Clinical trial results:
A 12-month prospective, randomized, interventional, global, multi-center, active-controlled study comparing sustained benefit of two treatment paradigms (erenumab qm vs. oral prophylactics) in adult episodic migraine patients

Summary

EudraCT number	2018-001228-20
Trial protocol	BE DE CZ FI GB SK PT GR PL ES IT
Global end of trial date	30 September 2022

Results information

Result version number	v1 (current)
This version publication date	21 September 2023
First version publication date	21 September 2023

Trial information

Trial identification

Sponsor protocol code	CAMG334A2401

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03927144
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.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	30 September 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate the superiority of subcutaneous AMG334 compared to oral prophylactics on sustained benefit defined as % subjects completing one-year on the randomized treatment and achieving at least a 50% reduction from baseline in monthly migraine days at month 12.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 May 2019
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	Argentina: 15
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Belgium: 60
Country: Number of subjects enrolled	Czechia: 105
Country: Number of subjects enrolled	Finland: 18
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 65
Country: Number of subjects enrolled	Greece: 32
Country: Number of subjects enrolled	Israel: 32
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	Netherlands: 17
Country: Number of subjects enrolled	Poland: 80
Country: Number of subjects enrolled	Portugal: 37
Country: Number of subjects enrolled	Slovakia: 39
Country: Number of subjects enrolled	Spain: 48
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 31
Worldwide total number of subjects	621
EEA total number of subjects	541

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)	615
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in 84 investigative sites in 17 countries.

Pre-assignment

Screening details:

The screening period began once patients had signed the study informed consent. Screening evaluations were performed during 2 weeks. After the Screening Period there was a Baseline Period of 4 weeks.

Period 1

Period 1 title	Core Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	AMG334 70mg / 140mg (Core Phase)

Arm description:

Participants randomized to erenumab in the Core Phase

Arm type	Experimental
Investigational medicinal product name	erenumab
Investigational medicinal product code	AMG334
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Pre-filled 1mL syringes (PFS) containing 70 mg/1mL of erenumab (AMG334) for subcutaneous administration for 70 mg or 140 mg dose were supplied to the investigators. Participants randomized to erenumab were dosed every 4 weeks from Day 1 up to Week 48. The investigator could treat the subject with either 70 mg or 140 mg. Dose modification/escalation was allowed as per the approved label.

Arm title	Oral SOC prophylactics (Core Phase)

Arm description:

Participants randomized to oral SOC prophylactics in the Core Phase

Arm type	Active comparator
Investigational medicinal product name	Oral SOC prophylactics
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral standard of care (SOC) prophylactics was locally approved oral prophylactic migraine medication. Participants randomized to oral SOC prophylactics continued to be dosed through Week 52 as per label.

Number of subjects in period 1	AMG334 70mg / 140mg (Core Phase)	Oral SOC prophylactics (Core Phase)
Started	413	208
Completed	377	146
Not completed	36	62
Physician decision	2	8
Subject decision	16	40
Protocol deviation	2	2
Adverse event	9	5
No longer clinically benefiting	4	4
Lost to follow-up	3	2
New therapy for study indication	-	1

Period 2

Period 2 title	PTA (Extension) Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	AMG334 70mg / 140mg (PTA Phase)

Arm description:

Subjects who continued with erenumab treatment in the PTA (extension) Phase

Arm type	Experimental
Investigational medicinal product name	erenumab
Investigational medicinal product code	AMG334
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Erenumab (70 mg or 140 mg) monthly from Week 52 up to Week 100.

Arm title	From oral SOC prophylactics to AMG334 (PTA Phase)

Arm description:

Subjects who switched from oral SOC to erenumab treatment in the PTA (extension) Phase

Arm type	Experimental
Investigational medicinal product name	erenumab
Investigational medicinal product code	AMG334
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Erenumab (70 mg or 140 mg) monthly from Week 52 up to Week 100.

Number of subjects in period 2[1]	AMG334 70mg / 140mg (PTA Phase)	From oral SOC prophylactics to AMG334 (PTA Phase)
Started	343	118
Completed	328	108
Not completed	15	10
Subject decision	8	3
Protocol deviation	-	1
Pregnancy	1	-
Adverse event	2	1
No longer clinically benefiting	4	5

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Not all subjects who completed the Core Phase started the PTA (Extension) Phase.

