Sponsor

Novartis

Generic Drug Name

Erenumab

Trial Indication(s)

Episodic migraine headaches

Protocol Number

CAMG334A2401

Protocol Title

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

Clinical Trial Phase

IV

Phase of Drug Development

Phase IV

Study Start/End Dates

15-May-2019 to 30-Sep-2022 (last subject last visit of Extension Phase)

Reason for Termination (N/A)

Study Design/Methodology

This was a single-cohort, 2-treatment arm, parallel-group randomized (2:1 [erenumab (70 mg or 140 mg): Standard of Care (SoC) oral prophylactic]), open-label study in adult subjects with episodic migraine who had previously failed 1 or 2 locally approved prophylactic migraine treatments. The following periods are included in the study design, with study visits at 4-week intervals after completion of screening:

Screening Period (0-2 weeks) – Required for all subjects to assess initial eligibility and to obtain informed consent.

Baseline Period (4 weeks) – All subjects who successfully completed the screening period were invited to participate. Eligibility for randomization was assessed based on migraine frequency and diary compliance during this period. Randomization was stratified by prior prophylactic migraine medication treatment failure (due to insufficient efficacy or poor tolerability) reported during Screening/Baseline Period: 1 treatment failure (TF1) vs 2 treatment failures (TF2). A 30% cap of randomized subjects to the TF2 strata was implemented.

Open-Label Randomized Treatment Period (52 weeks) – Core Phase: All subjects who successfully completed the Baseline period were invited to participate. Eligible subjects were randomized 2:1 to one of two treatment arms [erenumab s.c. once monthly versus SoC oral prophylactic (active comparator)]. Only monotherapy was allowed in both arms and no concomitant use of other prophylactics for migraine were permitted. Dose adjustment was permitted if allowed per label and patient was not a treatment failure.

Switching:

Patients on erenumab could change treatment to SoC but SoC patients were not permitted to switch to erenumab. The need to switch treatments was based on investigator assessment of efficacy and safety at study visits. This was a pragmatic trial where physicians prescribed locally approved pharmacological treatments for the prevention of migraine, as per local label.

Post-Trial Access (PTA) Open-Label Treatment Period (52 weeks) – **Extension Phase:** Patients completing visits through week 52 of the Core Phase were eligible to participate. Patient eligibility was determined by the investigators opinion as follows: 1) patients treated with erenumab must have benefited from erenumab treatment and 2) patients on Standard of Care (SoC) oral prophylactic must have been in need of a treatment switch. PTA to erenumab was provided for up to 52 weeks (based on continued benefit of erenumab treatment) in all eligible patients.

Centers

Argentina (2), Austria (1), Belgium (6), Czech Republic (9), Finland (3), France (5), Germany (5), Greece (6), Israel (5), Italy (3), Netherlands (3), Poland (4), Portugal (5), Slovakia (7), Spain (9), United Kingdom (1), United States (10)

Objectives:

Primary objective(s)

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

Secondary objective(s)

- To evaluate the effect of erenumab compared to oral prophylactics on overall subject retention defined as percentage of subjects completing treatment period at Month 12 on initially assigned treatment.
- To evaluate the effect of erenumab compared to oral prophylactics on the change from baseline in monthly migraine days during the treatment period.
- To evaluate the effect of erenumab compared to oral prophylactics on the subject's assessment of the change in clinical status since the start of treatment as measured by the Patient’s Global Impression of Change (PGIC) Scale.

Test Product (s), Dose(s), and Mode(s) of Administration

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. Active comparator (Oral SOC prophylactics**)** was locally approved oral prophylactic migraine medication.

In the Core Phase, 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. Participants randomized to oral SOC prophylactics continued to be dosed through Week 52 as per label.

In the PTA (extension) Phase, all participants received erenumab 70 mg or 140 mg monthly from Week 52 up to Week 100.

Statistical Methods

The primary analyses compared the proportion of subjects in the full analysis set (FAS) who achieved a net benefit between erenumab vs oral prophylactic medication for subjects completing 52 week treatment period on the initially assigned medication.

Null hypothesis: In subjects with episodic migraine, the erenumab treatment group has the same effect as oral prophylactics group, in terms of the net benefit i.e., net benefit odds ratio =1.

Alternative hypothesis: In subjects with episodic migraine, the erenumab treatment group was different from oral prophylactics group, in terms of the net benefit i.e., net benefit odds ratio ≠ 1.

A Cochran-Mantel-Haenszel (CMH) test stratified by number of previous treatment failures (1 vs. 2) was used under a 2-sided significance level of 0.05 to evaluate the association between the net benefit rate and the treatment. The p-value of the test, and the estimated odds ratio between erenumab and active comparator, as well as its 95% confidence interval, were also reported.

Analysis of primary and secondary endpoints was based on the FAS. The FAS comprised all subjects to whom study treatment had been assigned by randomization.

Analysis of safety was based on the Safety Set (SAF) in the Core Phare and on the PTA Safety Set (PTA SAF) in the PTA (Extension) Phase. The SAF included all subjects who received at least one dose of study treatment during Core Phase. The PTA SAF included all subjects who received at least one dose of study treatment during PTA Phase.

Study Population: Key Inclusion/Exclusion Criteria

The key inclusion criteria included:

1. Written informed consent must be obtained before any assessment is performed

2. Adults ≥18 of age upon entry into screening

3. Documented history of migraine (with or without aura) ≥12 months prior to screening according to the International Classification of Headache Disorders-3rd Edition (ICHD-3)

4. ≥4 and <15 days per month of migraine symptoms (based on ICHD-3 criteria) on average across 3 months prior to screening based on retrospective reporting

5. <15 days per month of headache symptoms (i.e., migraine and non-migraine)

6. Subjects in need for switching by documented failure of 1 or 2 prophylactic treatments in the last 6 months due to either lack of efficacy or poor tolerability. For subjects with 1 prior treatment failure, the failure should have occurred in the last 6 months. For subjects with 2 prior treatment failures, the second treatment failure should have occurred in the last 6 months

7. During baseline period, confirmed migraine frequency of 4 to 14 migraine days and <15 days of headache symptoms

8. During baseline period, ≥80% compliance with the headache diary

The key exclusion criteria included:

1. Older than 50 years of age at migraine onset

2. History of cluster headache or hemiplegic migraine headache

3. Unable to differentiate migraine from other headaches or active chronic pain syndromes (e.g.,fibromyalgia, chronic pelvic pain)

4. Lack of efficacy or poor tolerability with > 2 treatments from the following 7 medication categories for prophylactic treatment of migraine after an adequate therapeutic trial. These medication categories are:

Category 1: Divalproex sodium, sodium valproate

Category 2: Topiramate

Category 3: Beta blockers (for example: atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol)

Category 4: Tricyclic antidepressants (for example: amitriptyline, nortriptyline, protriptyline)

Category 5: Serotonin-norepinephrine reuptake inhibitors (for example: venlafaxine,desvenlafaxine, duloxetine, milnacipran)

Category 6: Flunarizine, verapamil

Category 7: Lisinopril, candesartan

5. Used a prohibited medication from the 7 categories of prior prophylactic medications within 3 months prior to the start of and during baseline for a non-migraine indication if dose was not stable

6. Exposure to botulinum toxin in the head and/or neck region within 4 months prior to the start of the baseline period or during the baseline period

7. Device, or procedure that potentially may interfere with the intensity or number of migraine days within 2 months prior to the start of or during baseline

8. Taken the following for any indication in any month during the 2 months prior to the start of the baseline period:

Ergotamines or triptans on ≥ 10 days per month, or

Simple analgesics (non-steroidal anti-inflammatory drugs [NSAIDs], acetaminophen) on ≥ 15 days per month, or

Opioid- or butalbital-containing analgesics on ≥4 days per month.

9. Previous exposure to erenumab or exposure to any other prophylactic CGRP-targeted therapy

10. History of seizure disorders or HIV infection or other unstable or clinically significant medical condition or test results; history or current evidence of major psychiatric disorders; malignancy within the past 5 years; cardiac disorders or suicidal ideation in the past 6 months or suicidal behaviors in the past 2 years; pregnant women

11. Evidence of drug or alcohol abuse or dependence within 12 months prior to screening, based on medical records or subject self-report

Participant Flow Table

Subject Disposition-Core Phase (FAS)

Disposition/Reason	AMG334 70mg / 140mg N=413 n (%)	Oral SOC prophylactics N=208 n (%)	All Subjects N=621 n (%)
Randomized	413 (100)	208 (100)	621 (100)
Completed 52 week core phase	377 (91.3)	146 (70.2)	523 (84.2)
- on initially assigned treatment	359 (86.9)	78 (37.5)	437 (70.4)
- on switched treatment	4 (1.0)	36 (17.3)	40 (6.4)
- off study treatment	14 (3.4)	32 (15.4)	46 (7.4)
Discontinued core phase of study prematurely	36 (8.7)	62 (29.8)	98 (15.8)
Primary reason for premature discontinuation of core phase of study			
Adverse event	9 (2.2)	5 (2.4)	14 (2.3)
Lost to follow-up	3 (0.7)	2 (1.0)	5 (0.8)
New Therapy for Study Indication	0	1 (0.5)	1 (0.2)
No longer clinically benefiting	4 (1.0)	4 (1.9)	8 (1.3)
Physician decision	2 (0.5)	8 (3.8)	10 (1.6)
Protocol Deviation	2 (0.5)	2 (1.0)	4 (0.6)
Subject decision	16 (3.9)	40 (19.2)	56 (9.0)
Subjects entered extension (PTA) phase	342 (82.8)	117 (56.3)	459 (73.9)
Subjects entered Follow up phase (FUP) phase*	2 (0.5)	4 (1.9)	6 (1.0)

-A subject is defined as a completer on core phase if subject completes 52 weeks on the study.
- On initially assigned treatment': Subjects who took randomized study drug until Week 52
-On switched treatment': Subjects who switched to Oral SOC prophylactics at least once and took study drug until Week 52.
-Off study treatment': Subjects who discontinued treatment early but continued on study for 52 Weeks.
*Safety follow up is applicable only for protocol version 0 and amendment 1.
All percentages are calculated based on the number of randomized subjects in respective treatment arms.
-The discontinuation reasons are the primary reasons from the Study Disposition page sorted alphabetically (except for Missing' category).

Subject Disposition-PTA (Extension) Phase (PTA SAF)

Oral SOC prophylactics refers to the subjects who had switched from oral SOC to AMG334 treatment in the PTA (extension) phase. AMG334 70mg/140mg refers to the subjects who received AMG334 in the Core phase and continued on AMG334 treatment in the PTA (extension) phase.

Disposition/Reason	AMG334 70mg / 140mg N=343 n (%)	Oral SOC prophylactics N=118 n (%)	All Subjects N=461 n (%)
Subjects switched at least once during core phase	0	45 (38.1)	45 (9.8)
Subjects completed PTA phase	328 (95.6)	108 (91.5)	436 (94.6)
Discontinued study prematurely during PTA phase	15 (4.4)	10 (8.5)	25 (5.4)
Primary reason for premature discontinuation of the study during PTA Phase			
Adverse event	2 (0.6)	1 (0.8)	3 (0.7)
Lost to follow-up	0	0	0
New Therapy for Study Indication	0	0	0
No longer clinically benefiting	4 (1.2)	5 (4.2)	9 (2.0)
Pregnancy	1 (0.3)	0	1 (0.2)
Physician decision	0	0	0
Protocol Deviation	0	1 (0.8)	1 (0.2)
Subject decision	8 (2.3)	3 (2.5)	11 (2.4)

- For two subjects, the exposure data at the last visit in the Core phase were not available at the time of the Core phase lock and the data extraction, hence the total number of subjects entering PTA (extension) phase provided in the Core phase clinical study report (CSR) (459 subjects) is different in than in the PTA phase and extension phase CSR (461 subjects).
- A subject is defined as a completer if the Subject Status is marked as “Completed” at the end of the study disposition page for subjects who entered PTA phase.
- All percentages are calculated based on N.
- The discontinuation reasons are the primary reasons from the Study Disposition page sorted alphabetically (except for 'Missing' category).

Baseline Characteristics

Demographic summary (FAS)

Characteristic	AMG334 70mg/140mg N=413	Oral SOC Prophylactics N=208	All Subjects N=621
Age group – n (%)			
< 65 years	407 (98.5)	208 (100.0)	615 (99.0)
>= 65 years	6 (1.5)	0	6 (1.0)
Age (years)			
n	413	208	621
Mean	41.1	41.5	41.3
SD	11.5	10.4	11.2
Min	18	19	18
Median	42.0	43.0	42.0
Max	72	62	72
Gender – n (%)			
Male	50 (12.1)	26 (12.5)	76 (12.2)
Female	363 (87.9)	182 (87.5)	545 (87.8)
Unknown	0	0	0
Undifferentiated	0	0	0
Race - n (%)			
White	406 (98.0)	206 (99.0)	614 (98.9)
Black or African American	2 (0.005)	0	3 (0.5)
Asian	0	1 (0.5)	2 (0.3)
Native Hawaiian or other Pacific Islander	0	0	0
American Indian or Alaska Native	1 (0.2)	0	1 (0.2)
Multiple	2 (0.5)	0	2 (0.3)

Characteristic	AMG334 70mg/140mg N=413	Oral SOC Prophylactics N=208	All Subjects N=621
Unknown	2 (0.5)	1 (0.5)	3 (0.5)
Ethnicity - n (%)			
Hispanic or Latino	25 (6.1)	17 (8.2)	42 (6.8)
Not Hispanic or Latino	381 (92.3)	190 (91.3)	571 (91.9)
Not Reported	6 (1.5)	1 (0.5)	7 (1.1)
Unknown	1 (0.2)	0	1 (0.2)
BMI (kg/m2)			
n	413	208	621
Mean	25.09	25.06	25.08
SD	5.39	5.21	5.33
Min	16.0	17.4	16.0
Median	24.03	24.10	24.09
Max	57.0	52.6	57.0

- Age is calculated from date of screening and date of birth.
- Weight and height are taken from screening vital signs evaluations.
- BMI (kg/m2): body mass index, computed as weight[kg] /(height[m]**2)
- If multiple races have been reported for a subject, the subject were categorized as multiple and in each selected race category.

Baseline characteristics (FAS)

Characteristic	AMG334 70mg / 140mg N=413	Oral SOC Prophylactics N=208	All Subjects N=621
Monthly migraine days			
n	413	208	621
Mean	9.54	9.05	9.37
SD	2.69	2.87	2.76

Characteristic	AMG334 70mg / 140mg N=413	Oral SOC Prophylactics N=208	All Subjects N=621
Min	4.0	3.2	3.2
Median	9.33	8.75	9.03
Max	25.0	19.7	25.0
Monthly migraine attacks (number of events)			
n	413	208	621
Mean	5.27	4.79	5.11
SD	1.43	1.53	1.48
Min	1.7	2.0	1.7
Median	5.09	4.83	5.00
Max	9.0	10.1	10.1
Monthly headache days			
n	413	208	621
Mean	10.31	9.95	10.19
SD	2.77	2.86	2.80
Min	4.0	4.0	4.0
Median	10.00	9.91	10.00
Max	25.0	19.7	25.0
Monthly acute migraine-specific medication use (days)			
n	413	208	621
Mean	4.80	4.15	4.58
SD	3.44	3.30	3.41
Min	0.0	0.0	0.0
Median	5.00	4.13	5.00
Max	23.0	13.1	23.0
Monthly acute headache medication use (days)			
n	413	208	621
Mean	7.05	6.48	6.86
SD	2.66	2.90	2.75

Characteristic	AMG334 70mg / 140mg N=413	Oral SOC Prophylactics N=208	All Subjects N=621
Min	0.0	0.0	0.0
Median	7.00	6.56	7.00
Max	23.0	14.0	23.0
Acute headache medication- n(%)			
None	2 (0.5)	1 (0.5)	3 (0.5)
Any acute medication	411 (99.5)	207 (99.5)	618 (99.5)
Migraine-specific	342 (82.8)	160 (76.9)	502 (80.8)
Non migraine-specific	69 (16.7)	47 (22.6)	116 (18.7)
Age at onset of migraine (years)			
n	413	208	621
Mean	19.77	22.31	20.62
SD	9.24	10.52	9.75
Min	3.0	6.0	3.0
Median	17.00	20.00	18.00
Max	48.0	49.0	49.0
Disease duration of migraine with or without aura (years)			
n	413	208	621
Mean	21.37	19.23	20.66
SD	12.21	11.59	12.04
Min	1.0	1.0	1.0
Median	20.00	18.00	19.00
Max	56.0	52.0	56.0
Aura status			
Migraine with aura	212 (51.3)	107 (51.4)	319 (51.4)
Migraine without aura	201 (48.7)	101 (48.6)	302 (48.6)
Number of prior prophylactic migraine treatment failure*			
1	291 (70.5)	146 (70.2)	437 (70.4)
2	122 (29.5)	62 (29.8)	184 (29.6)

Characteristic	AMG334 70mg / 140mg N=413	Oral SOC Prophylactics N=208	All Subjects N=621

- * it reflects the randomization strata. It might be different from the actual value at baseline.
- The baseline period is defined as the period between Week -4 visit and the day prior to first dose. The baseline value is the prorated number to 28-day equivalents during baseline period.

Primary Outcome Result(s)

Responder rate - proportion of subjects completing Core phase on the initially assigned treatment and achieving at least 50% reduction from baseline in monthly migraine days at Week 52, NRI, CMH test FAS

Treatment group	n/N (%)	Comparison	Odds ratio	95% CI (Lower, upper)	p-value
AMG334 70mg / 140mg	232/413 (56.2)	AMG334 70mg / 140mg vs Oral SOC prophylactics	6.48	(4.28, 9.82)	<0.0001
Oral SOC prophylactics	35/208 (16.8)				

- Responder is defined as subject completing one year on the initially assigned treatment and achieving at least 50% reduction from baseline in MMD at Week 52.
- n: The number of subjects who responded.
- N: The total number of subjects in the treatment group.
- Statistical analysis utilizes a Cochran-Mantel-Haenszel (CMH) test adjusting for stratification factor (no. of prior prophylactic migraine treatment failures=1 vs 2) after missing data are imputed as non-response (NRI).

Secondary Outcome Result(s)

Responder rate - proportion of subjects completing treatment at Week 52 on the initially assigned treatment, CMH test FAS

Treatment group	n/N (%)	Comparison	Odds ratio	95% CI (Lower, upper)	p-value
AMG334 70mg / 140mg	359 / 413 (86.9)	AMG334 70mg / 140mg vs Oral SOC prophylactics	11.27	(7.53, 16.87)	<0.0001
Oral SOC prophylactics	78 / 208 (37.5)				

- Subject was considered as responder if subject completes 52 weeks on initially assigned treatment.
- n: the number of subjects who responded.
- N: The total number of subjects in the treatment group.
- Statistical analysis utilizes a Cochran-Mantel-Haenszel (CMH) test adjusting for stratification factor (no. of prior prophylactic migraine treatment failures=1 vs 2) after missing data are imputed as non-response (NRI).

Change from baseline in cumulative average monthly migraine days by visit, observed, mixed model repeated measures on initially assigned treatment FAS

		n		Adjusted mean change (SE)		Comparison of adjusted means: Test vs Ref			
Test vs Ref. (Comparison)	Week	AMG334	Oral prophylactics	AMG334	Oral prophy -lactics	Difference (Test-Ref.)	SE	95% CI	2-sided p-value
AMG334	Week 4	406	184	-2.55 (0.17)	-0.55 (0.25)	-2.00	0.29	(-2.57, -1.43)	<0.001
70mg /	Week 8	404	151	-3.00 (0.17)	-1.01 (0.25)	-1.98	0.29	(-2.56, -1.40)	<0.001
140mg	Week 12	399	131	-3.27 (0.17)	-1.05 (0.26)	-2.22	0.30	(-2.81, -1.64)	<0.001
(N=413) vs	Week 16	398	121	-3.45 (0.17)	-1.22 (0.26)	-2.23	0.30	(-2.82, -1.64)	<0.001
Oral SOC	Week 20	391	111	-3.63 (0.17)	-1.35 (0.26)	-2.27	0.30	(-2.86, -1.68)	<0.001
prophylactics	Week 24	387	101	-3.75 (0.17)	-1.56 (0.26)	-2.19	0.30	(-2.78, -1.59)	<0.001

		n		Adjusted mean change (SE)		Comparison of adjusted means: Test vs Ref			
Test vs Ref. (Comparison)	Week	AMG334	Oral prophylactics	AMG334	Oral prophy -lactics	Difference (Test-Ref.)	SE	95% CI	2-sided p-value
(N=208)	Week 28	383	94	-3.84 (0.17)	-1.73 (0.26)	-2.11	0.31	(-2.71, -1.52)	<0.001
	Week 32	378	89	-3.93 (0.17)	-1.91 (0.27)	-2.02	0.31	(-2.63, -1.42)	<0.001
	Week 36	375	83	-3.99 (0.17)	-1.99 (0.27)	-2.00	0.31	(-2.61, -1.40)	<0.001
	Week 40	371	82	-4.05 (0.17)	-2.06 (0.27)	-1.99	0.31	(-2.60, -1.38)	<0.001
	Week 44	368	80	-4.12 (0.17)	-2.11 (0.27)	-2.01	0.31	(-2.62, -1.40)	<0.001
	Week 48	365	78	-4.18 (0.17)	-2.07 (0.27)	-2.11	0.31	(-2.72, -1.50)	<0.001
	Week 52	359	78	-4.24 (0.17)	-2.11 (0.27)	-2.13	0.31	(-2.74, -1.52)	<0.001

- N: The number of subjects included in the analysis set.
- n: number of Subjects with non-missing value at the corresponding time point of interest.
- 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.

Responder rate-proportion of responders as measured by PGIC at Week 52 on the initially assigned treatment, NRI, CMH test FAS

Treatment group	n/N (%)	Comparison	Odds ratio	95% CI (Lower, Upper)	p-value
AMG334 70mg / 140mg	314/413 (76.0)	AMG334 70mg / 140mg vs. Oral SOC prophylactics	13.75	(9.08, 20.83)	<0.001
Oral SOC prophylactics	39/208 (18.8)				

-Subject was considered as responder if PGIC score is >=5 at Week 52 on initially assigned treatment where score 5=moderately better, 6=better, 7=a great deal better.
- n: the number of subjects who responded.
- N: The total number of subjects in the treatment group.
- Statistical analysis utilizes a Cochran-Mantel-Haenszel (CMH) test adjusting for stratification factor (no. of prior prophylactic migraine treatment failures=1 vs 2) after missing data are imputed as non-response (NRI).

Safety Results

Time Frame	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).
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.
Source Vocabulary for Table Default	MedDRA (25.1)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	Core Phase: AMG334 70mg / 140mg N = 408	**Core Phase: Oral SOC prophylactics N = 206**	**PTA (extension) Phase: AMG334 70mg / 140mg N = 343**	**PTA (extension) Phase: From oral SOC prophylactics to AMG334 N = 118**
Arm/Group Description	Subjects randomized to erenumab in the Core Phase (Day 1 to Week 52)	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	Subjects who continued with erenumab treatment in the PTA (extension) Phase (Week 52 to Week 104)	Subjects who switched from oral SOC to erenumab treatment in the PTA (extension) Phase
Total Number Affected	0	0	0	0
Total Number At Risk	408	206	343	118

Serious Adverse Events

	Core Phase: AMG334 70mg / 140mg N = 408	Core Phase: Oral SOC prophylactics N = 206	PTA (extension) Phase: AMG334 70mg / 140mg N = 343	PTA (extension) Phase: From oral SOC prophylactics to AMG334 N = 118
Arm/Group Description	Subjects randomized to erenumab in the Core Phase (Day 1 to Week 52)	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.	Subjects who continued with erenumab treatment in the PTA (extension) Phase (Week 52 to Week 104)	Subjects who switched from oral SOC to erenumab treatment in the PTA (extension) Phase
Total # Affected by any Serious Adverse Event	15	9	9	4
Total # at Risk by any Serious Adverse Event	408	206	343	118
Ear and labyrinth disorders				
Tympanic membrane perforation	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.85%)
Endocrine disorders				
Goitre	0 (0.00%)	0 (0.00%)	1 (0.29%)	0 (0.00%)
Eye disorders				
Ulcerative keratitis	0 (0.00%)	0 (0.00%)	1 (0.29%)	0 (0.00%)
Gastrointestinal disorders				
Umbilical hernia	0 (0.00%)	1 (0.49%)	0 (0.00%)	0 (0.00%)
General disorders and administration site conditions				
Medical device pain	1 (0.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Immune system disorders				

Anaphylactic reaction	1 (0.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Food allergy	0 (0.00%)	1 (0.49%)	0 (0.00%)	0 (0.00%)
Infections and infestations				
COVID-19 pneumonia	1 (0.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Diverticulitis	1 (0.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastroenteritis	0 (0.00%)	1 (0.49%)	0 (0.00%)	0 (0.00%)
Pyelonephritis acute	0 (0.00%)	0 (0.00%)	1 (0.29%)	0 (0.00%)
Injury, poisoning and procedural complications				
Ankle fracture	1 (0.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hand fracture	1 (0.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hip fracture	1 (0.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ligament sprain	1 (0.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Meniscus injury	1 (0.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Muscle hernia	0 (0.00%)	0 (0.00%)	1 (0.29%)	0 (0.00%)
Procedural pain	0 (0.00%)	0 (0.00%)	1 (0.29%)	0 (0.00%)
Radius fracture	1 (0.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Wound	0 (0.00%)	0 (0.00%)	1 (0.29%)	0 (0.00%)
Musculoskeletal and connective tissue disorders				
Diastasis recti abdominis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.85%)
Femoroacetabular impingement	1 (0.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Joint stiffness	1 (0.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Metatarsalgia	0 (0.00%)	0 (0.00%)	1 (0.29%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				

Papillary thyroid cancer	0 (0.00%)	0 (0.00%)	1 (0.29%)	0 (0.00%)
Salivary gland neoplasm	1 (0.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Thyroid cancer	0 (0.00%)	0 (0.00%)	1 (0.29%)	0 (0.00%)
Uterine leiomyoma	0 (0.00%)	1 (0.49%)	0 (0.00%)	0 (0.00%)
Nervous system disorders				
Headache	1 (0.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Migraine	1 (0.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Psychiatric disorders				
Mood altered	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.85%)
Suicide attempt	1 (0.25%)	1 (0.49%)	0 (0.00%)	0 (0.00%)
Renal and urinary disorders				
Hydronephrosis	0 (0.00%)	0 (0.00%)	1 (0.29%)	0 (0.00%)
Nephrolithiasis	0 (0.00%)	1 (0.49%)	0 (0.00%)	0 (0.00%)
Ureteric rupture	0 (0.00%)	0 (0.00%)	1 (0.29%)	0 (0.00%)
Reproductive system and breast disorders				
Breast fibrosis	0 (0.00%)	1 (0.49%)	0 (0.00%)	0 (0.00%)
Endometrial hyperplasia	0 (0.00%)	1 (0.49%)	0 (0.00%)	0 (0.00%)
Endometriosis	1 (0.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Menometrorrhagia	0 (0.00%)	1 (0.49%)	0 (0.00%)	0 (0.00%)
Ovarian cyst	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.85%)
Skin and subcutaneous tissue disorders				
Skin laxity	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.85%)

Other (Not Including Serious) Adverse Events

Frequent Event Reporting Threshold 5%

	Core Phase: AMG334 70mg / 140mg N = 408	Core Phase: Oral SOC prophylactics N = 206	PTA (extension) Phase: AMG334 70mg / 140mg N = 343	PTA (extension) Phase: From oral SOC prophylactics to AMG334 N = 118
Arm/Group Description	Subjects randomized to erenumab in the Core Phase (Day 1 to Week 52)	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.	Subjects who continued with erenumab treatment in the PTA (extension) Phase (Week 52 to Week 104)	Subjects who switched from oral SOC to erenumab treatment in the PTA (extension) Phase
Total # Affected by any Other Adverse Event	131	91	106	47
Total # at Risk by any Other Adverse Event	408	206	343	118
Gastrointestinal disorders				
Constipation	53 (12.99%)	2 (0.97%)	10 (2.92%)	16 (13.56%)
General disorders and administration site conditions				
Fatigue	18 (4.41%)	33 (16.02%)	4 (1.17%)	2 (1.69%)
Infections and infestations				
COVID-19	20 (4.90%)	12 (5.83%)	61 (17.78%)	18 (15.25%)
Nasopharyngitis	36 (8.82%)	15 (7.28%)	28 (8.16%)	10 (8.47%)
Injury, poisoning and procedural complications				
Vaccination complication	9 (2.21%)	2 (0.97%)	16 (4.66%)	8 (6.78%)
Investigations				

Weight increased	12 (2.94%)	22 (10.68%)	0 (0.00%)	2 (1.69%)
Nervous system disorders				
Dizziness	7 (1.72%)	18 (8.74%)	6 (1.75%)	1 (0.85%)
Paraesthesia	5 (1.23%)	15 (7.28%)	3 (0.87%)	1 (0.85%)
Somnolence	5 (1.23%)	15 (7.28%)	0 (0.00%)	2 (1.69%)

Conclusion:

- This was the first global study comparing the long-term (1 year treatment) benefit of two treatment paradigms: erenumab subcutaneous every 4 weeks vs locally approved daily oral standard of care (SoC) prophylactic medications.
- The study met all primary and secondary endpoints and, therefore, demonstrated that treatment with erenumab showed superiority in efficacy compared to daily oral standard of care prophylactic medications as used in clinical practice.
- Subjects on erenumab were almost 3 times more likely to stay on the initially assigned treatment and achieve at least a 50% reduction in Monthly Migraine Days (MMDs) as compared to SoC treatment. Subject retention on initially assigned treatment at Week 52 was more than 2 times higher with erenumab than oral SoC preventives. At Week 52, 76% of subjects on erenumab reported a clinically meaningful improvement in well-being, as compared to 19% of subjects on oral SOC preventatives as measured by the subject reported Patient Global Impression of Change (PGIC) scale.
- The safety assessments reflected a better tolerability and safety profile for erenumab vs.SoC.
- The results of the long-term PTA (extension) phase confirmed the manageable safety of AMG334 70 mg/140 mg for episodic migraine subjects who failed on previous medications and are in need of other options.

Clinical Study Report

15 March 2022 (Core Phase) and 31 March 2023 (Extension Phase)