



Clinical trial results:

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy, Safety, and Tolerability of Atogepant for the Prevention of Chronic Migraine (Progress)

Summary

EudraCT number	2018-004337-32
Trial protocol	FR CZ SE PL DE DK ES GB IT
Global end of trial date	20 January 2022

Results information

Result version number	v1 (current)
This version publication date	07 February 2023
First version publication date	07 February 2023

Trial information

Trial identification

Sponsor protocol code	3101-303-002
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03855137
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Allergan Limited
Sponsor organisation address	Allergan Limited Marlow International The Parkway, Marlow Buckinghamshire, United Kingdom, SL7 1YL
Public contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.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	20 January 2022
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	20 January 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the efficacy, safety and tolerability of atogepant in subjects with chronic migraine.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 March 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	China: 28
Country: Number of subjects enrolled	Czechia: 117
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Italy: 23
Country: Number of subjects enrolled	Japan: 157
Country: Number of subjects enrolled	Korea, Republic of: 68
Country: Number of subjects enrolled	Poland: 49
Country: Number of subjects enrolled	Russian Federation: 36
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	Taiwan: 22
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	United States: 214
Worldwide total number of subjects	778
EEA total number of subjects	238

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)	754
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total of 778 subjects were randomised in a 1:1:1 ratio to receive atogepant matching placebo and, atogepant 30 mg twice daily (BID), or atogepant 60 mg once daily (QD) for up to 12 weeks in a double-blind (DB) treatment period followed by a 4 week follow up (FU) period till the end of the study up to approximately 16 weeks.

Period 1

Period 1 title	DB Treatment Period (Day 1 to Week 12)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received atogepant-matching placebo tablets, orally, twice BID for 12 weeks in a DB treatment period.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Atogepant-matching placebo tablets administered orally.

Arm title	Atogepant 60 mg QD
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Arm description:

Subjects received atogepant 60 mg, orally, QD along with atogepant-matching placebo 30 mg as morning dose followed by atogepant-matching placebo 30 mg and 60 mg as evening doses for up to 12 weeks in a DB treatment period.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Atogepant-matching placebo tablets administered orally.

Investigational medicinal product name	Atogepant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Atogepant tablets administered orally.

Arm title	Atogepant 30 mg BID
Arm description:	
Subjects received atogepant 30 mg tablet, orally, BID and atogepant-matching placebo tablets orally, BID for up to 12 weeks in a DB treatment period.	
Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Atogepant-matching placebo tablets administered orally.	
Investigational medicinal product name	Atogepant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Atogepant tablets administered orally.	

Number of subjects in period 1	Placebo	Atogepant 60 mg QD	Atogepant 30 mg BID
Started	259	262	257
Safety Population	255	261	257
Modified Intent-to-Treat Population	246	256	253
Off-treatment Hypothetical Estimand	249	256	254
Completed	230	233	231
Not completed	29	29	26
Adverse event	10	9	13
Non-compliance with study drug	1	-	-
Lost to follow-up	-	3	1
Lack of efficacy	5	1	2
Withdrawal by subject	8	14	7
Protocol deviation	5	2	3

Period 2	
Period 2 title	FU Period (Week 12 to Week 16)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
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Arm title	Placebo
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Arm description:

Subjects received atogepant-matching placebo tablets, orally, BID for 12 weeks in a DB treatment period.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Atogepant-matching placebo tablets administered orally.

Arm title	Atogepant 60 mg QD
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Arm description:

Subjects received atogepant 60 mg, orally, QD along with atogepant-matching placebo 30 mg as morning dose followed by atogepant-matching placebo 30 mg and 60 mg as evening doses for up to 12 weeks in a DB treatment period.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Atogepant-matching placebo tablets administered orally.

Investigational medicinal product name	Atogepant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Atogepant tablets administered orally.

Arm title	Atogepant 30 mg BID
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Arm description:

Subject sreceived atogepant 30 mg tablet, orally, BID and atogepant-matching placebo tablets orally, BID for up to 12 weeks in a DB treatment period.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Atogepant-matching placebo tablets administered orally.

Investigational medicinal product name	Atogepant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
Atogepant tablets administered orally.

Number of subjects in period 2^[1]	Placebo	Atogepant 60 mg QD	Atogepant 30 mg BID
Started	169	169	179
Completed	161	165	170
Not completed	8	4	9
Protocol deviation	2	-	-
Reason not specified	1	-	-
Lost to follow-up	-	1	3
Withdrawal by subject	5	3	6

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: Out of 694 subjects who completed the double-blind treatment period, only 517 subjects continued the follow-up period.

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received atogepant-matching placebo tablets, orally, twice BID for 12 weeks in a DB treatment period.	
Reporting group title	Atogepant 60 mg QD
Reporting group description:	
Subjects received atogepant 60 mg, orally, QD along with atogepant-matching placebo 30 mg as morning dose followed by atogepant-matching placebo 30 mg and 60 mg as evening doses for up to 12 weeks in a DB treatment period.	
Reporting group title	Atogepant 30 mg BID
Reporting group description:	
Subjects received atogepant 30 mg tablet, orally, BID and atogepant-matching placebo tablets orally, BID for up to 12 weeks in a DB treatment period.	

Reporting group values	Placebo	Atogepant 60 mg QD	Atogepant 30 mg BID
Number of subjects	259	262	257
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	42.0	41.7	42.6
standard deviation	± 12.43	± 12.30	± 11.89
Gender categorical			
Units: Subjects			
Female	229	226	227
Male	30	36	30
Ethnicity			
Units: Subjects			
Hispanic or Latino	13	6	12
Not Hispanic or Latino	246	256	245
Unknown or Not Reported	0	0	0
Race			
Units: Subjects			
American Indian or Alaska Native	1	1	1
Asian	95	93	95
Native Hawaiian or Other Pacific Islander	1	0	0
Black or African American	7	9	8
White	154	157	151
More than one race	1	2	2
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	778		

Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	682		
Male	96		
Ethnicity Units: Subjects			
Hispanic or Latino	31		
Not Hispanic or Latino	747		
Unknown or Not Reported	0		
Race Units: Subjects			
American Indian or Alaska Native	3		
Asian	283		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	24		
White	462		
More than one race	5		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Subjects received atogepant-matching placebo tablets, orally, twice BID for 12 weeks in a DB treatment period.	
Reporting group title	Atogepant 60 mg QD
Reporting group description: Subjects received atogepant 60 mg, orally, QD along with atogepant-matching placebo 30 mg as morning dose followed by atogepant-matching placebo 30 mg and 60 mg as evening doses for up to 12 weeks in a DB treatment period.	
Reporting group title	Atogepant 30 mg BID
Reporting group description: Subjects received atogepant 30 mg tablet, orally, BID and atogepant-matching placebo tablets orally, BID for up to 12 weeks in a DB treatment period.	
Reporting group title	Placebo
Reporting group description: Subjects received atogepant-matching placebo tablets, orally, BID for 12 weeks in a DB treatment period.	
Reporting group title	Atogepant 60 mg QD
Reporting group description: Subjects received atogepant 60 mg, orally, QD along with atogepant-matching placebo 30 mg as morning dose followed by atogepant-matching placebo 30 mg and 60 mg as evening doses for up to 12 weeks in a DB treatment period.	
Reporting group title	Atogepant 30 mg BID
Reporting group description: Subject sreceived atogepant 30 mg tablet, orally, BID and atogepant-matching placebo tablets orally, BID for up to 12 weeks in a DB treatment period.	

Primary: Change From Baseline in Mean Monthly Migraine Days Across 12-Week Treatment Period in mITT Population

End point title	Change From Baseline in Mean Monthly Migraine Days Across 12-Week Treatment Period in mITT Population
End point description: Subjects recorded daily duration of migraine in a diary. Migraine day was any calendar day on which the subject experienced a migraine headache. Monthly (4-week) migraine days were defined as the total number of reported migraine days in diary divided by total number of days with diary records during each 4-week period and multiplied by 28. Each 4-week period was averaged. Baseline is defined as the number of migraine days during the last 28 days prior to the randomisation date. Negative change from Baseline indicates improvement. A contrast from Mixed-effects model for repeated measures (MMRM) was used to obtain the average treatment effects across the 12-week treatment period. Modified Intent-to-Treat (mITT) Population=all randomised subjects who received at least 1 dose of study intervention, had an evaluable baseline period of eDiary data, and had at least 1 evaluable post-baseline 4-week period (Weeks 1 to 4, 5 to 8, and 9 to 12) of eDiary data during the DB treatment period.	
End point type	Primary
End point timeframe: Baseline to Week 12	

End point values	Placebo	Atogepant 60 mg QD	Atogepant 30 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	246	256	253	
Units: migraine days per month				
median (full range (min-max))				
Baseline	18.0 (8.0 to 28.0)	19.0 (9.0 to 28.0)	18.0 (8.0 to 28.0)	
Change From Baseline at Week 12	-4.63 (-21.9 to 9.7)	-7.27 (-22.3 to 12.9)	-7.13 (-27.0 to 7.7)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Atogepant 30 mg BID
Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	< 0.0001 ^[2]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.48
upper limit	-1.33
Variability estimate	Standard error of the mean
Dispersion value	0.547

Notes:

[1] - Adjusted p-value using graphical approach to control the overall type 1 error rate for multiple comparisons.

[2] - MMRM model=treatment group,visit,stratification by acute medication overuse,migraine prevention medication use and number of failures,region,and treatment group-by-visit as fixed factors and baseline and baseline-by-visit interaction as covariates.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Atogepant 60 mg QD
Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.0009 ^[4]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.89
upper limit	-0.75
Variability estimate	Standard error of the mean
Dispersion value	0.545

Notes:

[3] - Adjusted p-value using graphical approach to control the overall type 1 error rate for multiple comparisons.

[4] - MMRM model=treatment group,visit,stratification by acute medication overuse,migraine prevention medication use and number of failures,region,and treatment group-by-visit as fixed factors and baseline and baseline-by-visit interaction as covariates.

Primary: Change From Baseline in Mean Monthly Migraine Days Across 12-Week Treatment Period in OTHE Population

End point title	Change From Baseline in Mean Monthly Migraine Days Across 12-Week Treatment Period in OTHE Population
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End point description:

Participants recorded daily duration of migraine in a diary. A migraine day was any calendar day on which the participant experienced a migraine headache. The monthly(4-week) migraine days were defined as the total number of reported migraine days in diary divided by total number of days with diary records during each 4-week period and multiplied by 28. Each 4-week period was averaged. Baseline is defined as the number of migraine days during the last 28 days prior to the randomization date. Negative change from Baseline=improvement. A contrast from MMRM was used to obtain the average treatment effects across the 12-week treatment period. Off-treatment hypothetical estimand population:all randomized participants who received ≥ 1 dose of study intervention, had an evaluable baseline period of eDiary data and had ≥ 1 evaluable postbaseline 4-week period (Weeks 1 to 4, 5 to 8, 9 to 12) of eDiary data during the study, regardless of whether on study treatment or off study treatment.

End point type	Primary
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End point timeframe:

Baseline to Week 12

End point values	Placebo	Atogepant 60 mg QD	Atogepant 30 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	249	257	254	
Units: migraine days per month				
median (full range (min-max))				
Baseline	18.0 (8 to 28)	18.0 (8 to 28)	19.0 (9 to 28)	
Change From Baseline at Week 12	-4.65 (-21.9 to 9.7)	-7.19 (-22.3 to 12.9)	-7.00 (-27.0 to 7.7)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Atogepant 30 mg BID
Number of subjects included in analysis	503
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.0001 ^[6]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.24

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.31
upper limit	-1.16
Variability estimate	Standard error of the mean
Dispersion value	0.547

Notes:

[5] - MMRM model=treatment group,visit,stratification by acute medication overuse,migraine prevention medication use and number of failures,region,and treatment group-by-visit as fixed factors and baseline and baseline-by-visit interaction as covariates.

[6] - Adjusted p-value using graphical approach to control the overall type 1 error rate for multiple comparisons.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Atogepant 60 mg QD
Number of subjects included in analysis	506
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	= 0.0024 ^[8]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.72
upper limit	-0.59
Variability estimate	Standard error of the mean
Dispersion value	0.544

Notes:

[7] - MMRM model=treatment group,visit,stratification by acute medication overuse,migraine prevention medication use and number of failures,region,and treatment group-by-visit as fixed factors and baseline and baseline-by-visit interaction as covariates.

[8] - Adjusted p-value using graphical approach to control the overall type 1 error rate for multiple comparisons.

Secondary: Change From Baseline in Migraine Specific Quality of Life (QoL) Questionnaire, Version 2.1 (MSQ v2.1) Role Function-Restrictive Domain Score at Week 12 in OTHE Population

End point title	Change From Baseline in Migraine Specific Quality of Life (QoL) Questionnaire, Version 2.1 (MSQ v2.1) Role Function-Restrictive Domain Score at Week 12 in OTHE Population
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End point description:

MSQ v2.1=14-item questionnaire measuring health-related QoL impairments for migraine in past 4 weeks,divided into 3 domains:Role Function Restrictive(question no.1-7,score ranges 7-42)assesses how migraines limits daily social, work-related activities;Role Function Preventive(question no.8-11,score ranges 4-24)assesses how migraine prevent activities;Emotional Function(question no.12-14,score ranges 3-18) assesses emotions.Subjects respond using 6-point scale ranging from none to all time.Raw dimension score=sum of item responses rescaled to 0 to 100,higher scores=better quality of life.Contrast from MMRM was used to obtain average treatment effects across 12-week treatment period.Off-treatment hypothetical estimand population:subjects receiving ≥1 dose of drug, had an evaluable baseline period, ≥1 evaluable postbaseline 4-week period(Weeks 1-4, 5-8, 9-12) of eDiary data, regardless of on study or off study treatment.Subjects analysed=no. of subjects with data available for analyses.

End point type	Secondary
End point timeframe:	
At Week 12	

End point values	Placebo	Atogepant 60 mg QD	Atogepant 30 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	249	257	254	
Units: score on a scale				
arithmetic mean (standard deviation)	17.56 (± 21.901)	23.72 (± 24.335)	25.73 (± 23.137)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Atogepant 30 mg BID
Number of subjects included in analysis	503
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	< 0.0001 ^[10]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	7.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.77
upper limit	11.09
Variability estimate	Standard error of the mean
Dispersion value	1.864

Notes:

[9] - Adjusted p-value using graphical approach to control the overall type 1 error rate for multiple comparisons.

[10] - MMRM model=treatment group,visit,stratification by acute medication overuse,migraine prevention medication use and number of failures,region,and treatment group-by-visit as fixed factors and baseline and baseline-by-visit interaction as covariates.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Atogepant 60 mg QD
Number of subjects included in analysis	506
Analysis specification	Pre-specified
Analysis type	superiority ^[11]
P-value	= 0.0018 ^[12]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	5.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.15
upper limit	9.41

Variability estimate	Standard error of the mean
Dispersion value	1.848

Notes:

[11] - Adjusted p-value using graphical approach to control the overall type 1 error rate for multiple comparisons.

[12] - MMRM model=treatment group,visit,stratification by acute medication overuse,migraine prevention medication use and number of failures,region,and treatment group-by-visit as fixed factors and baseline and baseline-by-visit interaction as covariates.

Secondary: Change From Baseline in Mean Monthly Acute Medication use Days Across 12-Week Treatment Period in mITT Population

End point title	Change From Baseline in Mean Monthly Acute Medication use Days Across 12-Week Treatment Period in mITT Population
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End point description:

An acute medication use day was defined as any day on which a subject reports, per eDiary, the intake of allowed medication(s) to treat an acute migraine. The monthly (4-week) acute medication use days were defined as the total number of reported acute medication use days in the diary divided by the total number of days with diary records during each 4-week period and multiplied by 28. Each 4-week period was averaged. Baseline is defined as the number of migraine days during the last 28 days prior to the randomisation date. A negative change from Baseline indicates improvement. A contrast from MMRM was used to obtain the average treatment effects across the 12-week treatment period. mITT Population included all randomised subjects who received at least 1 dose of study intervention, had an evaluable baseline period of eDiary data, and had at least 1 evaluable post-baseline 4-week period (Weeks 1 to 4, 5 to 8, and 9 to 12) of eDiary data during the double-blind treatment period.

End point type	Secondary
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End point timeframe:

Baseline to Week 12

End point values	Placebo	Atogepant 60 mg QD	Atogepant 30 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	246	256	253	
Units: acute medication use days per month				
median (full range (min-max))	-3.57 (-23.7 to 20.7)	-6.33 (-26.0 to 14.2)	-6.23 (-26.1 to 7.4)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Atogepant 30 mg BID
Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority ^[13]
P-value	< 0.0001 ^[14]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.63

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.63
upper limit	-1.63
Variability estimate	Standard error of the mean
Dispersion value	0.51

Notes:

[13] - Adjusted p-value using graphical approach to control the overall type 1 error rate for multiple comparisons.

[14] - MMRM model=treatment group,visit,stratification by acute medication overuse,migraine prevention medication use and number of failures,region,and treatment group-by-visit as fixed factors and baseline and baseline-by-visit interaction as covariates.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Atogepant 60 mg QD
Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	superiority ^[15]
P-value	= 0.0009 ^[16]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.13
upper limit	-1.13
Variability estimate	Standard error of the mean
Dispersion value	0.508

Notes:

[15] - Adjusted p-value using graphical approach to control the overall type 1 error rate for multiple comparisons.

[16] - MMRM model=treatment group,visit,stratification by acute medication overuse,migraine prevention medication use and number of failures,region,and treatment group-by-visit as fixed factors and baseline and baseline-by-visit interaction as covariates.

Secondary: Change From Baseline in Mean Monthly Headache Days Across 12-Week Treatment Period in mITT Population

End point title	Change From Baseline in Mean Monthly Headache Days Across 12-Week Treatment Period in mITT Population
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End point description:

Subjects recorded daily total duration of a headache in a diary. A headache day is any calendar day on which the subject experienced a headache pain lasting 2 hours or longer unless an acute headache medication was used after the start of the headache. The monthly (4-week) headache days were defined as the total number of reported headache days in the diary divided by the total number of days with diary records during each 4-week period and multiplied by 28. Each 4-week period was averaged. Baseline is defined as the number of headache days during the last 28 days prior to the randomisation date. Negative change from Baseline indicates improvement. MMRM was used for analysis. mITT Population included all randomised subjects who received at least 1 dose of study intervention, had an evaluable baseline period of eDiary data, and had at least 1 evaluable post-baseline 4-week period (Weeks 1 to 4, 5 to 8, and 9 to 12) of eDiary data during the double-blind treatment period.

End point type	Secondary
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End point timeframe:

Baseline to Week 12

End point values	Placebo	Atogepant 60 mg QD	Atogepant 30 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	246	256	253	
Units: headache days per month				
median (full range (min-max))	-4.26 (-23.7 to 6.7)	-6.71 (-22.3 to 9.0)	-7.16 (-26.3 to 9.0)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Atogepant 30 mg BID
Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority ^[17]
P-value	< 0.0001 ^[18]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.38
upper limit	-1.26
Variability estimate	Standard error of the mean
Dispersion value	0.541

Notes:

[17] - Adjusted p-value using graphical approach to control the overall type 1 error rate for multiple comparisons.

[18] - MMRM model=treatment group,visit,stratification by acute medication overuse,migraine prevention medication use and number of failures,region,and treatment group-by-visit as fixed factors and baseline and baseline-by-visit interaction as covariates.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Atogepant 60 mg QD
Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	superiority ^[19]
P-value	= 0.0009 ^[20]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.93
upper limit	-0.81

Variability estimate	Standard error of the mean
Dispersion value	0.538

Notes:

[19] - Adjusted p-value using graphical approach to control the overall type 1 error rate for multiple comparisons.

[20] - MMRM model=treatment group,visit,stratification by acute medication overuse,migraine prevention medication use and number of failures,region,and treatment group-by-visit as fixed factors and baseline and baseline-by-visit interaction as covariates.

Secondary: Change From Baseline in Mean Monthly Physical Impairment Domain Score of the AIM-D Across 12-Week 12 Treatment Period in mITT Population

End point title	Change From Baseline in Mean Monthly Physical Impairment Domain Score of the AIM-D Across 12-Week 12 Treatment Period in mITT Population
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End point description:

AIM-D= 11-item PRO measure that assesses impact of migraine on performance of daily activities and physical impairment using a 6-point rating scale where 0=not difficult at all, 1=a little difficult, 2=somewhat difficult, 3=very difficult, 4=extremely difficult, and 5=I could not do it at all. Raw physical impairment domain scores were transformed to 0-100 scale, with higher scores indicating greater impact of migraine (higher disease burden). Baseline is defined as the number of migraine days during last 28 days prior to the randomisation date. A contrast from MMRM was used to obtain average treatment effects across 12-week treatment period. mITT Population=all randomised subjects who received at least 1 dose of study intervention, had an evaluable baseline period of eDiary data, and had at least 1 evaluable post-baseline 4-week period (Weeks 1 to 4, 5 to 8, and 9 to 12) of eDiary data during DB treatment period. Subjects analysed=number of subjects with data available for analyses.

End point type	Secondary
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End point timeframe:

Baseline to Week 12

End point values	Placebo	Atogepant 60 mg QD	Atogepant 30 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	226	231	225	
Units: score on a scale				
arithmetic mean (standard deviation)	-8.05 (± 10.923)	-11.65 (± 12.172)	-12.34 (± 12.237)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Atogepant 30 mg BID
Number of subjects included in analysis	451
Analysis specification	Pre-specified
Analysis type	superiority ^[21]
P-value	= 0.0003 ^[22]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-4.19

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.95
upper limit	-2.43
Variability estimate	Standard error of the mean
Dispersion value	0.897

Notes:

[21] - Adjusted p-value using graphical approach to control the overall type 1 error rate for multiple comparisons.

[22] - MMRM model=treatment group,visit,stratification by acute medication overuse,migraine prevention medication use and number of failures,region,and treatment group-by-visit as fixed factors and baseline and baseline-by-visit interaction as covariates.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Atogepant 60 mg QD
Number of subjects included in analysis	457
Analysis specification	Pre-specified
Analysis type	superiority ^[23]
P-value	= 0.0025 ^[24]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.47
upper limit	-0.96
Variability estimate	Standard error of the mean
Dispersion value	0.893

Notes:

[23] - Adjusted p-value using graphical approach to control the overall type 1 error rate for multiple comparisons.

[24] - MMRM model=treatment group,visit,stratification by acute medication overuse,migraine prevention medication use and number of failures,region,and treatment group-by-visit as fixed factors and baseline and baseline-by-visit interaction as covariates.

Secondary: Percentage of Subjects With at Least a 50% Reduction in 3-Month Average of Monthly Migraine Days in mITT Population

End point title	Percentage of Subjects With at Least a 50% Reduction in 3-Month Average of Monthly Migraine Days in mITT Population
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End point description:

Data is reported for 50% responders averaged at each 4-week period. 50% responders are subjects with at least a 50 percent reduction from baseline in monthly migraine days. Subjects recorded daily duration of migraine in a diary. A migraine day was any calendar day on which the subject experienced a migraine headache. The monthly (4-week) migraine days were equal to total number of reported migraine days in diary divided by total number of days with diary records in each 4-week period multiplied by 28. The values are rounded off to the first decimal value. mITT Population included all randomised subjects who received at least 1 dose of study intervention, had an evaluable baseline period of eDiary data, and had at least 1 evaluable post-baseline 4-week period (Weeks 1 to 4, 5 to 8, and 9 to 12) of eDiary data during the double-blind treatment period.

End point type	Secondary
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End point timeframe:

At Week 12

End point values	Placebo	Atogepant 60 mg QD	Atogepant 30 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	246	256	253	
Units: percentage of subjects				
number (not applicable)	26.0	41.0	42.7	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Atogepant 30 mg BID
Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority ^[25]
P-value	= 0.0003 ^[26]
Method	Logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	2.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.45
upper limit	3.14

Notes:

[25] - Adjusted p-value using graphical approach to control the overall type 1 error rate for multiple comparisons.

[26] - Logistic regression for each atogepant group versus placebo with baseline monthly migraine days as covariate, stratification of region, acute medication overuse, migraine prevention medication and number of failures, treatment group as fixed factors.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Atogepant 60 mg QD
Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	superiority ^[27]
P-value	= 0.0009 ^[28]
Method	Logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	2.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.38
upper limit	3

Notes:

[27] - Adjusted p-value using graphical approach to control the overall type 1 error rate for multiple comparisons.

[28] - Logistic regression for each atogepant group versus placebo with baseline monthly migraine days as covariate, stratification of region, acute medication overuse, migraine prevention medication and number of failures, treatment group as fixed factors.

Secondary: Change From Baseline in the Headache Impact Test (HIT-6) Total Score at Week 12 in Off-treatment Hypothetical Estimand (OTHE) Population

End point title	Change From Baseline in the Headache Impact Test (HIT-6) Total Score at Week 12 in Off-treatment Hypothetical Estimand (OTHE) Population
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End point description:

HIT-6 is a 6-question assessment used to measure the impact headaches have on a subject's ability to function on the job, at school, at home, and in social situations. It assesses the effect that headaches have on normal daily life and the subject's ability to function. Responses are based on frequency using a 5-point scale ranging from "never" to "always." The HIT-6 total score, which ranges from 36 to 78, is the sum of the responses - each of which is assigned a score ranging from 6 points (never) to 13 points (always). Off-treatment hypothetical estimand population: subjects receiving ≥ 1 dose of drug, had an evaluable baseline period, ≥ 1 evaluable postbaseline 4-week period (Weeks 1-4, 5-8, 9-12) of eDiary data, regardless of on study or off study treatment. MMRM was used for the analyses.

End point type	Secondary
End point timeframe:	
At Week 12	

End point values	Placebo	Atogepant 60 mg QD	Atogepant 30 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	249	257	254	
Units: score on a scale				
arithmetic mean (standard deviation)	-5.18 (\pm 6.682)	-7.97 (\pm 8.209)	-8.97 (\pm 8.475)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Atogepant 30 mg BID
Number of subjects included in analysis	503
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[29]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.67
upper limit	-1.93
Variability estimate	Standard error of the mean
Dispersion value	0.697

Notes:

[29] - MMRM model=treatment group,visit,stratification by acute medication overuse,migraine prevention medication use and number of failures,region,and treatment group-by-visit as fixed factors and baseline and baseline-by-visit interaction as covariates.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Atogepant 60 mg QD
Number of subjects included in analysis	506
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 ^[30]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.02
upper limit	-1.3
Variability estimate	Standard error of the mean
Dispersion value	0.69

Notes:

[30] - MMRM model=treatment group,visit,stratification by acute medication overuse,migraine prevention medication use and number of failures,region,and treatment group-by-visit as fixed factors and baseline and baseline-by-visit interaction as covariates.

Secondary: Change From Baseline in Mean Monthly Performance of Daily Activities Domain Score of the AIM-D Across 12-Week Treatment Period in mITT Population

End point title	Change From Baseline in Mean Monthly Performance of Daily Activities Domain Score of the AIM-D Across 12-Week Treatment Period in mITT Population
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End point description:

AIM-D= 11-item patient-reported outcome(PRO) measure assessing impact of migraine on performance of daily activities and physical impairment using 6-point rating scale where 0=not difficult at all,1=a little difficult,2=somewhat difficult,3=very difficult,4=extremely difficult, and5=I could not do it at all. Raw performance of daily activities domain scores were transformed to 0-100 scale, with higher scores indicating greater impact of migraine (higher disease burden). Baseline=number of migraine days during last 28 days prior to randomisation date.Contrast from MMRM was used to obtain average treatment effects across 12-week treatment period.mITT Population=all randomised subjects receiving at least 1 dose of study intervention,had an evaluable baseline period of eDiary data,had at least 1 evaluable post-baseline 4-week period(Weeks 1 to 4, 5 to 8, and 9 to 12) of eDiary data during double-blind treatment period.Subjects analysed=number of subjects with data available for analyses.

End point type	Secondary
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End point timeframe:

Baseline to Week 12

End point values	Placebo	Atogepant 60 mg QD	Atogepant 30 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	226	231	225	
Units: score on a scale				
arithmetic mean (standard deviation)	-9.80 (± 11.311)	-13.90 (± 12.625)	-14.56 (± 13.042)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Atogepant 30 mg BID
Number of subjects included in analysis	451
Analysis specification	Pre-specified
Analysis type	superiority ^[31]
P-value	= 0.0003 ^[32]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-4.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.75
upper limit	-2.95
Variability estimate	Standard error of the mean
Dispersion value	0.968

Notes:

[31] - Adjusted p-value using graphical approach to control the overall type 1 error rate for multiple comparisons.

[32] - MMRM model=treatment group,visit,stratification by acute medication overuse,migraine prevention medication use and number of failures,region,and treatment group-by-visit as fixed factors and baseline and baseline-by-visit interaction as covariates.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Atogepant 60 mg QD
Number of subjects included in analysis	457
Analysis specification	Pre-specified
Analysis type	superiority ^[33]
P-value	= 0.0009 ^[34]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-3.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.27
upper limit	-1.49
Variability estimate	Standard error of the mean
Dispersion value	0.963

Notes:

[33] - Adjusted p-value using graphical approach to control the overall type 1 error rate for multiple comparisons.

[34] - MMRM model=treatment group,visit,stratification by acute medication overuse,migraine prevention medication use and number of failures,region,and treatment group-by-visit as fixed factors and baseline and baseline-by-visit interaction as covariates.

Secondary: Change From Baseline in Mean Monthly Headache Days Across 12-Week Treatment Period in OTHE Population

End point title	Change From Baseline in Mean Monthly Headache Days Across 12-Week Treatment Period in OTHE Population
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End point description:

Participants recorded daily total duration of a headache in a diary. Headache day: any calendar day on which the participant experienced a headache pain lasting 2 hours or longer unless an acute headache medication was used after the start of the headache. Monthly (4-week) headache days: the total number of reported headache days in the diary divided by the total number of days with diary records during each 4-week period multiplied by 28. Each 4-week period was averaged. Baseline: the number of headache days during last 28 days prior to the randomization date. Negative change from Baseline=improvement. A contrast from MMRM was used to obtain the average treatment effects across the 12-week treatment period. OTHE population.

End point type	Secondary
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End point timeframe:

Baseline to Week 12

End point values	Placebo	Atogepant 60 mg QD	Atogepant 30 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	249	257	254	
Units: headache days per month				
median (full range (min-max))	-4.33 (-23.7 to 6.7)	-6.59 (-22.3 to 9.0)	-7.04 (-26.3 to 9.0)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Atogepant 30 mg BID
Number of subjects included in analysis	503
Analysis specification	Pre-specified
Analysis type	superiority ^[35]
P-value	= 0.0002 ^[36]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	-1.09
Variability estimate	Standard error of the mean
Dispersion value	0.539

Notes:

[35] - MMRM model=treatment group, visit, stratification by acute medication overuse, migraine prevention medication use and number of failures, region, and treatment group-by-visit as fixed factors and baseline and baseline-by-visit interaction as covariates.

[36] - Adjusted p-value using graphical approach to control the overall type 1 error rate for multiple comparisons.

	Statistical Analysis 2
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Statistical analysis title	
Comparison groups	Placebo v Atogepant 60 mg QD
Number of subjects included in analysis	506
Analysis specification	Pre-specified
Analysis type	superiority ^[37]
P-value	= 0.0024 ^[38]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.78
upper limit	-0.67
Variability estimate	Standard error of the mean
Dispersion value	0.536

Notes:

[37] - MMRM model=treatment group,visit,stratification by acute medication overuse,migraine prevention medication use and number of failures,region,and treatment group-by-visit as fixed factors and baseline and baseline-by-visit interaction as covariates.

[38] - Adjusted p-value using graphical approach to control the overall type 1 error rate for multiple comparisons.

Secondary: Change From Baseline in Mean Monthly Acute Medication Use Days Across 12-Week Treatment Period in OTHE

End point title	Change From Baseline in Mean Monthly Acute Medication Use Days Across 12-Week Treatment Period in OTHE
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End point description:

An acute medication use day is defined as any day on which a participant reports, per eDiary, the intake of allowed medication(s) to treat an acute migraine. The monthly (4-week) acute medication use days were defined as the total number of reported acute medication use days in the diary divided by the total number of days with diary records during each 4-week period and multiplied by 28. Each 4-week period was averaged. Baseline is defined as the number of migraine days during the last 28 days prior to the randomization date. A negative change from Baseline indicates improvement. A contrast from MMRM was used to obtain the average treatment effects across the 12-week treatment period. OTHE population.

End point type	Secondary
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End point timeframe:

Baseline to Week 12

End point values	Placebo	Atogepant 60 mg QD	Atogepant 30 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	249	257	254	
Units: acute medication use days per month				
median (full range (min-max))	-3.56 (-23.7 to 20.7)	-6.00 (-26.0 to 14.2)	-6.21 (-26.1 to 7.4)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Atogepant 30 mg BID
Number of subjects included in analysis	503
Analysis specification	Pre-specified
Analysis type	superiority ^[39]
P-value	= 0.0002 ^[40]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.52
upper limit	-1.53
Variability estimate	Standard error of the mean
Dispersion value	0.507

Notes:

[39] - MMRM model=treatment group,visit,stratification by acute medication overuse,migraine prevention medication use and number of failures,region,and treatment group-by-visit as fixed factors and baseline and baseline-by-visit interaction as covariates.

[40] - Adjusted p-value using graphical approach to control the overall type 1 error rate for multiple comparisons.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Atogepant 60 mg QD
Number of subjects included in analysis	506
Analysis specification	Pre-specified
Analysis type	superiority ^[41]
P-value	= 0.0024 ^[42]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.09
upper limit	-1.1
Variability estimate	Standard error of the mean
Dispersion value	0.505

Notes:

[41] - MMRM model=treatment group,visit,stratification by acute medication overuse,migraine prevention medication use and number of failures,region,and treatment group-by-visit as fixed factors and baseline and baseline-by-visit interaction as covariates.

[42] - Adjusted p-value using graphical approach to control the overall type 1 error rate for multiple comparisons.

Secondary: Percentage of Participants With at Least a 50% Reduction in 3-Month Average of Monthly Migraine Days in OTHE

End point title	Percentage of Participants With at Least a 50% Reduction in 3-Month Average of Monthly Migraine Days in OTHE
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End point description:

Data is reported for 50% responders averaged at each 4-week period. 50% responders are participants with at least a 50 percent reduction from baseline in 3-month average of monthly migraine days. Participants recorded daily duration of migraine in a diary. A migraine day was any calendar day on which the participant experienced a migraine headache. The monthly (4-week) migraine days is equal to

total number of reported migraine days in diary divided by total number of days with diary records in each 4-week period multiplied by 28. The values are rounded off to the first decimal value. OTHE population.

End point type	Secondary
End point timeframe:	
Baseline to Week 12	

End point values	Placebo	Atogepant 60 mg QD	Atogepant 30 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	249	257	254	
Units: percentage of participants				
number (not applicable)	26.5	40.1	42.1	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Atogepant 30 mg BID
Number of subjects included in analysis	503
Analysis specification	Pre-specified
Analysis type	superiority ^[43]
P-value	= 0.0006 ^[44]
Method	Logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	2.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.38
upper limit	2.98

Notes:

[43] - Logistic regression for each atogepant group versus placebo with baseline monthly migraine days as covariate, stratification of region, acute medication overuse, migraine prevention medication and number of failures, treatment group as fixed factors.

[44] - Adjusted p-value using graphical approach to control the overall type 1 error rate for multiple comparisons.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Atogepant 60 mg QD
Number of subjects included in analysis	506
Analysis specification	Pre-specified
Analysis type	superiority ^[45]
P-value	= 0.0024 ^[46]
Method	Logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	1.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.29
upper limit	2.79

Notes:

[45] - Logistic regression for each atogepant group versus placebo with baseline monthly migraine days as covariate, stratification of region, acute medication overuse, migraine prevention medication and number of failures, treatment group as fixed factors.

[46] - Adjusted p-value using graphical approach to control the overall type 1 error rate for multiple comparisons.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to end of study (Up to approximately 16 weeks)

Adverse event reporting additional description:

Safety population included all participants who received at least 1 dose of study intervention and was used for serious adverse events and non-serious adverse events.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Subjects received atogepant-matching placebo tablets, orally, BID for 12 weeks in a DB treatment period.

Reporting group title	Atogepant 60 mg QD
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Reporting group description:

Subjects received atogepant 60 mg, orally, QD along with atogepant-matching placebo 30 mg as morning dose followed by atogepant-matching placebo 30 mg and 60 mg as evening doses for up to 12 weeks in a DB treatment period.

Reporting group title	Atogepant 30 mg BID
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Reporting group description:

Subjects received atogepant 30 mg tablet, orally, BID and atogepant-matching placebo tablets orally, BID for up to 12 weeks in a DB treatment period.

Serious adverse events	Placebo	Atogepant 60 mg QD	Atogepant 30 mg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 255 (1.18%)	7 / 261 (2.68%)	4 / 257 (1.56%)
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)			
BENIGN OVARIAN TUMOUR			
subjects affected / exposed	0 / 255 (0.00%)	0 / 261 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLASMA CELL MYELOMA			
subjects affected / exposed	1 / 255 (0.39%)	0 / 261 (0.00%)	0 / 257 (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
SPINAL CORD NEOPLASM			

subjects affected / exposed	0 / 255 (0.00%)	1 / 261 (0.38%)	0 / 257 (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			
HIP FRACTURE			
subjects affected / exposed	0 / 255 (0.00%)	1 / 261 (0.38%)	0 / 257 (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
FALL			
subjects affected / exposed	0 / 255 (0.00%)	1 / 261 (0.38%)	0 / 257 (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
EPICONDYLITIS			
subjects affected / exposed	1 / 255 (0.39%)	0 / 261 (0.00%)	0 / 257 (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
ROAD TRAFFIC ACCIDENT			
subjects affected / exposed	0 / 255 (0.00%)	1 / 261 (0.38%)	0 / 257 (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
VACCINATION COMPLICATION			
subjects affected / exposed	0 / 255 (0.00%)	1 / 261 (0.38%)	0 / 257 (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	0 / 255 (0.00%)	1 / 261 (0.38%)	0 / 257 (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
Respiratory, thoracic and mediastinal disorders			
NASAL SEPTUM DEVIATION			

subjects affected / exposed	0 / 255 (0.00%)	1 / 261 (0.38%)	0 / 257 (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 / 255 (0.39%)	0 / 261 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders SPINAL PAIN			
subjects affected / exposed	0 / 255 (0.00%)	1 / 261 (0.38%)	0 / 257 (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
Infections and infestations COVID-19			
subjects affected / exposed	0 / 255 (0.00%)	1 / 261 (0.38%)	0 / 257 (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
ANAL ABSCESS			
subjects affected / exposed	0 / 255 (0.00%)	0 / 261 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 PNEUMONIA			
subjects affected / exposed	0 / 255 (0.00%)	0 / 261 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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	Atogepant 60 mg QD	Atogepant 30 mg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 255 (6.27%)	46 / 261 (17.62%)	44 / 257 (17.12%)
Gastrointestinal disorders			

NAUSEA			
subjects affected / exposed	9 / 255 (3.53%)	25 / 261 (9.58%)	20 / 257 (7.78%)
occurrences (all)	9	27	21
CONSTIPATION			
subjects affected / exposed	8 / 255 (3.14%)	26 / 261 (9.96%)	28 / 257 (10.89%)
occurrences (all)	8	26	28

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 April 2019	The following changes were implemented with Amendment 1: Added instructions for study conducted in China and Canada. Clarified primary and secondary endpoints for China, and Canada. Clarified prohibited medications. Updated laboratory parameters. Updated the subgroup analyses. Corrected the study diagram for the estimand framework. Updated the definition of failed migraine preventive medication.
23 September 2019	The following changes were implemented with Amendment 2: Added instructions for study conducted in Japan. Added instruction regarding Visit 8 (follow-up) for subjects in Japan and China who may rollover to a regional, long-term, extension, safety study. Clarified secondary efficacy endpoints for Europe and Canada, and for all other regions except Europe and Canada. Updated description of the AIM-D health outcomes measure and endpoints. Described the Hochberg procedure to be used to control the overall Type I error rate at a 0.05 level (2-sided) for multiple comparisons of 2 atogepant doses with placebo for the primary efficacy endpoint, only for the analysis in Japan. Described weekly data analysis procedures for other efficacy analyses. Described planned subgroup analyses to evaluate consistency of treatment across regions and subpopulations. Updated description of safety analysis. Clarified criteria for sexual abstinence to be considered as a highly effective contraceptive method. Added a benefit/risk assessment. Added definition of the end of the study. Clarified exclusion criterion based on hypersensitivity to study interventions. Clarified the instructions regarding prohibited medication/treatments. Clarified instructions for the subjects. Clarified instructions regarding assessment of causality of adverse events. Added definition of adverse reaction, serious adverse reaction, and suspected unexpected serious adverse reaction. Clarified instruction regarding changes to the protocol.
29 May 2020	The following changes were implemented with Amendment 3: Updated the requirements by French authorities. Updated the enrollment criteria based on data review of recent migraine prevention studies. Clarified the randomization and stratification process to include region. Clarified participation in Visit 8/EOS for rollover subjects, by region and respective long-term safety extension study, and added information to allow for subjects to roll over to the respective open-label (OL) long-term extension study. Adapted description of regions for consistency with stratification. Clarified the description of the ITT and mITT population, and the analysis population for off-treatment hypothetical estimand for the primary efficacy analysis to support filing in Europe. Clarified primary endpoint and added the statistical model term 'region' to the MMRM model for primary analysis. Clarified the AIM-D related secondary endpoint, based on psychometric evidence of the AIM-D consisting of 2 domains, performance of daily activities and physical impairment. Clarified secondary endpoints and statistical analysis model for secondary analysis. Outlined conduct of study when remote visits are necessary due to COVID-19. Updated the Close Out Visit to comply with Russian requirement. Updated the masking/blinding and dosage schedule. Updated the additional efficacy endpoints. Clarified that 50% responder will be assessed for each individual.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported