Clinical trial results:
A Phase 2a Randomized Double-blind Placebo Controlled Study to Evaluate the Efficacy and Safety of AMG 301 in Migraine Prevention

Summary

EudraCT number	2017-000630-57
Trial protocol	CZ DK SE FI DE AT NL
Global end of trial date	04 February 2019

Results information

Result version number	v1 (current)
This version publication date	15 February 2020
First version publication date	15 February 2020

Trial information

Trial identification

Sponsor protocol code	20150308

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03238781
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen, Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, 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	04 February 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of AMG 301 compared to placebo on the change from the baseline period in monthly migraine days in subjects with migraine.

Protection of trial subjects:

The protocol, protocol amendments, informed consent form, Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) were submitted to an Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs) by the investigator and reviewed and approved by the IRB/IEC. A copy of the written approval of the protocol and informed consent form were received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

The investigator or his/her delegated representative (a physician) explained to the subject the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) were administered, and answered all questions regarding the study.

Subjects must be informed that their participation is voluntary.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 September 2017
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: 24
Country: Number of subjects enrolled	United States: 129
Country: Number of subjects enrolled	Austria: 15
Country: Number of subjects enrolled	Czech Republic: 61
Country: Number of subjects enrolled	Denmark: 33
Country: Number of subjects enrolled	Finland: 32
Country: Number of subjects enrolled	Germany: 33
Country: Number of subjects enrolled	Sweden: 16
Worldwide total number of subjects	343
EEA total number of subjects	190

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)	343
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 510 subjects were screened.

Pre-assignment

Screening details:

Participants were randomized 4:3:3
to placebo, AMG 301 210 mg Q4W, or AMG 301 420 mg Q2W, respectively.
The randomization was stratified by
- chronic migraine versus episodic migraine and
- North America versus Rest of World.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject

Blinding implementation details:

Individual subject treatment assignments were maintained by the IVR/IWR System.
Any unplanned unblinding occurring during the study period were documented and reported in the final clinical study report.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants randomized to Placebo were administered 6 subcutaneous (SC) injections on day 1 and weeks 2, 4, 6, 8 and 10 during the 12 week double-blind treatment period.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo was presented in identical containers, stored/packaged the same as AMG 301. All injections were administered within 30 minutes on treatment days.

Arm title	AMG 301 210 mg Q4W

Arm description:

Participants randomized to AMG 301 210 mg every fourth week (Q4W) received a total of 3 AMG 301 subcutaneous (SC) injections (70 mg/mL in each injection) plus 3 matching placebo injections on day 1 and weeks 4 and 8. Participants also received 6 SC placebo injections on weeks 2, 6, and 10 during the 12 week double-blind treatment period.

Arm type	Experimental
Investigational medicinal product name	AMG 301
Investigational medicinal product code	
Other name	human monoclonal immunoglobulin G1 antagonist
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

AMG 301 was packaged in 5 mL clear glass vials containing 1 mL of 70 mg/mL of AMG 301. All injections were administered within 30 minutes on treatment days.

Arm title	AMG 301 420 mg Q2W

Arm description:

Participants randomized to AMG 301 420 mg every second week (Q2W) received a total of 6 AMG 301 subcutaneous (SC) injections (70 mg/mL in each injection) on day 1 and weeks 2, 4, 6, 8, and 10 during the 12 week double-blind treatment period.

Arm type	Experimental
Investigational medicinal product name	AMG 301
Investigational medicinal product code	
Other name	human monoclonal immunoglobulin G1 antagonist
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

AMG 301 was packaged in 5 mL clear glass vials containing 1 mL of 70 mg/mL of AMG 301. All injections were administered within 30 minutes on treatment days.

Number of subjects in period 1	Placebo	AMG 301 210 mg Q4W	AMG 301 420 mg Q2W
Started	137	104	102
Completed	111	87	82
Not completed	26	17	20
Consent withdrawn by subject	23	14	16
Adverse event, non-fatal	1	1	2
Lost to follow-up	2	1	2
Decision by sponsor	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants randomized to Placebo were administered 6 subcutaneous (SC) injections on day 1 and weeks 2, 4, 6, 8 and 10 during the 12 week double-blind treatment period.	
Reporting group title	AMG 301 210 mg Q4W
Reporting group description:	
Participants randomized to AMG 301 210 mg every fourth week (Q4W) received a total of 3 AMG 301 subcutaneous (SC) injections (70 mg/mL in each injection) plus 3 matching placebo injections on day 1 and weeks 4 and 8. Participants also received 6 SC placebo injections on weeks 2, 6, and 10 during the 12 week double-blind treatment period.	
Reporting group title	AMG 301 420 mg Q2W
Reporting group description:	
Participants randomized to AMG 301 420 mg every second week (Q2W) received a total of 6 AMG 301 subcutaneous (SC) injections (70 mg/mL in each injection) on day 1 and weeks 2, 4, 6, 8, and 10 during the 12 week double-blind treatment period.	

Reporting group values	Placebo	AMG 301 210 mg Q4W	AMG 301 420 mg Q2W
Number of subjects	137	104	102
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)	137	104	102
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	41.8	42.3	42.5
standard deviation	± 9.9	± 9.7	± 9.4
Sex: Female, Male Units:			
Female	117	94	90
Male	20	10	12
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	6	6	3
Not Hispanic or Latino	131	98	99
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	1	0
Asian	0	0	2

Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	6	2	4
White	129	100	96
More than one race	1	0	0
Unknown or Not Reported	1	1	0
Baseline Migraine Type			
Chronic migraine (CM) was defined as: >= 15 headache days of which >= 8 headache days meet criteria as migraine days during the baseline period based on the electronic diary (eDiary) calculations. Episodic migraine was defined as: <15 headache days of which >=4 headache days meet criteria as migraine days during the baseline period based on the eDiary calculations.			
Units: Subjects			
Chronic migraine	44	39	36
Episodic migraine	93	65	66
Weight			
Units: kg			
arithmetic mean	71.8	73.8	72.1
standard deviation	± 15.0	± 17.2	± 14.9
Height			
Units: cm			
arithmetic mean	168.27	167.05	167.55
standard deviation	± 7.82	± 8.56	± 7.72
Body Mass Index			
Units: kg/m^2			
arithmetic mean	25.29	26.37	25.64
standard deviation	± 4.66	± 5.45	± 4.78
Monthly Migraine Days			
A migraine day is any calendar day from the eDiary in which the participant experienced a migraine headache. A migraine headache is a headache with or without aura, lasting for >= 4 hours, and meeting >=1 of the criteria: a) >= 2 pain features (unilateral, throbbing, moderate to severe, exacerbated with exercise/physical activity) b) >= 1 symptoms (nausea and/or vomiting, photophobia and phonophobia) If the participant took a migraine-specific medication during aura or to treat headache, it was counted as a migraine day. Baseline timeframe was the 28-day period prior to study treatment.			
Units: days			
arithmetic mean	12.18	12.47	12.14
standard deviation	± 5.14	± 4.78	± 5.32
Monthly Headache Days			
A headache day is any calendar day from the eDiary in which the participant experiences a headache (initial onset, continuation or recurrence of the headache). A qualified headache is defined as: - a migraine headache (including an aura-only event that is treated with acute migraine-specific medication), or - a non-migraine headache, which is a headache that lasts >= 4 hours and is not a migraine headache, or - a headache of any duration for which acute headache treatment is administered. Baseline timeframe was the 28-day period prior to study treatment.			
Units: days			
arithmetic mean	13.45	13.85	13.09
standard deviation	± 5.27	± 4.90	± 5.24

Reporting group values	Total		
Number of subjects	343		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	343		
From 65-84 years	0		
85 years and over	0		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units:			
Female	301		
Male	42		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	15		
Not Hispanic or Latino	328		
Unknown or Not Reported	0		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	1		
Asian	2		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	12		
White	325		
More than one race	1		
Unknown or Not Reported	2		
Baseline Migraine Type			
Chronic migraine (CM) was defined as: >= 15 headache days of which >= 8 headache days meet criteria as migraine days during the baseline period based on the electronic diary (eDiary) calculations. Episodic migraine was defined as: <15 headache days of which >=4 headache days meet criteria as migraine days during the baseline period based on the eDiary calculations.			
Units: Subjects			
Chronic migraine	119		
Episodic migraine	224		
Weight			
Units: kg			
arithmetic mean			
standard deviation	-		
Height			
Units: cm			
arithmetic mean			
standard deviation	-		
Body Mass Index			
Units: kg/m^2			
arithmetic mean			
standard deviation	-		
Monthly Migraine Days			
A migraine day is any calendar day from the eDiary in which the participant experienced a migraine headache. A migraine headache is a headache with or without aura, lasting for >= 4 hours, and meeting			

>=1 of the criteria: a) >= 2 pain features (unilateral, throbbing, moderate to severe, exacerbated with exercise/physical activity) b) >= 1 symptoms (nausea and/or vomiting, photophobia and phonophobia) If the participant took a migraine-specific medication during aura or to treat headache, it was counted as a migraine day. Baseline timeframe was the 28-day period prior to study treatment.			
Units: days arithmetic mean standard deviation	- 		
Monthly Headache Days			
A headache day is any calendar day from the eDiary in which the participant experiences a headache (initial onset, continuation or recurrence of the headache). A qualified headache is defined as: - a migraine headache (including an aura-only event that is treated with acute migraine-specific medication), or - a non-migraine headache, which is a headache that lasts >= 4 hours and is not a migraine headache, or - a headache of any duration for which acute headache treatment is administered. Baseline timeframe was the 28-day period prior to study treatment.			
Units: days arithmetic mean standard deviation	- 		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants randomized to Placebo were administered 6 subcutaneous (SC) injections on day 1 and weeks 2, 4, 6, 8 and 10 during the 12 week double-blind treatment period.	
Reporting group title	AMG 301 210 mg Q4W
Reporting group description:	
Participants randomized to AMG 301 210 mg every fourth week (Q4W) received a total of 3 AMG 301 subcutaneous (SC) injections (70 mg/mL in each injection) plus 3 matching placebo injections on day 1 and weeks 4 and 8. Participants also received 6 SC placebo injections on weeks 2, 6, and 10 during the 12 week double-blind treatment period.	
Reporting group title	AMG 301 420 mg Q2W
Reporting group description:	
Participants randomized to AMG 301 420 mg every second week (Q2W) received a total of 6 AMG 301 subcutaneous (SC) injections (70 mg/mL in each injection) on day 1 and weeks 2, 4, 6, 8, and 10 during the 12 week double-blind treatment period.	

Primary: Change from Baseline in Monthly Migraine Days to the Last 4 Weeks of the 12 Week Double-Blind Treatment Period

End point title	Change from Baseline in Monthly Migraine Days to the Last 4 Weeks of the 12 Week Double-Blind Treatment Period
End point description:	
A migraine day is any calendar day from the eDiary in which the participant experienced a migraine headache. A migraine headache is a headache with or without aura, lasting for >= 4 hours, and meeting >=1 of the criteria: a) >= 2 pain features (unilateral, throbbing, moderate to severe, exacerbated with exercise/physical activity) b) >= 1 symptoms (nausea and/or vomiting, photophobia and phonophobia) If the participant took a migraine-specific medication during aura or to treat headache, it was counted as a migraine day. Days without eDiary data in each monthly interval are handled by proration. Negative change from baseline values indicated improvement (i.e. fewer migraine days after treatment as compared to baseline).	
End point type	Primary
End point timeframe:	
Baseline Day -28 to Day -1; Weeks 9-12	

End point values	Placebo	AMG 301 210 mg Q4W	AMG 301 420 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119	93	85	
Units: days				
least squares mean (standard error)	-2.45 (± 0.40)	-2.20 (± 0.45)	-2.19 (± 0.46)	

Statistical analyses

Statistical analysis title	Monthly Migraine Days: AMG301 210mg Q4W - Placebo

Statistical analysis description:

An adjusted analysis is presented that utilized a generalized linear mixed model which included treatment, visit, treatment-by-visit interaction, stratification factors of region and baseline migraine frequency (chronic migraine vs episodic migraine), and baseline value as covariates and assuming a first-order autoregressive covariance structure. The p-values for pairwise comparisons versus placebo are nominal p-values without multiplicity adjustment.

Comparison groups	Placebo v AMG 301 210 mg Q4W
Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.66 [1]
Method	Mixed models analysis
Parameter estimate	difference in least square mean
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	1.4

Notes:

[1] - 2-sided significance level of 0.05

Statistical analysis title	Monthly Migraine Days: AMG301 420mg Q2W - Placebo

Statistical analysis description:

An adjusted analysis is presented that utilized a generalized linear mixed model which included treatment, visit, treatment-by-visit interaction, stratification factors of region and baseline migraine frequency (chronic migraine vs episodic migraine), and baseline value as covariates and assuming a first-order autoregressive covariance structure. The p-values for pairwise comparisons versus placebo are nominal p-values without multiplicity adjustment.

Comparison groups	Placebo v AMG 301 420 mg Q2W
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.65 [2]
Method	Mixed models analysis
Parameter estimate	difference in least square mean
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.89
upper limit	1.43

Notes:

[2] - 2-sided significance level of 0.05

Secondary: Percentage of Participants Who Responded, Defined as At Least a 50% Reduction from the Baseline Period in Monthly Migraine Days in the Last 4 Weeks of the 12-Week Double-Blind Treatment Period

End point title	Percentage of Participants Who Responded, Defined as At Least a 50% Reduction from the Baseline Period in Monthly Migraine Days in the Last 4 Weeks of the 12-Week Double-Blind Treatment Period

End point description:

Responders are participants who had at least a 50% reduction from baseline in monthly migraine days during the last 4 weeks of treatment in the 12-week double blind period.

End point type	Secondary

End point timeframe:

Baseline Day -28 to Day -1; Weeks 9-12

End point values	Placebo	AMG 301 210 mg Q4W	AMG 301 420 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119	93	85	
Units: percentage of participants				
number (not applicable)	22.7	19.4	18.8	

Statistical analyses

Statistical analysis title	50% Migraine Days: AMG301 210mg Q4W - Placebo

Statistical analysis description:

The common odds ratios and p-values are obtained from a Cochran-Mantel-Haenszel test, stratified by stratification factors of region and baseline migraine frequency (chronic migraine vs episodic migraine).

Comparison groups	Placebo v AMG 301 210 mg Q4W
Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.57 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	1.62

Notes:

[3] - 2-sided significance level of 0.05

Statistical analysis title	50% Migraine Days: AMG301 420mg Q2W - Placebo

Statistical analysis description:

The common odds ratios and p-values are obtained from a Cochran-Mantel-Haenszel test, stratified by stratification factors of region and baseline migraine frequency (chronic migraine vs episodic migraine).

Comparison groups	Placebo v AMG 301 420 mg Q2W

Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.45 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	1.54

Notes:

[4] - 2-sided significance level of 0.05

Secondary: Change from Baseline Period in Monthly Acute Migraine-Specific Medication Days in the Last 4 Weeks of the 12-Week Double-Blind Treatment Period

End point title	Change from Baseline Period in Monthly Acute Migraine-Specific Medication Days in the Last 4 Weeks of the 12-Week Double-Blind Treatment Period

End point description:

Number of days on which acute headache medications (triptans and ergotamine-derivatives, alone or in combination) are used as recorded in eDiary. Monthly acute headache medication treatment days at baseline are the number of acute headache medication treatment days in the baseline period. Days without eDiary data are handled by proration.

Negative change from baseline values indicate improvement (i.e. fewer days requiring acute migraine-specific medications after treatment as compared to baseline).

End point type	Secondary

End point timeframe:

Baseline Day -28 to Day -1; Weeks 9-12

End point values	Placebo	AMG 301 210 mg Q4W	AMG 301 420 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	103	84	76	
Units: days				
least squares mean (standard error)	-1.25 (± 0.29)	-1.28 (± 0.33)	-1.34 (± 0.34)	

Statistical analyses

Statistical analysis title	Migraine Meds: AMG301 210mg Q4W - Placebo

Statistical analysis description:

Adjusted analysis utilizes a generalized linear mixed model which includes treatment, visit, treatment-by-visit interaction, stratification factors of region and baseline migraine frequency (CM versus EM), and baseline value as covariates and assuming a first-order autoregressive covariance structure. The p-values for pairwise comparisons versus placebo are nominal p-values without multiplicity adjustment.

Comparison groups	Placebo v AMG 301 210 mg Q4W

Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.94 [5]
Method	Mixed models analysis
Parameter estimate	difference in least square mean
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.87
upper limit	0.81

Notes:

[5] - 2-sided significance level of 0.05

Statistical analysis title	Migraine Meds: AMG301 420mg Q2W - Placebo
Comparison groups	Placebo v AMG 301 420 mg Q2W
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.84 [6]
Method	Mixed models analysis
Parameter estimate	difference in least square mean
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.94
upper limit	0.77

Notes:

[6] - 2-sided significance level of 0.05

Secondary: Change from Baseline in Mean Physical Impairment Domain Scores as Measured by the Migraine Physical Function Impact Diary (MPFID) Over the Last 4 Weeks of the 12-Week Double-Blind Treatment Period

End point title	Change from Baseline in Mean Physical Impairment Domain Scores as Measured by the Migraine Physical Function Impact Diary (MPFID) Over the Last 4 Weeks of the 12-Week Double-Blind Treatment Period

End point description:

Participants complete the MPFID every day during baseline (Days -28 to Day -1) and the 12-week Double Blind Treatment Period. The MPFID has 2 domains, Impact on Everyday Activities (7 items) and Physical Impairment (5 items), and 1 stand-alone global question that provides an assessment of the overall impact of migraine on participants' everyday activities. The recall period for each item is the past 24 hours.
The Physical Impairment Domain Score is reported here.
A participant's response to the difficulty of the 5 physical impairment items is measured using a 5-point scale, with difficulty measurements ranging from 1 to 5. The sum was rescaled to a 0 to 100 scale, with 0=no difficulty and 100=unable to do (maximum burden). Negative change from baseline values indicate improvement in migraine impact.

End point type	Secondary

End point timeframe:

Baseline Day -28 to Day -1; Weeks 9-12

End point values	Placebo	AMG 301 210 mg Q4W	AMG 301 420 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119	93	86	
Units: units on a scale				
least squares mean (standard error)	-2.44 (± 0.78)	-2.72 (± 0.89)	-2.13 (± 0.91)	

Statistical analyses

Statistical analysis title	Phys Impair: AMG301 210mg Q4W - Placebo

Statistical analysis description:

An adjusted analysis is presented that utilized a generalized linear mixed model which included treatment, visit, treatment-by-visit interaction, stratification factors of region and baseline migraine frequency (chronic migraine vs episodic migraine), and baseline value as covariates and assuming a first-order autoregressive covariance structure. The p-values for pairwise comparisons versus placebo are nominal p-values without multiplicity adjustment.

Comparison groups	Placebo v AMG 301 210 mg Q4W
Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.81 [7]
Method	Mixed models analysis
Parameter estimate	difference in least square mean
Point estimate	-0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.56
upper limit	2.01

Notes:

[7] - 2-sided significance level of 0.05

Statistical analysis title	Phys Impair: AMG301 420mg Q2W - Placebo

Statistical analysis description:

An adjusted analysis is presented that utilized a generalized linear mixed model which included treatment, visit, treatment-by-visit interaction, stratification factors of region and baseline migraine frequency (chronic migraine vs episodic migraine), and baseline value as covariates and assuming a first-order autoregressive covariance structure. The p-values for pairwise comparisons versus placebo are nominal p-values without multiplicity adjustment.

Comparison groups	Placebo v AMG 301 420 mg Q2W
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.79 [8]
Method	Mixed models analysis
Parameter estimate	difference in least square mean
Point estimate	0.31

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.01
upper limit	2.63

Notes:

[8] - 2-sided significance level of 0.05

Secondary: Change from Baseline in Mean Impact on Everyday Activity Domain Scores as Measured by the Migraine Physical Function Impact Diary (MPFID) Over the Last 4 Weeks of the 12-Week Double-Blind Treatment Period

End point title	Change from Baseline in Mean Impact on Everyday Activity Domain Scores as Measured by the Migraine Physical Function Impact Diary (MPFID) Over the Last 4 Weeks of the 12-Week Double-Blind Treatment Period

End point description:

Participants complete the MPFID every day during baseline (Days -28 to Day -1) and the 12-week Double Blind Treatment Period. The MPFID has 2 domains, Impact on Everyday Activities (7 items) and Physical Impairment (5 items), and 1 stand-alone global question that provides an assessment of the overall impact of migraine on participants' everyday activities. The recall period for each item is the past 24 hours.
The Impact on Everyday Activities Domain Score is reported here.
A participant's response to the Impact on Everyday Activities 7 items is measured using a 5-point scale, with difficulty measurements ranging from 1 to 5. The sum was rescaled to a 0 to 100 scale, with 0=no difficulty and 100=unable to do (maximum burden). Negative change from baseline values indicate improvement in migraine impact.

End point type	Secondary

End point timeframe:

Baseline Day -28 to Day -1; Weeks 9-12

End point values	Placebo	AMG 301 210 mg Q4W	AMG 301 420 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119	93	86	
Units: units on a scale				
least squares mean (standard error)	-3.42 (± 0.79)	-4.28 (± 0.89)	-2.86 (± 0.92)	

Statistical analyses

Statistical analysis title	Everyday Act: AMG301 210mg Q4W - Placebo

Statistical analysis description:

An adjusted analysis is presented that utilized a generalized linear mixed model which included treatment, visit, treatment-by-visit interaction, stratification factors of region and baseline migraine frequency (chronic migraine vs episodic migraine), and baseline value as covariates and assuming a first-order autoregressive covariance structure. The p-values for pairwise comparisons versus placebo are nominal p-values without multiplicity adjustment.

Comparison groups	Placebo v AMG 301 210 mg Q4W

Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.46 [9]
Method	Mixed models analysis
Parameter estimate	difference in least square mean
Point estimate	-0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.15
upper limit	1.44

Notes:

[9] - 2-sided significance level of 0.05

Statistical analysis title	Everyday Act: AMG301 420mg Q2W - Placebo

Statistical analysis description:

An adjusted analysis is presented that utilized a generalized linear mixed model which included treatment, visit, treatment-by-visit interaction, stratification factors of region and baseline migraine frequency (chronic migraine vs episodic migraine), and baseline value as covariates and assuming a first-order autoregressive covariance structure. The p-values for pairwise comparisons versus placebo are nominal p-values without multiplicity adjustment.

Comparison groups	Placebo v AMG 301 420 mg Q2W
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.64 [10]
Method	Mixed models analysis
Parameter estimate	difference in least square mean
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.77
upper limit	2.89

Notes:

[10] - 2-sided significance level of 0.05

Secondary: Participants with Treatment-Emergent Adverse Events (TEAEs)

End point title	Participants with Treatment-Emergent Adverse Events (TEAEs)

End point description:

Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4, where:

Grade 1 = Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; Grade 2 = Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL); Grade 3 = Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL; Grade 4 = Life-threatening consequences; urgent intervention indicated Grade 5 = Death related to AE.

End point type	Secondary

End point timeframe:

Day 1 up to Week 28 (12 weeks of double-blind treatment plus 16 weeks follow-up after last dose of investigational product)

End point values	Placebo	AMG 301 210 mg Q4W	AMG 301 420 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	137	104	102	
Units: participants				
>= 1 TEAE	90	71	65	
Severity grade >= 2	41	43	39	
Severity grade >= 3	9	5	8	
Severity grade >= 4	0	1	0	
Serious TEAE	3	1	2	
TEAE leading to discontinuation of IP	3	2	5	
Fatal TEAE	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Met Hy’s Law Criteria at Baseline and On Study

End point title	Percentage of Participants Who Met Hy’s Law Criteria at Baseline and On Study

End point description:

Hy's law predicts potential for drug-related hepatotoxicity. Hy's Law cases have three components:

- The drug causes hepatocellular injury, generally defined as an elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) by 3-fold or greater above the upper limit of normal (ULN).
- Among participants showing such aminotransferase elevations, they also have elevation of their serum total bilirubin of greater than 2 times the ULN, without findings of cholestasis (defined as serum alkaline phosphatase activity less than 2 times the upper limit of normal).
- No other reason can be found to explain the combination of increased aminotransferase and serum total bilirubin, such as viral hepatitis, alcohol abuse, ischemia, preexisting liver disease, or another drug capable of causing the observed injury.

End point type	Secondary

End point timeframe:

Baseline: Day 1 On study: Weeks 4, 6, 12, 20, 28

End point values	Placebo	AMG 301 210 mg Q4W	AMG 301 420 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	137	104	102	
Units: percentage of participants				
Baseline	0	0	0	
On study (n=136, 104, 100)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Aminotransferase Test Abnormalities > 3 Times the Upper Limit of Normal (ULN) at Baseline and On Study

End point title	Percentage of Participants With Aminotransferase Test Abnormalities > 3 Times the Upper Limit of Normal (ULN) at Baseline and On Study

End point description:

Aminotransferase tests included alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Percentage of participants with results that were greater than 3 * ULN for either test are reported.

End point type	Secondary

End point timeframe:

Baseline: Day 1 On study: Weeks 4, 6, 12, 20, 28

End point values	Placebo	AMG 301 210 mg Q4W	AMG 301 420 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	137	104	102	
Units: percentage of participants				
number (not applicable)				
Baseline	0	1.9	0	
On study (n=136, 104, 100)	0.7	1.9	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Total Bilirubin Test Abnormalities > 2 Times the Upper Limit of Normal (ULN) at Baseline and On Study

End point title	Percentage of Participants With Total Bilirubin Test Abnormalities > 2 Times the Upper Limit of Normal (ULN) at Baseline and On Study

End point description:

Percentage of participants with total bilirubin results that were greater than 2 * ULN are reported.

End point type	Secondary

End point timeframe:

Baseline: Day 1 On study: Weeks 4, 6, 12, 20, 28

End point values	Placebo	AMG 301 210 mg Q4W	AMG 301 420 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	137	104	102	
Units: percentage of participants				
Baseline	0	0	0	
On study (n=136, 104, 100)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Systolic Blood Pressure (SBP) in Categories by Visit

End point title	Percentage of Participants with Systolic Blood Pressure (SBP) in Categories by Visit

End point description:

Participant was expected to be in a supine position (or the most recumbent position possible) in a rested and calm state for at least 5 minutes before blood pressure assessments were conducted. Blood pressure units are millimeters of mercury (mmHg).

End point type	Secondary

End point timeframe:

Day 1, Weeks 2, 4, 6, 8, 10, 12,16, 20, 24, 28

End point values	Placebo	AMG 301 210 mg Q4W	AMG 301 420 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	137	104	102	
Units: percentage of participants				
number (not applicable)				
Day 1 SBP <90 mmHg	0.9	0.0	0.0	
Day 1 SBP > 140 mmHg	5.5	7.9	4.9	
Day 1 SBP > 160 mmHg	0.9	0.0	0.0	
Week 2 SBP < 90 mmHg	1.5	0.0	0.0	
Week 2 SBP > 140 mmHg	5.2	2.9	8.0	
Week 2 SBP > 160 mmHg	0.0	0.0	1.0	
Week 4 SBP < 90 mmHg	0.0	0.0	0.0	
Week 4 SBP > 140 mmHg	3.0	3.0	6.2	
Week 4 SBP > 160 mmHg	0.7	0.0	1.0	
Week 6 SBP < 90 mmHg	0.8	0.0	0.0	
Week 6 SBP > 140 mmHg	3.1	3.1	3.2	
Week 6 SBP > 160 mmHg	0.0	0.0	0.0	
Week 8 SBP < 90 mmHg	0.0	0.0	0.0	
Week 8 SBP > 140 mmHg	2.3	5.4	8.5	
Week 8 SBP > 160 mmHg	0.0	0.0	1.1	
Week 10 SBP < 90 mmHg	0.0	0.0	0.0	
Week 10 SBP > 140 mmHg	4.1	1.1	2.2	
Week 10 SBP > 160 mmHg	0.0	0.0	2.2	

Week 12 SBP < 90 mmHg	0.8	0.0	0.0	
Week 12 SBP > 140 mmHg	6.4	2.2	5.7	
Week 12 SBP > 160 mmHg	0.0	0.0	0.0	
Week 16 SBP < 90 mmHg	0.9	0.0	0.0	
Week 16 SBP > 140 mmHg	4.4	4.4	5.7	
Week 16 SBP > 160 mmHg	0.0	0.0	3.4	
Week 20 SBP < 90 mmHg	0.9	0.0	0.0	
Week 20 SBP > 140 mmHg	4.4	8.1	7.3	
Week 20 SBP > 160 mmHg	0.9	0.0	0.0	
Week 24 SBP < 90 mmHg	0.0	1.2	0.0	
Week 24 SBP > 140 mmHg	4.7	6.1	8.9	
Week 24 SBP > 160 mmHg	0.0	0.0	0.0	
Week 28 SBP < 90 mmHg	0.9	1.2	0.0	
Week 28 SBP > 140 mmHg	8.3	4.7	6.3	
Week 28 SBP > 160 mmHg	0.9	1.2	0.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Diastolic Blood Pressure (DBP) in Categories by Visit

End point title	Percentage of Participants with Diastolic Blood Pressure (DBP) in Categories by Visit

End point description:

Participant was expected to be in a supine position (or the most recumbent position possible) in a rested and calm state for at least 5 minutes before blood pressure assessments were conducted. Blood pressure units are millimeters of mercury (mmHg).

End point type	Secondary

End point timeframe:

Day 1, Weeks 2, 4, 6, 8, 10, 12,16, 20, 24, 28

End point values	Placebo	AMG 301 210 mg Q4W	AMG 301 420 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	137	104	102	
Units: percentage of participants				
number (not applicable)				
Day 1 DBP <50 mmHg	0.0	0.0	0.0	
Day 1 DBP > 90 mmHg	4.5	6.7	7.4	
Day 1 DBP > 100 mmHg	0.0	1.1	0.0	
Week 2 DBP <50 mmHg	0.7	0.0	0.0	
Week 2 DBP > 90 mmHg	3.7	4.9	11.0	
Week 2 DBP > 100 mmHg	0.7	1.0	0.0	
Week 4 DBP <50 mmHg	0.7	0.0	0.0	
Week 4 DBP > 90 mmHg	5.2	7.0	9.3	
Week 4 DBP > 100 mmHg	0.7	2.0	1.0	
Week 6 DBP <50 mmHg	0.0	0.0	0.0	

Week 6 DBP > 90 mmHg	9.2	3.1	7.4	
Week 6 DBP > 100 mmHg	0.0	0.0	1.1	
Week 8 DBP <50 mmHg	0.0	0.0	0.0	
Week 8 DBP > 90 mmHg	4.6	6.5	9.6	
Week 8 DBP > 100 mmHg	0.0	1.1	0.0	
Week 10 DBP <50 mmHg	0.0	0.0	0.0	
Week 10 DBP > 90 mmHg	6.6	4.3	9.9	
Week 10 DBP > 100 mmHg	0.0	0.0	1.1	
Week 12 DBP <50 mmHg	0.0	0.0	0.0	
Week 12 DBP > 90 mmHg	7.2	3.3	8.0	
Week 12 DBP > 100 mmHg	0.0	0.0	1.1	
Week 16 DBP <50 mmHg	0.0	0.0	0.0	
Week 16 DBP > 90 mmHg	5.3	5.6	12.5	
Week 16 DBP > 100 mmHg	0.0	0.0	2.3	
Week 20 DBP <50 mmHg	0.0	0.0	0.0	
Week 20 DBP > 90 mmHg	8.0	8.1	7.3	
Week 20 DBP > 100 mmHg	0.0	1.2	1.2	
Week 24 DBP <50 mmHg	0.0	0.0	0.0	
Week 24 DBP > 90 mmHg	4.7	7.3	11.4	
Week 24 DBP > 100 mmHg	0.0	2.4	1.3	
Week 28 DBP <50 mmHg	0.0	0.0	0.0	
Week 28 DBP > 90 mmHg	4.6	10.6	10.0	
Week 28 DBP > 100 mmHg	0.0	1.2	1.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Pulse Rate in Categories by Visit

End point title	Percentage of Participants with Pulse Rate in Categories by Visit

End point description:

Participant was expected to be in a supine position (or the most recumbent position possible) in a rested and calm state for at least 5 minutes before pulse assessments were conducted. Pulse rate units are beats per minute (BPM)

End point type	Secondary

End point timeframe:

Day 1, Weeks 2, 4, 6, 8, 10, 12,16, 20, 24, 28

End point values	Placebo	AMG 301 210 mg Q4W	AMG 301 420 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	137	104	102	
Units: percentage of participants				
number (not applicable)				
Day 1 Pulse rate <60 bpm	15.5	13.5	6.2	
Day 1 Pulse rate >100 bpm	0.0	0.0	0.0	
Week 2 Pulse rate <60 bpm	11.2	4.9	6.0	

Week 2 Pulse rate >100 bpm	0.7	1.0	0.0	
Week 4 Pulse rate <60 bpm	10.4	8.0	6.2	
Week 4 Pulse rate >100 bpm	0.7	0.0	0.0	
Week 6 Pulse rate <60 bpm	6.9	8.2	9.6	
Week 6 Pulse rate >100 bpm	0.8	0.0	1.1	
Week 8 Pulse rate <60 bpm	9.2	7.6	12.8	
Week 8 Pulse rate >100 bpm	1.5	0.0	0.0	
Week 10 Pulse rate <60 bpm	11.5	8.6	6.6	
Week 10 Pulse rate >100 bpm	0.0	0.0	0.0	
Week 12 Pulse rate <60 bpm	13.6	13.0	8.0	
Week 12 Pulse rate >100 bpm	0.0	1.1	1.1	
Week 16 Pulse rate <60 bpm	10.6	8.9	8.0	
Week 16 Pulse rate >100 bpm	0.0	0.0	0.0	
Week 20 Pulse rate <60 bpm	10.6	9.3	9.8	
Week 20 Pulse rate >100 bpm	0.9	1.2	1.2	
Week 24 Pulse rate <60 bpm	10.4	8.5	7.6	
Week 24 Pulse rate >100 bpm	0.0	1.2	1.3	
Week 28 Pulse rate <60 bpm	8.3	11.8	10.0	
Week 28 Pulse rate >100 bpm	0.9	1.2	0.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Temperature in Categories by Visit

End point title	Percentage of Participants with Temperature in Categories by Visit

End point description:

Participant was expected to be in a supine position (or the most recumbent position possible) in a rested and calm state for at least 5 minutes before vital sign assessments were conducted. Temperature units are reported in degrees Celsius (C).

End point type	Secondary

End point timeframe:

Day 1, Weeks 2, 4, 6, 8, 10, 12,16, 20, 24, 28

End point values	Placebo	AMG 301 210 mg Q4W	AMG 301 420 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	137	104	102	
Units: percentage of participants				
number (not applicable)				
Day 1 Temperature < 36 C	5.5	10.1	7.4	
Day 1 Temperature > 38 C	0.0	0.0	0.0	
Week 2 Temperature < 36 C	11.2	9.8	8.0	
Week 2 Temperature > 38 C	0.0	0.0	0.0	
Week 4 Temperature < 36 C	8.9	12.0	10.3	
Week 4 Temperature > 38 C	0.0	0.0	0.0	
Week 6 Temperature < 36 C	6.1	12.4	8.5	

Week 6 Temperature > 38 C	0.0	0.0	0.0	
Week 8 Temperature < 36 C	7.7	7.6	8.5	
Week 8 Temperature > 38 C	0.0	0.0	0.0	
Week 10 Temperature < 36 C	9.0	14.0	7.7	
Week 10 Temperature > 38 C	0.0	0.0	0.0	
Week 12 Temperature < 36 C	8.0	13.0	12.5	
Week 12 Temperature > 38 C	0.8	0.0	0.0	
Week 16 Temperature < 36 C	6.2	7.8	13.6	
Week 16 Temperature > 38 C	0.0	0.0	0.0	
Week 20 Temperature < 36 C	10.6	7.0	9.8	
Week 20 Temperature > 38 C	0.0	0.0	0.0	
Week 24 Temperature < 36 C	5.7	8.5	11.4	
Week 24 Temperature > 38 C	0.0	0.0	0.0	
Week 28 Temperature < 36 C	6.5	9.4	11.3	
Week 28 Temperature > 38 C	0.0	0.0	0.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Respiratory Rates in Categories by Visit

End point title	Percentage of Participants with Respiratory Rates in Categories by Visit

End point description:

Participant was expected to be in a supine position (or the most recumbent position possible) in a rested and calm state for at least 5 minutes before vital sign assessments were conducted. Respiratory rate (RR) is reported in breaths/minute.

End point type	Secondary

End point timeframe:

Day 1, Weeks 2, 4, 6, 8, 10, 12,16, 20, 24, 28

End point values	Placebo	AMG 301 210 mg Q4W	AMG 301 420 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	137	104	102	
Units: percentage of participants				
number (not applicable)				
Day 1 RR < 12 breaths/min	4.6	2.2	3.8	
Day 1 RR > 20 breaths/min	0.0	2.2	1.3	
Week 2 RR < 12 breaths/min	5.2	2.9	5.0	
Week 2 RR > 20 breaths/min	0.0	0.0	0.0	
Week 4 RR < 12 breaths/min	2.2	3.0	5.2	
Week 4 RR > 20 breaths/min	0.0	0.0	2.1	
Week 6 RR < 12 breaths/min	6.1	1.0	4.3	
Week 6 RR > 20 breaths/min	0.8	0.0	0.0	
Week 8 RR < 12 breaths/min	3.1	2.2	1.1	
Week 8 RR > 20 breaths/min	0.0	2.2	0.0	
Week 10 RR < 12 breaths/min	5.7	1.1	4.4	

Week 10 RR > 20 breaths/min	0.0	2.2	0.0	
Week 12 RR < 12 breaths/min	4.0	1.1	0.0	
Week 12 RR > 20 breaths/min	0.0	0.0	0.0	
Week 16 RR < 12 breaths/min	4.4	2.2	4.5	
Week 16 RR > 20 breaths/min	0.0	1.1	0.0	
Week 20 RR < 12 breaths/min	5.3	0.0	1.2	
Week 20 RR > 20 breaths/min	0.0	1.2	0.0	
Week 24 RR < 12 breaths/min	1.9	0.0	0.0	
Week 24 RR > 20 breaths/min	0.0	4.9	0.0	
Week 28 RR < 12 breaths/min	3.7	1.2	2.5	
Week 28 RR > 20 breaths/min	0.9	2.4	1.3	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Week 28 (12 weeks of double-blind treatment plus 16 weeks follow-up after last dose of investigational product)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants randomized to Placebo were administered 6 subcutaneous (SC) injections on day 1 and weeks 2, 4, 6, 8 and 10 during the 12 week double-blind treatment period.

Reporting group title	AMG 301 210 mg Q4W

Reporting group description:

Participants randomized to AMG 301 210 mg every fourth week (Q4W) received a total of 3 AMG 301 subcutaneous (SC) injections (70 mg/mL in each injection) plus 3 matching placebo injections on day 1 and weeks 4 and 8. Participants also received 6 SC placebo injections on weeks 2, 6, and 10 during the 12 week double-blind treatment period.

Reporting group title	AMG 301 420 mg Q2W

Reporting group description:

Participants randomized to AMG 301 420 mg every second week (Q2W) received a total of 6 AMG 301 subcutaneous (SC) injections (70 mg/mL in each injection) on day 1 and weeks 2, 4, 6, 8, and 10 during the 12 week double-blind treatment period.

Serious adverse events	Placebo	AMG 301 210 mg Q4W	AMG 301 420 mg Q2W
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 137 (2.19%)	1 / 104 (0.96%)	2 / 102 (1.96%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Migraine with aura			
subjects affected / exposed	1 / 137 (0.73%)	0 / 104 (0.00%)	0 / 102 (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
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 137 (0.00%)	0 / 104 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			

Polycystic ovaries			
subjects affected / exposed	0 / 137 (0.00%)	1 / 104 (0.96%)	0 / 102 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 137 (0.73%)	0 / 104 (0.00%)	0 / 102 (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
Skin and subcutaneous tissue disorders			
Erythema nodosum			
subjects affected / exposed	0 / 137 (0.00%)	0 / 104 (0.00%)	1 / 102 (0.98%)
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			
Gastroenteritis			
subjects affected / exposed	1 / 137 (0.73%)	0 / 104 (0.00%)	0 / 102 (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

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

Non-serious adverse events	Placebo	AMG 301 210 mg Q4W	AMG 301 420 mg Q2W
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 137 (23.36%)	27 / 104 (25.96%)	31 / 102 (30.39%)
Nervous system disorders			
Migraine			
subjects affected / exposed	3 / 137 (2.19%)	2 / 104 (1.92%)	6 / 102 (5.88%)
occurrences (all)	3	3	7
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 137 (5.84%)	5 / 104 (4.81%)	9 / 102 (8.82%)
occurrences (all)	8	5	12
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	0 / 137 (0.00%)	4 / 104 (3.85%)	6 / 102 (5.88%)
occurrences (all)	0	4	6
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	8 / 137 (5.84%)	3 / 104 (2.88%)	1 / 102 (0.98%)
occurrences (all)	8	3	1
Infections and infestations			
Influenza			
subjects affected / exposed	5 / 137 (3.65%)	5 / 104 (4.81%)	6 / 102 (5.88%)
occurrences (all)	5	5	6
Nasopharyngitis			
subjects affected / exposed	13 / 137 (9.49%)	10 / 104 (9.62%)	7 / 102 (6.86%)
occurrences (all)	16	13	10

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 May 2017	- Clarified the number of subjects that were to be screened and enter baseline in order to achieve the target randomization - Clarified when vital signs, PK sampling, and Headache Impact Test were to be collected during the study - Clarified the risks and benefits of the study - Removal of legally acceptable representative from the study - Clarified that upon early discontinuation, a safety follow-up visit was to be performed approximately 30 (+-5) days after the last dosing interval of investigation product - Added additional information for sample size calculation for each AMG 301 group versus placebo - Clarified that the primary analysis set was also known as the efficacy analysis set - Clarified which primary and secondary endpoints were to be included in the interim analysis - Added the responsibilities of the Data Review Team during the double-blind treatment period - Clarified Amgen's regulatory responsibilities when an amendment was determined to be substantial
17 October 2017	- Updated schedule of activities and footnotes to maintain consistency with the protocol - Updated the exclusion screening criterion to maintain accordance with the World Health Organization's guidelines of assessing impaired glucose regulation/prediabetes with glycosylated hemoglobin (HbA1c) values

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported