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

Summary

EudraCT number	2013-005311-27
Trial protocol	SE DE DK NO PL CZ FI GB
Global end of trial date	26 May 2017

Results information

Result version number	v1 (current)
This version publication date	09 June 2018
First version publication date	09 June 2018

Trial information

Trial identification

Sponsor protocol code	20130255

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02174861
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to characterize the safety and tolerability of long-term administration of erenumab.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines, the GCPs applicable to all regions where the study was conducted and in accordance with the ethical principles set forth in the Declaration of Helsinki.
The study protocol and all amendments, the informed consent form, and any accompanying materials provided to subjects were reviewed and approved by an independent Ethics Committee (IEC) or Institutional Review Board (IRB), as appropriate, at each center/country.
The investigator or his/her designee informed the subject of all aspects pertaining to the subject's participation in the study before any screening procedures were performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 June 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	United States: 276
Country: Number of subjects enrolled	Czech Republic: 52
Country: Number of subjects enrolled	Denmark: 24
Country: Number of subjects enrolled	Finland: 35
Country: Number of subjects enrolled	Germany: 69
Country: Number of subjects enrolled	Norway: 31
Country: Number of subjects enrolled	Poland: 31
Country: Number of subjects enrolled	Sweden: 63
Country: Number of subjects enrolled	United Kingdom: 18
Worldwide total number of subjects	609
EEA total number of subjects	323

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	608
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 64 centers across North America and Europe from 30 June 2014 to 4 March 2016. Participants who completed the 12-week double-blind treatment of the parent Study 20120295 (2013-001707-36) and met all Study 20130255 eligibility criteria were eligible for enrollment into this study.

Pre-assignment

Screening details:

Participants at sites in the United States, Sweden, and Germany had the option of enrolling in the Clinical Home Use (CHU) Substudy to assess their ability to self-administer 140 mg erenumab for in-home use. Participants in the substudy were randomized 1:1 to self-administer erenumab using either a prefilled syringe or autoinjector/pen.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Erenumab

Arm description:

Participants received erenumab 70 mg once a month (QM) and/or 140 mg QM by subcutaneous injection for up to 52 weeks.
Participants who enrolled prior to amendment 2 received erenumab 70 mg once a month (QM). Participants who had not completed the week 28 visit at the time of amendment 2 had their dose increased to 140 mg QM at their next visit whereas participants who had already completed the week 28 visit remained on erenumab 70 mg QM. Participants who enrolled after amendment 2 received erenumab 140 mg QM for the duration of the study.

Arm type	Experimental
Investigational medicinal product name	Erenumab
Investigational medicinal product code	AMG 334
Other name	Aimovig™
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection once a month

Number of subjects in period 1	Erenumab
Started	609
Received Erenumab 70 mg QM at Any Time	549
Received Erenumab 70 mg QM Only	350 [1]
Received Erenumab 70 mg and 140 mg QM	199 [2]
Received Erenumab 140 mg QM Only	60 [3]
Enrolled in CHU Substudy	53 [4]

Completed	451
Not completed	158
Consent withdrawn by subject	124
Lost to follow-up	26
Decision by sponsor	8

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Data represent the number of subjects who enrolled prior to implementation of protocol amendment 2 and received erenumab 70 mg QM for the entire study.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Data represent the number of subjects who enrolled prior to implementation of protocol amendment 2 and initially received erenumab 70 mg QM and whose dose was increased to 140 mg QM after protocol amendment 2.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Data represent the number of subjects who enrolled after implementation of protocol amendment 2 and received erenumab 140 mg QM for the duration of the study.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Data represent the number of subjects who enrolled in the CHU substudy

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description:

Participants received erenumab 70 mg once a month (QM) and/or 140 mg QM by subcutaneous injection for up to 52 weeks.
Participants who enrolled prior to amendment 2 received erenumab 70 mg once a month (QM). Participants who had not completed the week 28 visit at the time of amendment 2 had their dose increased to 140 mg QM at their next visit whereas participants who had already completed the week 28 visit remained on erenumab 70 mg QM. Participants who enrolled after amendment 2 received erenumab 140 mg QM for the duration of the study.

Reporting group values	Overall Study	Total	
Number of subjects	609	609	
Age Categorical Units: Subjects			
18 - 64 years	608	608	
65 - 74 years	1	1	
Age Continuous Units: years			
arithmetic mean	42.5		
standard deviation	± 11.3	-	
Gender Categorical Units: Subjects			
Female	509	509	
Male	100	100	
Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	7	7	
Black or African American	25	25	
Native Hawaiian or Other Pacific Islander	0	0	
White	574	574	
Other	3	3	
Ethnicity Units: Subjects			
Hispanic or Latino	25	25	
Not Hispanic or Latino	584	584	

End points

End points reporting groups

Reporting group title	Erenumab

Reporting group description:

Participants received erenumab 70 mg once a month (QM) and/or 140 mg QM by subcutaneous injection for up to 52 weeks.
Participants who enrolled prior to amendment 2 received erenumab 70 mg once a month (QM). Participants who had not completed the week 28 visit at the time of amendment 2 had their dose increased to 140 mg QM at their next visit whereas participants who had already completed the week 28 visit remained on erenumab 70 mg QM. Participants who enrolled after amendment 2 received erenumab 140 mg QM for the duration of the study.

Subject analysis set title	Erenumab 140 mg PFS
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the CHU substudy self-administered erenumab 140 mg on days 29 and 57 by subcutaneous injection using a prefilled syringe (PFS).

Subject analysis set title	Erenumab 140 mg AI/Pen
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the CHU substudy self-administered erenumab 140 mg on days 29 and 57 by subcutaneous injection using a autoinjector/pen (AI/Pen).

Primary: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events[1]

End point description:

Adverse events (AEs) were graded for severity using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, where
Grade 1 = mild AE, asymptomatic or mild symptoms;
Grade 2 = Moderate AE;
Grade 3 = Severe or medically significant but not immediately life-threatening;
Grade 4 = Life-threatening consequences; urgent intervention indicated;
Grade 5 = Death related to AE.

End point type	Primary

End point timeframe:

From first dose of erenumab in extension study 20130255 to the end of the 12-week safety follow-up period (up to 64 weeks).

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The clinical hypothesis was that long-term exposure of erenumab would be safe and well tolerated in subjects with chronic migraine. No formal hypothesis was tested. This was a single-arm estimation study.

End point values	Erenumab			
Subject group type	Reporting group			
Number of subjects analysed	609			
Units: participants				
Any adverse event	398			
Adverse event grade ≥ 2	302			
Adverse event grade ≥ 3	34			
Adverse event grade ≥ 4	0			
Treatment-related adverse events	114			
Serious adverse events	24			
AE leading to discontinuation of erenumab	16			

Fatal adverse events	0			

Statistical analyses

No statistical analyses for this end point

Primary: CHU Substudy: Number of Participants Able to Administer a Full Dose of Erenumab in Home-use

End point title	CHU Substudy: Number of Participants Able to Administer a Full Dose of Erenumab in Home-use[2]

End point description:

At the CHU substudy day 28 and day 56 visits, the site provided erenumab 140 mg to participants to self-administer at home on the following day. Study site staff then called the participants and asked if they administered a full, partial, or no dose of erenumab. A full dose was defined when the entire volume of both prefilled syringes or autoinjector/pens were injected.

End point type	Primary

End point timeframe:

Day 29 (week 4) and day 57 (week 8) of the substudy

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: In the CHU substudy it was hypothesized that users were able to administer a full dose of erenumab comparably using either the prefilled syringe or autoinjector/pen. No formal hypotheses were tested.

End point values	Erenumab 140 mg PFS	Erenumab 140 mg AI/Pen		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	26		
Units: participants				
Week 4	25	26		
Week 8	25	25		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Study 20120295 Baseline in Monthly Migraine Days

End point title	Change from Study 20120295 Baseline in Monthly Migraine Days

End point description:

A migraine day was any calendar day in which the participant experienced a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). A qualified migraine headache was defined either as a migraine with or without aura.
The change from baseline in monthly migraine days was calculated as the number of migraine days during the 4 weeks prior to each study visit – the number of migraine days during the 4-week baseline phase.
The number of participants analyzed includes enrolled participants who received at least one dose of erenumab and had at least one change from baseline measurement in monthly migraine day in study 20130255 and with available data at each time point.

End point type	Secondary

End point timeframe:

4-week baseline phase of Study 20120295 and the 4 weeks prior to the week 4, 8, 12, 24, 40, and 52 visits of Study 20130255

End point values	Erenumab			
Subject group type	Reporting group			
Number of subjects analysed	605			
Units: migraine days / month				
arithmetic mean (standard deviation)				
Baseline	18.11 (± 4.53)			
Change from baseline at week 4 (n = 561)	-6.72 (± 6.22)			
Change from baseline at week 8 (n = 574)	-7.38 (± 6.50)			
Change from baseline at week 12 (n = 560)	-7.63 (± 6.49)			
Change from baseline at week 24 (n = 481)	-8.36 (± 6.29)			
Change from baseline at week 40 (n = 430)	-8.72 (± 6.53)			
Change from baseline at week 52 (n = 383)	-9.29 (± 6.64)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with at Least a 50% Reduction in Monthly Migraine Days From Study 20120295 Baseline

End point title	Percentage of Participants with at Least a 50% Reduction in Monthly Migraine Days From Study 20120295 Baseline

End point description:

A migraine day was any calendar day in which the participant experienced a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). A qualified migraine headache was defined either as a migraine without aura or a migraine with aura. Monthly migraine days were calculated as the number of migraine days in the 4-week baseline phase and during the 4 weeks prior to each study visit.
At least a 50% reduction from baseline (of study 20120295) in monthly migraine days was determined if the change in monthly migraine days from the 4-week baseline phase to the 4 weeks prior to each study visit * 100 / baseline monthly migraine days was less than or equal to -50%.
The number of participants analyzed includes enrolled participants who received at least one dose of erenumab and had at least one change from baseline measurement in monthly migraine day in study 20130255 and with available data at each time point.

End point type	Secondary

End point timeframe:

4-week baseline phase of Study 20120295 and the 4 weeks prior to the week 4, 8, 12, 24, 40, and 52 visits of Study 20130255

End point values	Erenumab			
Subject group type	Reporting group			
Number of subjects analysed	605			
Units: percentage of participants				
number (confidence interval 95%)				
Week 4 (n = 561)	39.2 (35.3 to 43.3)			
Week 8 (n = 574)	45.6 (41.6 to 49.7)			
Week 12 (n = 560)	45.7 (41.6 to 49.9)			
Week 24 (n = 481)	53.6 (49.2 to 58.0)			
Week 40 (n = 430)	55.6 (50.9 to 60.2)			
Week 52 (n = 383)	59.0 (54.0 to 63.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Study 20120295 Baseline in Monthly Acute Migraine-Specific Medication Treatment Days

End point title	Change From Study 20120295 Baseline in Monthly Acute Migraine-Specific Medication Treatment Days

End point description:

Monthly acute migraine-specific medication treatment days is the number of days on which migraine specific medications were used between monthly doses of study drug. Migraine-specific medications includes two categories of medications: triptan-based migraine medications and ergotamine-based migraine medications.
The number of participants analyzed includes enrolled participants who received at least one dose of erenumab and had at least one change from baseline measurement in monthly migraine day in study 20130255 and with available data at each time point.

End point type	Secondary

End point timeframe:

4-week baseline phase of Study 20120295 and the 4 weeks prior to the week 4, 8, 12, 24, 40, and 52 visits of Study 20130255

End point values	Erenumab			
Subject group type	Reporting group			
Number of subjects analysed	605			
Units: acute migraine treatment days / month				
arithmetic mean (standard deviation)				
Baseline	9.53 (± 7.26)			
Change from baseline at Week 4 (n = 561)	-3.59 (± 4.62)			
Change from baseline at Week 8 (n = 574)	-4.01 (± 4.96)			

Change from baseline at Week 12 (n = 560)	-3.96 (± 5.03)			
Change from baseline at Week 24 (n = 481)	-4.39 (± 4.99)			
Change from baseline at Week 40 (n = 430)	-4.58 (± 5.00)			
Change from baseline at Week 52 (n = 383)	-4.97 (± 5.33)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Study 20120295 Baseline in Cumulative Monthly Headache Hours

End point title	Change From Study 20120295 Baseline in Cumulative Monthly Headache Hours

End point description:

The cumulative duration of any qualified headache between monthly doses of study drug regardless of acute treatment use.
A qualified headache was defined as follows:
• a qualified migraine headache (including an aura-only event that is treated with acute migraine-specific medication), or
• a qualified non-migraine headache, which is a headache that lasted continuously for ≥ 4 hours and was not a qualified migraine headache, or
• a headache of any duration for which acute headache treatment was administered.
The number of participants analyzed includes enrolled participants who received at least one dose of erenumab and had at least one change from baseline measurement in monthly migraine day in study 20130255 and with available data at each time point.

End point type	Secondary

End point timeframe:

4-week baseline phase of Study 20120295 and the 4 weeks prior to the week 4, 8, 12, 24, 40, and 52 visits of Study 20130255

End point values	Erenumab			
Subject group type	Reporting group			
Number of subjects analysed	605			
Units: hours / month				
arithmetic mean (standard deviation)				
Baseline	226.84 (± 125.54)			
Change from baseline at week 4 (n = 561)	-79.38 (± 107.56)			
Change from baseline at week 8 (n = 574)	-85.24 (± 110.24)			
Change from baseline at week 12 (n = 560)	-89.30 (± 111.47)			
Change from baseline at week 24 (n = 481)	-100.41 (± 112.30)			
Change from baseline at week 40 (n = 430)	-101.07 (± 111.77)			
Change from baseline at week 52 (n = 383)	-107.44 (± 113.60)			

Statistical analyses

No statistical analyses for this end point

Secondary: CHU Substudy: Number of Participants with Adverse Events

End point title	CHU Substudy: Number of Participants with Adverse Events

End point description:

Adverse events were graded for severity using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
Injection site reactions were derived from a Medical Dictionary for Regulatory Activities (MedDRA) query using a list of pre-specified preferred terms.
An adverse device effect (ADE) is any adverse event related to the use of a medical device.

End point type	Secondary

End point timeframe:

From first dose of erenumab in the CHU substudy to 28 days after last dose of erenumab in the CHU substudy; up to 12 weeks.

End point values	Erenumab 140 mg PFS	Erenumab 140 mg AI/Pen		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	26		
Units: participants				
Any adverse event	2	6		
Adverse event grade ≥ 2	1	4		
Adverse event grade ≥ 3	0	0		
Adverse event grade ≥ 4	0	0		
Serious adverse events	0	0		
AE leading to discontinuation of erenumab	0	0		
Fatal adverse events	0	0		
Injection site reactions	0	1		
Adverse device effects	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of erenumab in extension study 20130255 to the end of the 12-week safety follow-up period (up to 64 weeks).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Erenumab

Reporting group description:

Participants received erenumab 70 mg once a month (QM) and/or 140 mg QM by subcutaneous injection for up to 52 weeks.

Serious adverse events	Erenumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 609 (3.94%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Post procedural oedema			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Myocardial bridging			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Medication overuse headache			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Migraine			

subjects affected / exposed	4 / 609 (0.66%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Radicular syndrome				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vestibular migraine				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Volvulus				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				

Alcoholic liver disease				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Alcoholism				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Depression				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Costochondritis				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intervertebral disc protrusion				
subjects affected / exposed	3 / 609 (0.49%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Rotator cuff syndrome				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Appendicitis				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				

subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Erenumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	162 / 609 (26.60%)		
Infections and infestations			
Sinusitis			
subjects affected / exposed	44 / 609 (7.22%)		
occurrences (all)	57		
Upper respiratory tract infection			
subjects affected / exposed	45 / 609 (7.39%)		
occurrences (all)	52		
Viral upper respiratory tract infection			
subjects affected / exposed	96 / 609 (15.76%)		
occurrences (all)	127		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 January 2015	- updated to extend treatment phase by 3 months to align with 20120295 parent study - added novel PRO substudy for English-speaking subjects in US only - added Event Adjudication Committee to cover data from this study - refined some eligibility criteria and clarified some protocol text
14 October 2015	- primary objective and secondary objective of CHU substudy were added; 2 secondary and 1 exploratory objectives were added to the main study; 1 secondary objective was deleted; and 1 exploratory objective was modified - Study Rationale section was updated to include results from AMG 334 2012078 global phase 2 study - AMG 334 was increased to 140 mg to provide additional 6-month and one-year safety data at this dose - sample size was increased from 490 subjects to 651 subjects to align with increase in parent study - expansion of novel PRO substudy to all subjects, not just English-speaking subjects - added clarification to text of CHU substudy - expanded description of C-SSRS - clarified protocol text
31 March 2016	- clarified language regarding length of time surrounding excluded treatments - aligned current protocol template language (Sections 9 and 12) - updated pregnancy and lactation notification worksheets - clarifications made to product complaints section - review of adverse events and serious adverse events added to Open-label treatment phase - serious adverse events collection added for CHU substudy - correct typographical, grammatical, and formatting errors throughout the protocol

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported