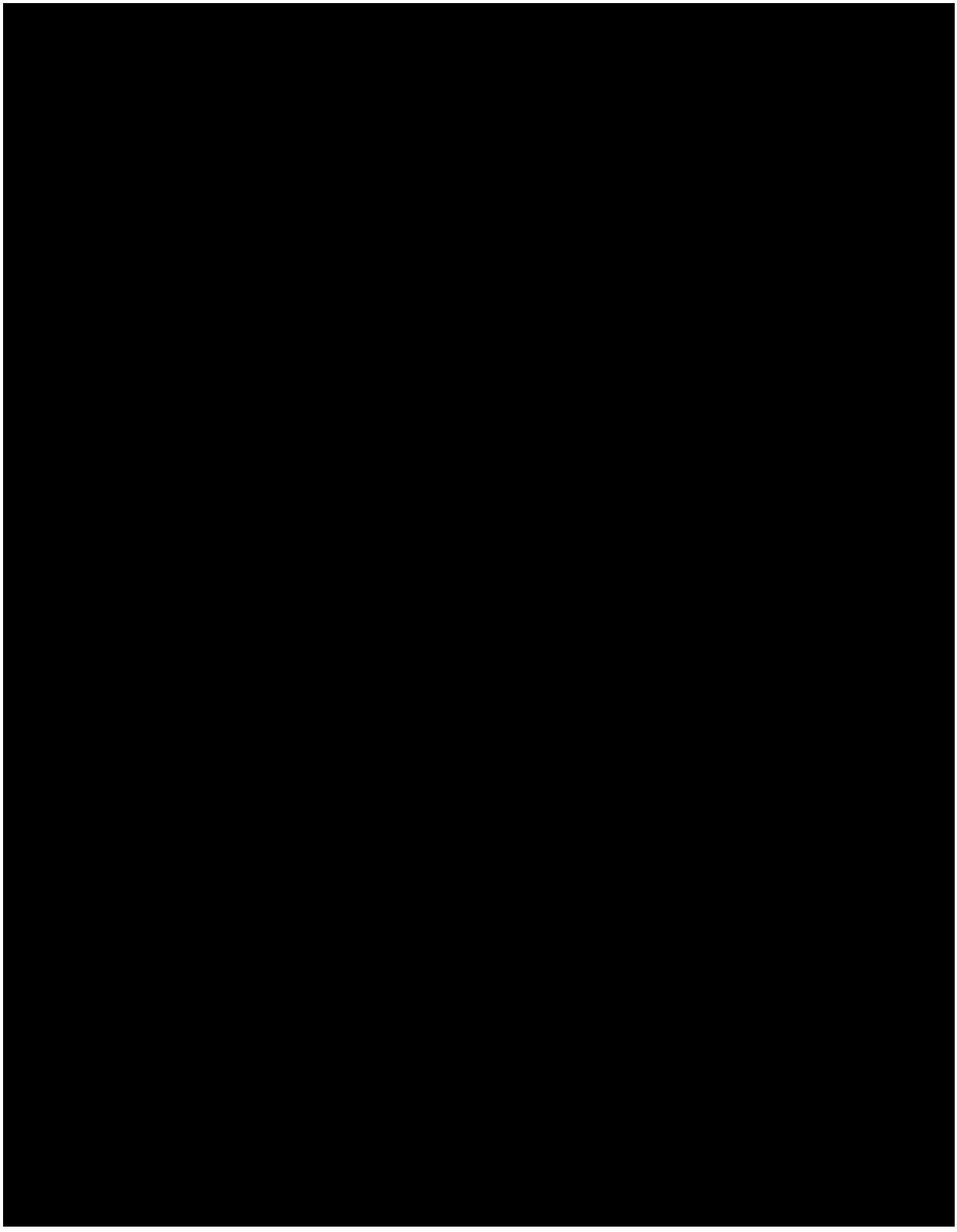












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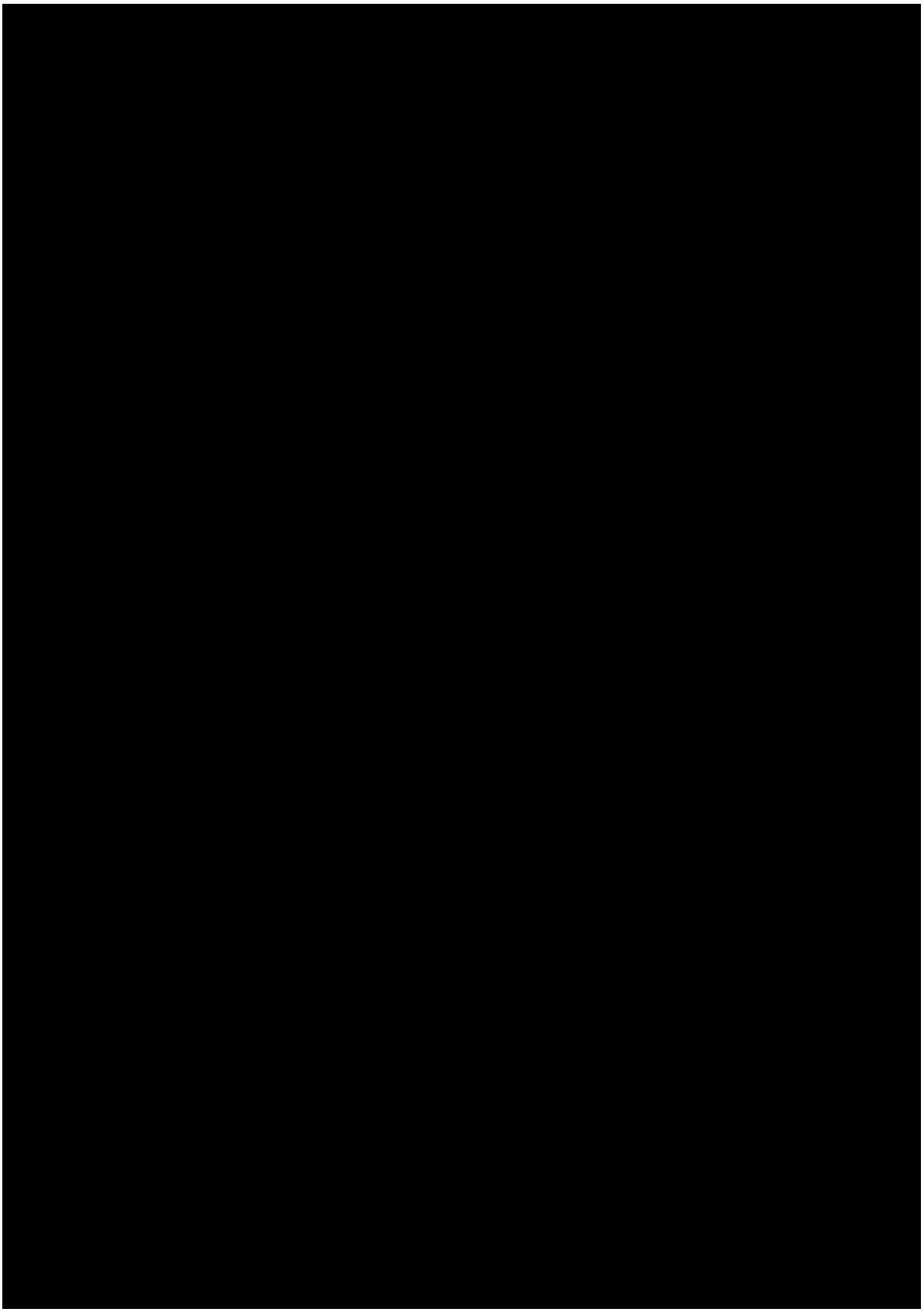
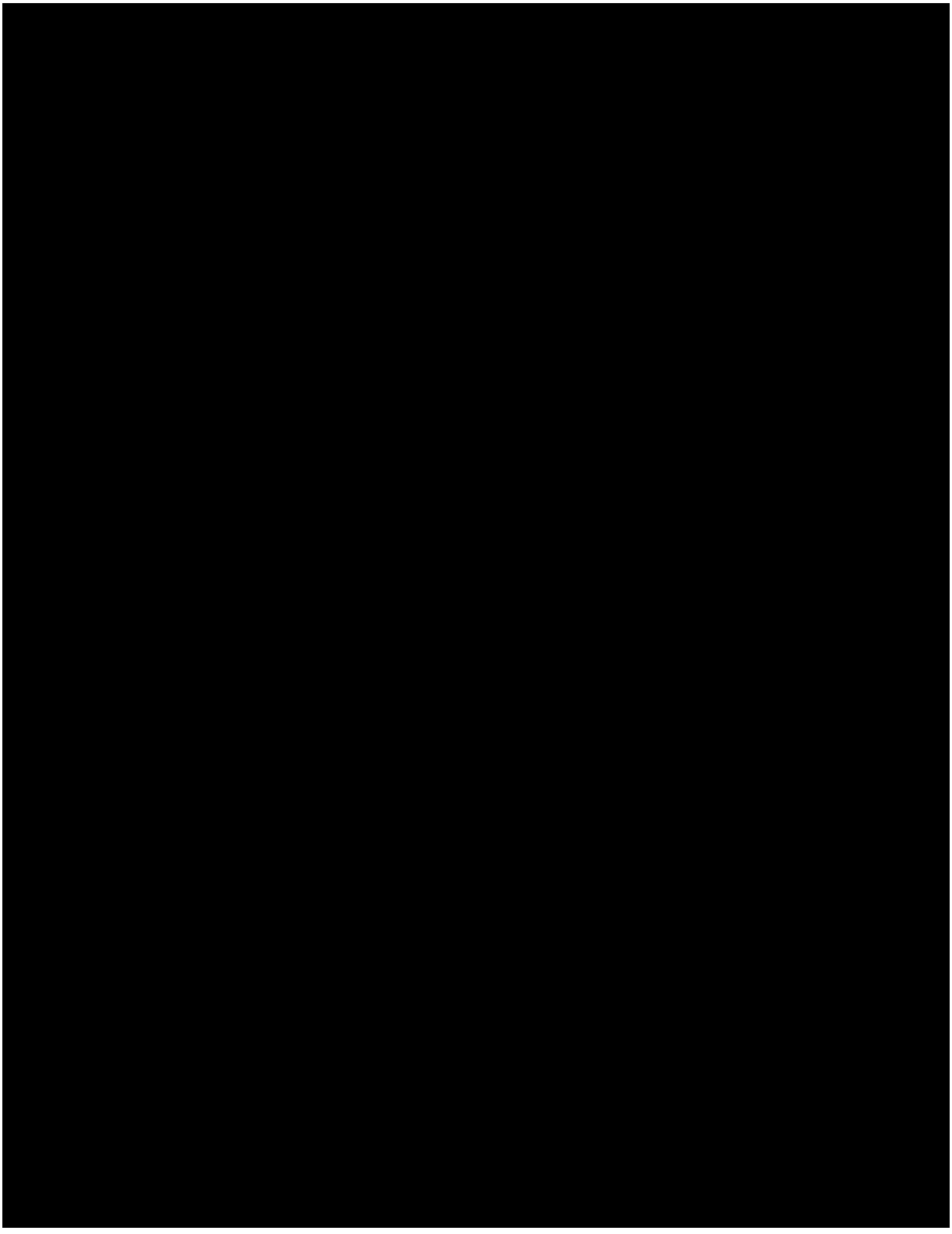
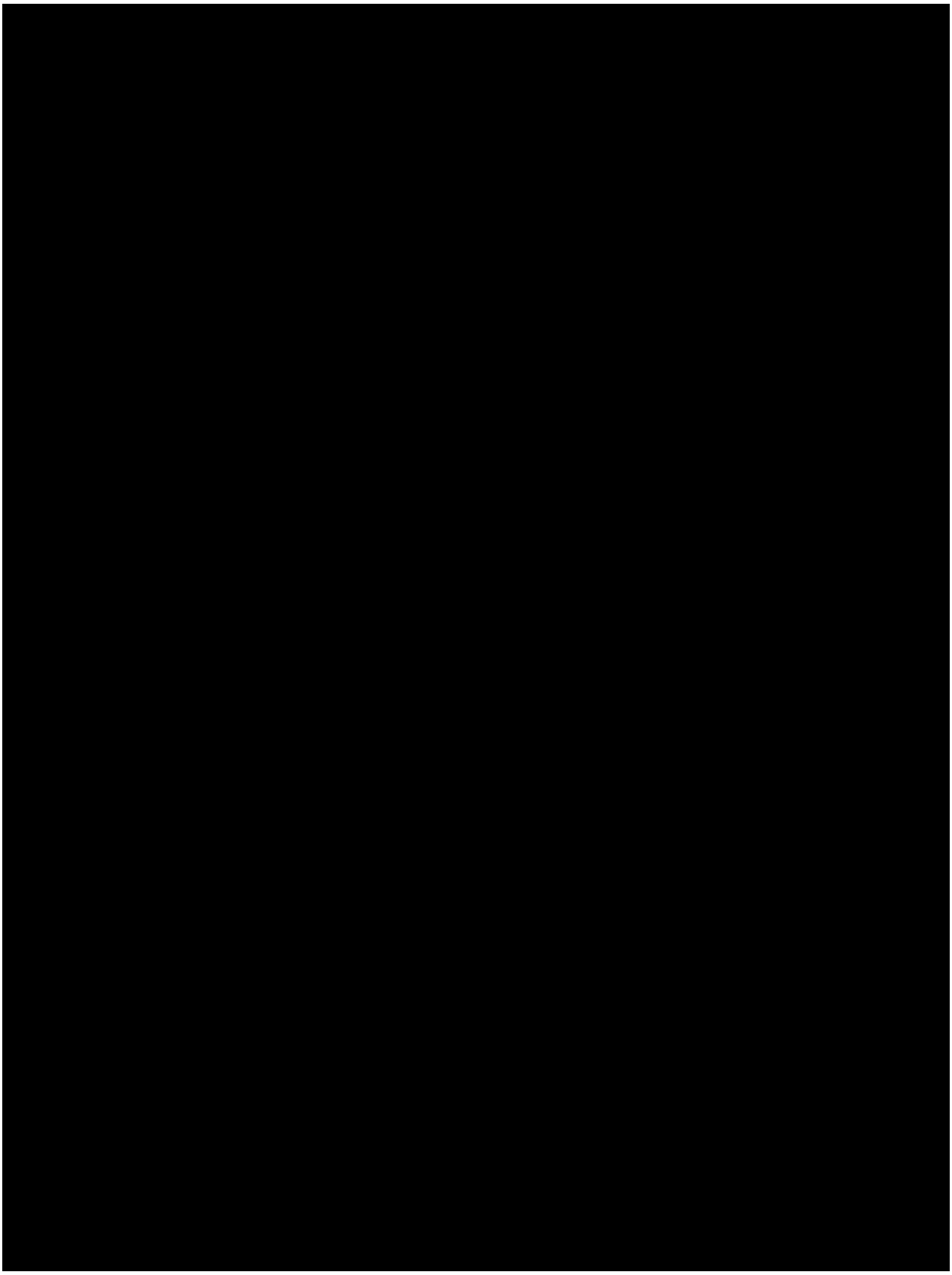






Appendix E. Sample PHQ-A

PHQ-9 modified for Adolescents (PHQ-A)

Name: _____ **Clinician:** _____ **Date:** _____

Instructions: How often have you been bothered by each of the following symptoms during the past **two weeks**? For each symptom put an **"X"** in the box beneath the answer that best describes how you have been feeling.

	(0) Not at all	(1) Several days	(2) More than half the days	(3) Nearly every day
1. Feeling down, depressed, irritable, or hopeless?				
2. Little interest or pleasure in doing things?				
3. Trouble falling asleep, staying asleep, or sleeping too much?				
4. Poor appetite, weight loss, or overeating?				
5. Feeling tired, or having little energy?				
6. Feeling bad about yourself – or feeling that you are a failure, or that you have let yourself or your family down?				
7. Trouble concentrating on things like school work, reading, or watching TV?				
8. Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you were moving around a lot more than usual?				
9. Thoughts that you would be better off dead, or of hurting yourself in some way?				

In the **past year** have you felt depressed or sad most days, even if you felt okay sometimes?

☐Yes ☐No

If you are experiencing any of the problems on this form, how **difficult** have these problems made it for you to do your work, take care of things at home or get along with other people?

☐Not difficult at all ☐Somewhat difficult ☐Very difficult ☐Extremely difficult

Has there been a time in the **past month** when you have had serious thoughts about ending your life?

☐Yes ☐No

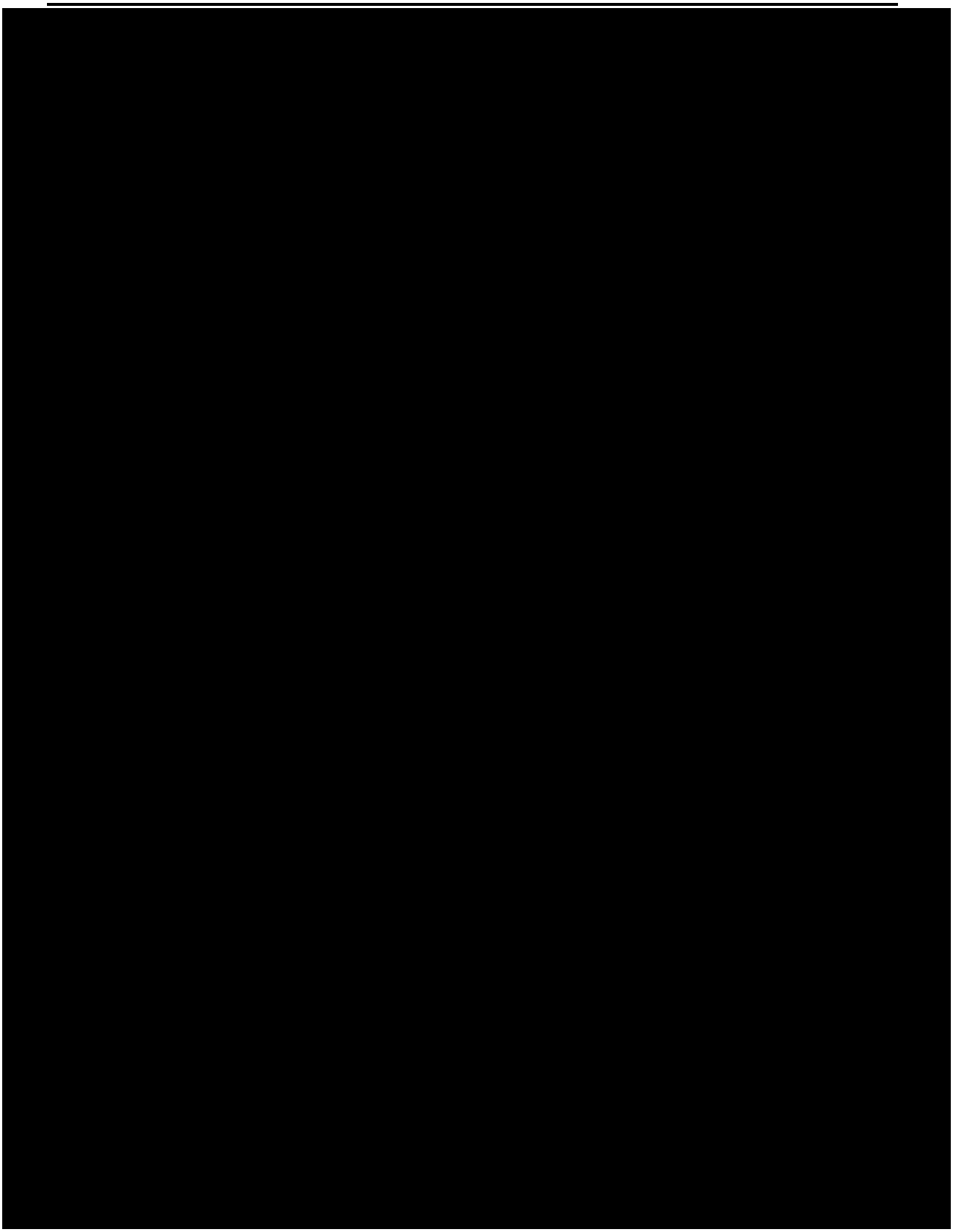
Have you **EVER**, in your WHOLE LIFE, tried to kill yourself or made a suicide attempt?

☐Yes ☐No

***If you have had thoughts that you would be better off dead or of hurting yourself in some way, please discuss this with your Health Care Clinician, go to a hospital emergency room or call 911.*

Office use only: **Severity score:** _____

Modified with permission from the PHQ (Spitzer, Williams & Kroenke, 1999) by J. Johnson (Johnson, 2002)



Amendment 5

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

Amgen Protocol Number: AMG 334 20160172

NCT Number: NCT03499119

IND Number BB-IND 116098

Amendment Date: 03 November 2021

Rationale:

The rationale of the amendment is to reflect the changes to the phase 1 trial agreed upon with the European Medicines Agency (EMA) in the pediatric investigation plan (PIP) modification. The modification of the PIP includes the following changes:

- Number of study participants of at least 52 subjects enrolled.
- At least 12 pediatric patients with body weight of less than 40 kg, from which:
    - At least 9 patients must be aged 6 to less than 12 years old
    - At least 2 patients must be aged 6 to less than 10 years old
- In the statistical plan, the second interim analysis must occur when 8 or more children aged 6 to less than 12 years have completed week 12 assessments and must include all data collected for all subjects during the first 12 weeks of study.

Amendment 4

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

Amgen Protocol Number AMG 334 20160172

IND number BB-IND 116098

Amendment Date: 26 March 2020

Rationale:

The protocol is being amended to:

- Increase number of sites
- Introduce enrolment caps for Cohort 1 age strata with stipulation of a maximum number of subjects to be enrolled under the adolescent and children between the ages of 10 - < 12yo (in line with PSP/PIP agreements)
- Reduce enrolment barriers by redacting unnecessary eligibility requirements and reducing subject-level burden through optimization of in-clinic visits and blood sample collection

Other changes include:

- Modify protocol indication to migraine *prevention* throughout the protocol
- Add clarity to protocol sections including: Protocol Synopsis, Study Design, Experimental Plan
- Update information in Background and Rationale
- Update administrative, typographical and formatting throughout the protocol. Updates aligned with the current template.

Amendment 3

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

Amgen Protocol Number AMG 334 20160172

IND number BB-IND 116098

Amendment Date: 18 April 2019

Rationale:

- The purpose of this amendment is to allow the enrollment of children 6 to < 12 years of age and to clarify that children 6 to < 12 years of age at the time of screening will only participate in the initial 12-week treatment phase, based on the totality of feedback received from both the FDA and EMA/PDCO. Adolescents 12 to < 18 years of age at time of screening 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 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.
- Study Schema footnote updates to clarify subject age groups and participation
- Exclusion criterion 226 was updated to clarify that subjects testing positive for illicit drugs are excluded.
- Exclusion criterion 227 was updated to maintain consistency with exclusion criterion 226.
- Protocol Synopsis – Statistical Consideration was updated to clarify how data will be summarized and the purpose of the interim analyses.
- Section 6.7 was updated to allow vaccinations after Day 85 assessments to allow flexibility for subjects needing vaccinations.
- Page 2 of the Schedule of Assessments and Section 7.2.18 were updated to correct the timing of the neurological exam at Day 365 instead of on Day 449.
- Section 7.2.5 Physical Examination was updated to allow the investigator to designate a qualified staff member to perform the physical examination.
- Section 10.3.1 was updated to provide more details regarding the interim analysis.

[redacted]

- Updated Amgen contact information

Amendment 2

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

Amgen Protocol Number AMG 334 20160172

IND number BB-IND 116098

Amendment Date: 20 June 2018

Rationale:

The purpose of this amendment is to implement the change requested by the FDA, which restricts enrollment of children ages 6 to <12 years old until the data from an ongoing juvenile toxicology study in cynomolgus monkeys become available.

Inclusion criterion 104 was changed from requiring the diagnosis of migraine to a history of migraine to be consistent with how migraine is documented in clinic medical records.

Exclusion criteria 217 was updated to clarify the Hepatitis B Core Antibody is also required.

References to urine alcohol screening were removed to provide clarity throughout the protocol that only breath alcohol screening will be performed.

Minor editorial changes have been made to improve overall clarity and consistency of the protocol language.

Amendment 1

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

Amgen Protocol Number AMG 334 *20160172*

IND number BB-IND 116098

Amendment Date: *05 December 2017*

Rationale:

The purpose of this amendment is to implement the change requested by the FDA, which is the inclusion of an additional low dose level to the study. In the original protocol a single dose was proposed for each body-weight cohort: 70 mg for the < 40 kg cohort and 140 mg for the ≥ 40 kg cohort. In this amendment each body weight cohort will include 2 doses: subjects in cohort 1 (< 40 kg) will be randomized to either 35 mg or 70 mg of AMG 334; subjects in cohort 2 (≥ 40 kg) will be randomized to either 70 mg or 140 mg of AMG 334. Due to this change, the overall number of subjects has been increased. Cohort 1 will enroll at least 18 subjects and up to approximately 22 subjects with body weight of < 40 kg. At least 15 subjects in cohort 1 will be aged 6 to < 12 years and at least 4 subjects will be aged 6 to < 10 years old. Cohort 2 will enroll at least 35 subjects and up to approximately 38 subjects with a body weight of ≥ 40 kg. Considering that body weight is the most important PK covariate, for consistency and clarity the 2 cohorts in the study are now categorized by body weight bands instead of age.

Safety labs originally required at Day 28 and Day 56 visits were moved 1 day (ie, to Day 29 and Day 58 visits respectively) in order to reduce the study burden for patients and parents while still collecting the necessary safety data. Day 28 and Day 56 visits, which only included the above mentioned safety labs, have therefore been removed.

The post dose observation period has been changed from 2 hours on Day 1, Day 29 and Day 57 visits to Day 1 visit only. This change is also intended to reduce the study burden for patients and parents while keeping consistency with available AMG 334 safety data in adults and with the pediatric phase 3 study protocols.

Selection criteria have been modified to provide clarity on the concomitant medications allowed and excluded from the study. The study population has not been changed.

The [redacted] exploratory endpoint language has been modified to improve clarity. The exploratory endpoint is: [redacted]

Minor editorial changes have been done to improve overall clarity and consistency of the protocol language.