Baseline characteristics

Reporting groups	
Reporting group title	AMG334 70mg / 140mg (Core Phase)
Reporting group description:	
Participants randomized to erenumab in the Core Phase	
Reporting group title	Oral SOC prophylactics (Core Phase)
Reporting group description:	
Participants randomized to oral SOC prophylactics in the Core Phase	

Reporting group values	AMG334 70mg / 140mg (Core Phase)	Oral SOC prophylactics (Core Phase)	Total
Number of subjects	413	208	621
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	407	208	615
From 65-84 years	6	0	6
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	41.1	41.5	
standard deviation	± 11.5	± 10.4	-
Gender Categorical Units: Subjects			
Female	363	182	545
Male	50	26	76
Race Units: Subjects			
White	406	206	612
Black or African American	2	0	2
Asian	0	1	1
Native Hawaiian or other Pacific Islander	0	0	0
American Indian or Alaska Native	1	0	1
Multiple	2	0	2
Unknown	2	1	3

End points

End points reporting groups

Reporting group title	AMG334 70mg / 140mg (Core Phase)
Reporting group description: Participants randomized to erenumab in the Core Phase	
Reporting group title	Oral SOC prophylactics (Core Phase)
Reporting group description: Participants randomized to oral SOC prophylactics in the Core Phase	
Reporting group title	AMG334 70mg / 140mg (PTA Phase)
Reporting group description: Subjects who continued with erenumab treatment in the PTA (extension) Phase	
Reporting group title	From oral SOC prophylactics to AMG334 (PTA Phase)
Reporting group description: Subjects who switched from oral SOC to erenumab treatment in the PTA (extension) Phase	

Primary: Proportion of subjects who complete initially assigned treatment and achieve at least 50% reduction from baseline in monthly migraine days at Month 12

End point title	Proportion of subjects who complete initially assigned treatment and achieve at least 50% reduction from baseline in monthly migraine days at Month 12

End point description:

Responder is defined as subject completing one year on the initially assigned treatment and achieving at least 50% reduction from baseline in monthly migraine days at Week 52. A migraine day was defined as any calendar day in which the subject experiences a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). A qualified migraine headache was defined as a migraine with or without aura, lasting for ≥ 30 minutes, and meeting specific criteria defined in the protocol. Missing data are imputed as non-response (NRI).

End point type	Primary

End point timeframe:

Month 12 (Week 52)

End point values	AMG334 70mg / 140mg (Core Phase)	Oral SOC prophylactics (Core Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	208		
Units: participants	232	35		

Statistical analyses

Statistical analysis title	AMG334 vs oral SOC prophylactics

Statistical analysis description:

Null hypothesis for primary analysis: In subjects with episodic migraine, AMG334 treatment group had the same effect as oral prophylactics group (net benefit OR =1).
Alternative hypothesis: In subjects with episodic migraine, AMG334 treatment group was different from oral prophylactics group (net benefit OR ≠1).

Statistical analysis utilizes a Cochran-Mantel-Haenszel test adjusting for stratification factor (no. of prior prophylactic migraine treatment failures=1 vs 2) after NRI for missing data

Comparison groups	AMG334 70mg / 140mg (Core Phase) v Oral SOC prophylactics (Core Phase)
Number of subjects included in analysis	621
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	6.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.28
upper limit	9.82

Secondary: Cumulative average change from baseline on the monthly migraine days during the treatment period for subjects on the initially assigned treatment (Months 1-12)

End point title	Cumulative average change from baseline on the monthly migraine days during the treatment period for subjects on the initially assigned treatment (Months 1-12)

End point description:

The average of monthly migraine days was obtained cumulatively every 4 weeks across 52 weeks (e.g. at Week 8 the average was based on data from Week 1 to Week 8; at Week 12 the average was based on Week 1 to Week 12 and so on). The cumulative average change from baseline in monthly migraine days was derived using difference between cumulative average of each month and baseline monthly migraine days.
The change from baseline was analyzed using a linear mixed effects repeated measures model including treatment group, baseline value, stratification factor(s), scheduled visit, and the interaction of treatment group with scheduled visit.

End point type	Secondary

End point timeframe:

From baseline to Week 52

End point values	AMG334 70mg / 140mg (Core Phase)	Oral SOC prophylactics (Core Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	208		
Units: monthly migraine days				
least squares mean (standard error)				
Week 4	-2.55 (± 0.17)	-0.55 (± 0.25)		
Week 8	-3.00 (± 0.17)	-1.01 (± 0.25)		
Week 12	-3.27 (± 0.17)	-1.05 (± 0.26)		
Week 16	-3.45 (± 0.17)	-1.22 (± 0.26)		
Week 20	-3.63 (± 0.17)	-1.35 (± 0.26)		
Week 24	-3.75 (± 0.17)	-1.56 (± 0.26)		
Week 28	-3.84 (± 0.17)	-1.73 (± 0.26)		

Week 32	-3.93 (± 0.17)	-1.91 (± 0.27)		
Week 36	-3.99 (± 0.17)	-1.99 (± 0.27)		
Week 40	-4.05 (± 0.17)	-2.06 (± 0.27)		
Week 44	-4.12 (± 0.17)	-2.11 (± 0.27)		
Week 48	-4.18 (± 0.17)	-2.07 (± 0.27)		
Week 52	-4.24 (± 0.17)	-2.11 (± 0.27)		

Statistical analyses

Statistical analysis title	AMG334 vs Oral SOC prophylactics - Week 52

Statistical analysis description:

A linear mixed effects model includes treatment group, baseline value, stratification factor, scheduled visit, and
the interaction of treatment group with scheduled visit. Unstructured covariance matrix assumed.
Comparison of adjusted means (Test - Ref.)

Comparison groups	AMG334 70mg / 140mg (Core Phase) v Oral SOC prophylactics (Core Phase)
Number of subjects included in analysis	621
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Linear mixed effects model
Parameter estimate	Mean difference (final values)
Point estimate	-2.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.74
upper limit	-1.52
Variability estimate	Standard error of the mean
Dispersion value	0.31

Secondary: Proportion of subjects completing the treatment period at Month 12 on the initially assigned treatment

End point title	Proportion of subjects completing the treatment period at Month 12 on the initially assigned treatment

End point description:

Subjects who completed one year on the initially assigned treatment were considered as responders for the analysis of this secondary endpoint.
A subject was considered as a non-responder if a subject did not complete one year on the initially assigned treatment. This included (a) subjects who discontinued initially assigned treatment permanently (b) subjects who switched to oral prophylactics other than initially assigned treatment. Missing data are imputed as non-response (NRI).

End point type	Secondary

End point timeframe:

Month 12 (Week 52)

End point values	AMG334 70mg / 140mg (Core Phase)	Oral SOC prophylactics (Core Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	208		
Units: participants	359	78		

Statistical analyses

Statistical analysis title	AMG334 vs Oral SOC prophylactics
Statistical analysis description:	
Statistical analysis utilizes a Cochran-Mantel-Haenszel (CMH) test adjusting for stratification factor (no. of prior prophylactic migraine treatment failures=1 vs 2) after NRI for missing data.	
Comparison groups	AMG334 70mg / 140mg (Core Phase) v Oral SOC prophylactics (Core Phase)
Number of subjects included in analysis	621
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	11.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.53
upper limit	16.87

Secondary: Proportion of responders (PGI-I score ≥5) as measured by PGIC at Month 12 for subjects completing the treatment period at Month 12 on initially assigned treatment

End point title	Proportion of responders (PGI-I score ≥5) as measured by PGIC at Month 12 for subjects completing the treatment period at Month 12 on initially assigned treatment

End point description:

The Patients' Global Impression of Change (PGIC) is a global assessment by the subject of the change in clinical status since the start of treatment. The PGIC is assessed periodically through the treatment period and at the end of the treatment period. The PGIC was rated with a 7-point scale, from 1 (no change or condition is worse) to 7 (a great deal better).
Subjects were considered as responder if PGIC score was 5, 6, or 7 at Month 12 on initially assigned treatment. Subject was considered as non-responder if subject did not complete 12 months on initially assigned treatment or if subject did not have score 5, 6 or 7 at Month 12. Missing data are imputed as non-response (NRI). The PGIC scores 5 to 7 are as follows:
5 = Moderately better, and a slight noticeable change
6 = Better, and a definite improvement that has made a real and worthwhile difference
7 = A great deal better, and a considerable difference that has made all the difference

End point type	Secondary

End point timeframe:

Month 12 (Week 52)

End point values	AMG334 70mg / 140mg (Core Phase)	Oral SOC prophylactics (Core Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	208		
Units: participants	314	39		

Statistical analyses

Statistical analysis title	AMG334 vs Oral SOC prophylactics
Statistical analysis description:	
Statistical analysis utilizes a Cochran-Mantel-Haenszel (CMH) test adjusting for stratification factor (no. of prior prophylactic migraine treatment failures=1 vs 2) after NRI for missing data.	
Comparison groups	AMG334 70mg / 140mg (Core Phase) v Oral SOC prophylactics (Core Phase)
Number of subjects included in analysis	621
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	13.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.08
upper limit	20.83

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Core Phase: From first dose of study medication (Day 1) up to 30 days after last dose (Week 52).
PTA (extension) Phase: From first dose of study medication (Week 52) up to 30 days after last dose (Week 104).

Adverse event reporting additional description:

In the core phase, for the patients who switched from AMG334 to oral SOC prophylactics, safety data collected before the switch is summarized in the AMG334 arm and safety data collected after the switch is summarized in the oral SOC prophylactics arm.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Core Phase: AMG334 70mg / 140mg

Reporting group description:

Subjects randomized to erenumab in the Core Phase (Day 1 to Week 52)

Reporting group title	PTA (extension) Phase: From oral SOC prophylactics to AMG334

Reporting group description:

Subjects who switched from oral SOC to erenumab treatment in the PTA (extension) Phase

Reporting group title	PTA (extension) Phase: AMG334 70mg / 140mg

Reporting group description:

Subjects who continued with erenumab treatment in the PTA (extension) Phase (Week 52 to Week 104)

Reporting group title	Core Phase: Oral SOC prophylactics

Reporting group description:

Subjects randomized to oral SOC prophylactics in the Core Phase (Day 1 to Week 52).
Includes 9 subjects switched from AMG334 to SOC prophylactics during the core phase.

Serious adverse events	Core Phase: AMG334 70mg / 140mg	PTA (extension) Phase: From oral SOC prophylactics to AMG334	PTA (extension) Phase: AMG334 70mg / 140mg
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 408 (3.68%)	4 / 118 (3.39%)	9 / 343 (2.62%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	0 / 408 (0.00%)	0 / 118 (0.00%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid cancer			

subjects affected / exposed	0 / 408 (0.00%)	0 / 118 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salivary gland neoplasm			
subjects affected / exposed	1 / 408 (0.25%)	0 / 118 (0.00%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer			
subjects affected / exposed	0 / 408 (0.00%)	0 / 118 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Medical device pain			
subjects affected / exposed	1 / 408 (0.25%)	0 / 118 (0.00%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Food allergy			
subjects affected / exposed	0 / 408 (0.00%)	0 / 118 (0.00%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic reaction			
subjects affected / exposed	1 / 408 (0.25%)	0 / 118 (0.00%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Menometrorrhagia			
subjects affected / exposed	0 / 408 (0.00%)	0 / 118 (0.00%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometriosis			

subjects affected / exposed	1 / 408 (0.25%)	0 / 118 (0.00%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial hyperplasia			
subjects affected / exposed	0 / 408 (0.00%)	0 / 118 (0.00%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast fibrosis			
subjects affected / exposed	0 / 408 (0.00%)	0 / 118 (0.00%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	0 / 408 (0.00%)	1 / 118 (0.85%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 408 (0.25%)	0 / 118 (0.00%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mood altered			
subjects affected / exposed	0 / 408 (0.00%)	1 / 118 (0.85%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Wound			
subjects affected / exposed	0 / 408 (0.00%)	0 / 118 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	1 / 408 (0.25%)	0 / 118 (0.00%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Procedural pain			
subjects affected / exposed	0 / 408 (0.00%)	0 / 118 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle hernia			
subjects affected / exposed	0 / 408 (0.00%)	0 / 118 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	1 / 408 (0.25%)	0 / 118 (0.00%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament sprain			
subjects affected / exposed	1 / 408 (0.25%)	0 / 118 (0.00%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 408 (0.25%)	0 / 118 (0.00%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	1 / 408 (0.25%)	0 / 118 (0.00%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	1 / 408 (0.25%)	0 / 118 (0.00%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Migraine			
subjects affected / exposed	1 / 408 (0.25%)	0 / 118 (0.00%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			

subjects affected / exposed	1 / 408 (0.25%)	0 / 118 (0.00%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Tympanic membrane perforation			
subjects affected / exposed	0 / 408 (0.00%)	1 / 118 (0.85%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Ulcerative keratitis			
subjects affected / exposed	0 / 408 (0.00%)	0 / 118 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Umbilical hernia			
subjects affected / exposed	0 / 408 (0.00%)	0 / 118 (0.00%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin laxity			
subjects affected / exposed	0 / 408 (0.00%)	1 / 118 (0.85%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 408 (0.00%)	0 / 118 (0.00%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 408 (0.00%)	0 / 118 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric rupture			

subjects affected / exposed	0 / 408 (0.00%)	0 / 118 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 408 (0.00%)	0 / 118 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Diastasis recti abdominis			
subjects affected / exposed	0 / 408 (0.00%)	1 / 118 (0.85%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoroacetabular impingement			
subjects affected / exposed	1 / 408 (0.25%)	0 / 118 (0.00%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint stiffness			
subjects affected / exposed	1 / 408 (0.25%)	0 / 118 (0.00%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metatarsalgia			
subjects affected / exposed	0 / 408 (0.00%)	0 / 118 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	1 / 408 (0.25%)	0 / 118 (0.00%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 408 (0.25%)	0 / 118 (0.00%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastroenteritis			
subjects affected / exposed	0 / 408 (0.00%)	0 / 118 (0.00%)	0 / 343 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 408 (0.00%)	0 / 118 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Core Phase: Oral SOC prophylactics		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 206 (4.37%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thyroid cancer			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Salivary gland neoplasm			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Papillary thyroid cancer			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Medical device pain			

subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Food allergy			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anaphylactic reaction			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Menometrorrhagia			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endometriosis			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endometrial hyperplasia			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast fibrosis			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ovarian cyst			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mood altered			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Wound			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radius fracture			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Procedural pain			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscle hernia			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Meniscus injury			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ligament sprain			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Hip fracture			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hand fracture			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ankle fracture			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Migraine			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Tympanic membrane perforation			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Ulcerative keratitis			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Umbilical hernia			

subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Skin laxity			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hydronephrosis			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ureteric rupture			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Diastasis recti abdominis			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Femoroacetabular impingement			

subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Joint stiffness			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metatarsalgia			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis acute			
subjects affected / exposed	0 / 206 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Core Phase: AMG334 70mg / 140mg	PTA (extension) Phase: From oral SOC prophylactics to AMG334	PTA (extension) Phase: AMG334 70mg / 140mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	131 / 408 (32.11%)	47 / 118 (39.83%)	106 / 343 (30.90%)
Investigations			
Weight increased			
subjects affected / exposed	12 / 408 (2.94%)	2 / 118 (1.69%)	0 / 343 (0.00%)
occurrences (all)	12	2	0
Injury, poisoning and procedural complications			
Vaccination complication			
subjects affected / exposed	9 / 408 (2.21%)	8 / 118 (6.78%)	16 / 343 (4.66%)
occurrences (all)	14	16	27
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	5 / 408 (1.23%)	1 / 118 (0.85%)	3 / 343 (0.87%)
occurrences (all)	6	1	3
Dizziness			
subjects affected / exposed	7 / 408 (1.72%)	1 / 118 (0.85%)	6 / 343 (1.75%)
occurrences (all)	7	1	6
Somnolence			
subjects affected / exposed	5 / 408 (1.23%)	2 / 118 (1.69%)	0 / 343 (0.00%)
occurrences (all)	6	2	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	18 / 408 (4.41%)	2 / 118 (1.69%)	4 / 343 (1.17%)
occurrences (all)	27	2	5
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	53 / 408 (12.99%)	16 / 118 (13.56%)	10 / 343 (2.92%)
occurrences (all)	71	17	10
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	36 / 408 (8.82%)	10 / 118 (8.47%)	28 / 343 (8.16%)
occurrences (all)	46	18	34
COVID-19			
subjects affected / exposed	20 / 408 (4.90%)	18 / 118 (15.25%)	61 / 343 (17.78%)
occurrences (all)	20	18	69

Non-serious adverse events	Core Phase: Oral SOC prophylactics		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	91 / 206 (44.17%)		
Investigations			
Weight increased			
subjects affected / exposed	22 / 206 (10.68%)		
occurrences (all)	22		
Injury, poisoning and procedural complications			
Vaccination complication			
subjects affected / exposed	2 / 206 (0.97%)		
occurrences (all)	4		
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	15 / 206 (7.28%)		
occurrences (all)	15		
Dizziness			
subjects affected / exposed	18 / 206 (8.74%)		
occurrences (all)	22		
Somnolence			
subjects affected / exposed	15 / 206 (7.28%)		
occurrences (all)	15		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	33 / 206 (16.02%)		
occurrences (all)	38		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 206 (0.97%)		
occurrences (all)	2		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	15 / 206 (7.28%)		
occurrences (all)	19		
COVID-19			
subjects affected / exposed	12 / 206 (5.83%)		
occurrences (all)	12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 June 2019	The purpose of this global amendment was to update the protocol language to reflect feedback received from Health Authorities on contraception/pregnancy language and on standard of care practices globally from participating investigators.
15 June 2020	The purpose of this amendment was to provide post trial access (PTA) to AMG334 for eligible subjects completing visits through Week 52 of the Core phase. PTA to AMG334 was provided for up to 52 Weeks (based on continued benefit of AMG334 treatment) in all eligible subjects for the PTA (extension) phase. In addition, details for potential trial conduct changes due to the COVID-19 pandemic were incorporated in this protocol amendment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported