Clinical trial results:
A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-controlled, Parallel-Group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prophylaxis of Migraine in Participants With Episodic Migraine Who Have Previously Failed 2 to 4 Classes of Oral Prophylactic Treatments (ELEVATE)

Summary

EudraCT number	2019-003448-58
Trial protocol	DE CZ DK HU NL GB IT
Global end of trial date	04 August 2022

Results information

Result version number	v1
This version publication date	19 August 2023
First version publication date	19 August 2023

Trial information

Trial identification

Sponsor protocol code	3101-304-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04740827
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co. KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6 4UB
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	04 August 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study assessed the safety, tolerability, and efficacy of Atogepant 60 milligrams (mg) compared with placebo in episodic migraines in subjects who previously failed 2 to 4 classes of oral prophylactic treatments.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 March 2021
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	Canada: 12
Country: Number of subjects enrolled	Czechia: 125
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 36
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Poland: 49
Country: Number of subjects enrolled	Russian Federation: 15
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	United States: 28
Worldwide total number of subjects	315
EEA total number of subjects	257

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)	311
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 315 subjects were randomised to receive atogepant-matching placebo or atogepant in a double-blind treatment period, and 313 subjects received at least 1 dose of study intervention (safety population).

Pre-assignment

Screening details:

From the 295 subjects who completed the double-blind period 87 subjects entered the follow-up period. Subjects who rolled over directly at Week 12 to study 3101-312-002 [NCT04686136] did not enter the safety-follow up period.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received atogepant-matching placebo tablets, orally, once daily (QD) for up to 12 weeks in a double-blind (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.

Arm title	Atogepant 60 mg

Arm description:

Subjects received atogepant 60 mg, orally, QD for up to 12 weeks in a DB treatment period.

Arm type	Experimental
Investigational medicinal product name	Atogepant 60 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Atogepant tablets.

Number of subjects in period 1	Placebo	Atogepant 60 mg
Started	158	157
Safety Population	157	156
Modified intent-to-treat Population	154	151
Off-treatment Hypothetical Estimand	155	154
Completed	151	144
Not completed	7	13
Adverse event, non-fatal	2	4
Pregnancy	-	1
Withdrawal by Subject	2	2
Protocol deviation	3	5
Lack of efficacy	-	1

Period 2

Period 2 title	Follow-up Period (Week 13 to Week 16)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received atogepant-matching placebo tablets, orally, once daily (QD) for up to 12 weeks in a double-blind (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.

Arm title	Atogepant 60 mg

Arm description:

Subjects received atogepant 60 mg, orally, QD for up to 12 weeks in a DB treatment period.

Arm type	Experimental
Investigational medicinal product name	Atogepant 60 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Atogepant tablets.

Number of subjects in period 2[1]	Placebo	Atogepant 60 mg
Started	43	44
Completed	42	44
Not completed	1	0
Withdrawal by Subject	1	-

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: Of 295 subjects who completed the double-blind period, 87 subjects entered the follow-up period. Subjects who rolled over directly at Week 12 to study 3101-312-002 [NCT04686136] did not enter the safety-follow up period.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received atogepant-matching placebo tablets, orally, once daily (QD) for up to 12 weeks in a double-blind (DB) treatment period.	
Reporting group title	Atogepant 60 mg
Reporting group description:	
Subjects received atogepant 60 mg, orally, QD for up to 12 weeks in a DB treatment period.	

Reporting group values	Placebo	Atogepant 60 mg	Total
Number of subjects	158	157	315
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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Intent-to-treat (ITT) population included all randomised subjects.			
Units: years			
arithmetic mean	43.5	40.8	
standard deviation	± 10.29	± 10.71	-
Gender categorical			
ITT population included all randomised subjects.			
Units: Subjects			
Female	141	140	281
Male	17	17	34
Ethnicity			
ITT population included all randomised subjects.			
Units: Subjects			
Hispanic or Latino	4	7	11
Not Hispanic or Latino	154	150	304
Unknown or Not Reported	0	0	0
Race			
ITT population included all randomised subjects.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	2	4
Native Hawaiian or Other Pacific Islander	0	0	0

Black or African American	4	3	7
White	152	150	302
More than one race	0	2	2
Unknown or Not Reported	0	0	0
Monthly Migraine Days in mITT Population			
A migraine day was any calendar day on which the subject experienced a migraine headache. The monthly (4-week) migraine days was 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. mITT population included all randomised subjects who received at least 1 dose of study treatment, had an evaluable baseline period of eDiary data, and had at least 1 evaluable post-baseline 4-week period of eDiary data during the double-blind treatment period.			
Units: Migraine days per month arithmetic mean standard deviation	±	±	-
Monthly Migraine Days in OTHE Population			
Migraine day: any calendar day on which subject experienced a migraine headache. Monthly (4-week) migraine days: 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. OTHE 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 postbaseline 4-week period (Weeks 1 to 4, 5 to 8, 9 to 12) of eDiary data, regardless of whether on study intervention or off study intervention.			
Units: Migraine days per month arithmetic mean standard deviation	±	±	-

Subject analysis sets

Subject analysis set title	mITT: Placebo
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Subjects received atogepant-matching placebo tablets, orally, QD for up to 12 weeks in a DB treatment period.	
Subject analysis set title	mITT: Atogepant 60 mg
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Subjects received atogepant 60 mg, orally, QD for up to 12 weeks in a DB treatment period.	
Subject analysis set title	OTHE: Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects received atogepant-matching placebo tablets, orally, QD for up to 12 weeks in a DB treatment period.	
Subject analysis set title	OTHE: Atogepant 60 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects received atogepant 60 mg, orally, QD for up to 12 weeks in a DB treatment period.	

Reporting group values	mITT: Placebo	mITT: Atogepant 60 mg	OTHE: Placebo
Number of subjects	154	151	155
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks)			

Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Intent-to-treat (ITT) population included all randomised subjects.			
Units: years arithmetic mean standard deviation	±	±	±
Gender categorical			
ITT population included all randomised subjects.			
Units: Subjects			
Female Male			
Ethnicity			
ITT population included all randomised subjects.			
Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported			
Race			
ITT population included all randomised subjects.			
Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported			
Monthly Migraine Days in mITT Population			
A migraine day was any calendar day on which the subject experienced a migraine headache. The monthly (4-week) migraine days was 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. mITT population included all randomised subjects who received at least 1 dose of study treatment, had an evaluable baseline period of eDiary data, and had at least 1 evaluable post-baseline 4-week period of eDiary data during the double-blind treatment period.			
Units: Migraine days per month arithmetic mean standard deviation	9.3 ± 2.41	9.0 ± 2.30	±
Monthly Migraine Days in OTHE Population			
Migraine day: any calendar day on which subject experienced a migraine headache. Monthly (4-week) migraine days: 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. OTHE 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 postbaseline 4-week period (Weeks 1 to 4, 5 to 8, 9 to 12) of eDiary data, regardless of whether on study intervention or off study intervention.			

Units: Migraine days per month			
arithmetic mean			9.3
standard deviation	±	±	± 2.40

Reporting group values	OTHE: Atogepant 60 mg		
Number of subjects	154		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Intent-to-treat (ITT) population included all randomised subjects.			
Units: years			
arithmetic mean			
standard deviation	±		
Gender categorical			
ITT population included all randomised subjects.			
Units: Subjects			
Female			
Male			
Ethnicity			
ITT population included all randomised subjects.			
Units: Subjects			
Hispanic or Latino			
Not Hispanic or Latino			
Unknown or Not Reported			
Race			
ITT population included all randomised subjects.			
Units: Subjects			
American Indian or Alaska Native			
Asian			
Native Hawaiian or Other Pacific Islander			
Black or African American			
White			
More than one race			
Unknown or Not Reported			
Monthly Migraine Days in mITT Population			
A migraine day was any calendar day on which the subject experienced a migraine headache. The monthly (4-week) migraine days was 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.			

mITT population included all randomised subjects who received at least 1 dose of study treatment, had an evaluable baseline period of eDiary data, and had at least 1 evaluable post-baseline 4-week period of eDiary data during the double-blind treatment period.			
Units: Migraine days per month arithmetic mean standard deviation	 ±		
Monthly Migraine Days in OTHE Population			
Migraine day: any calendar day on which subject experienced a migraine headache. Monthly (4-week) migraine days: 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. OTHE 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 postbaseline 4-week period (Weeks 1 to 4, 5 to 8, 9 to 12) of eDiary data, regardless of whether on study intervention or off study intervention.			
Units: Migraine days per month arithmetic mean standard deviation	 9.1 ± 2.29		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received atogepant-matching placebo tablets, orally, once daily (QD) for up to 12 weeks in a double-blind (DB) treatment period.	
Reporting group title	Atogepant 60 mg
Reporting group description:	
Subjects received atogepant 60 mg, orally, QD for up to 12 weeks in a DB treatment period.	
Reporting group title	Placebo
Reporting group description:	
Subjects received atogepant-matching placebo tablets, orally, once daily (QD) for up to 12 weeks in a double-blind (DB) treatment period.	
Reporting group title	Atogepant 60 mg
Reporting group description:	
Subjects received atogepant 60 mg, orally, QD for up to 12 weeks in a DB treatment period.	
Subject analysis set title	mITT: Placebo
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Subjects received atogepant-matching placebo tablets, orally, QD for up to 12 weeks in a DB treatment period.	
Subject analysis set title	mITT: Atogepant 60 mg
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Subjects received atogepant 60 mg, orally, QD for up to 12 weeks in a DB treatment period.	
Subject analysis set title	OTHE: Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received atogepant-matching placebo tablets, orally, QD for up to 12 weeks in a DB treatment period.	
Subject analysis set title	OTHE: Atogepant 60 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received atogepant 60 mg, orally, QD 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. A migraine day was any calendar day on which the subject 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 randomisation date. Negative change from baseline indicates improvement. Mixed-effects model for repeated measures (MMRM) was used for analysis. mITT population included all randomised subjects who received at least 1 dose of study treatment, had an evaluable baseline period of eDiary data, and had at least 1 evaluable post-baseline 4-week period of eDiary data during the double-blind treatment period.	
End point type	Primary
End point timeframe:	
Baseline to Week 12	

End point values	Placebo	Atogepant 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	151		
Units: migraine days per month				
least squares mean (standard error)	-1.86 (± 0.389)	-4.29 (± 0.397)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Atogepant 60 mg
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.27
upper limit	-1.59
Variability estimate	Standard error of the mean
Dispersion value	0.426

Notes:

[1] - MMRM=baseline monthly migraine days as covariate, treatment group, visit, region and number of classes of failed prior treatments as fixed factors; treatment group and baseline by-visit as interaction terms, with an unstructured covariance matrix.

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

End point description:

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 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. MMRM was used for analysis. OTHE population consisted of 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 postbaseline 4-week period (Weeks 1 to 4, 5 to 8, 9 to 12) of eDiary data, regardless of whether on study intervention or off study intervention.

End point type	Primary

End point timeframe:

Baseline to Week 12

End point values	Placebo	Atogepant 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	154		
Units: migraine days per month				
least squares mean (standard error)	-1.85 (± 0.388)	-4.20 (± 0.393)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Atogepant 60 mg
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.19
upper limit	-1.52
Variability estimate	Standard error of the mean
Dispersion value	0.425

Notes:

[2] - MMRM=baseline monthly migraine days as covariate, treatment group, visit, region and number of classes of failed prior treatments as fixed factors; treatment group and baseline by-visit as interaction terms, with an unstructured covariance matrix.

Secondary: Number of Subjects With At Least a 50% Reduction in 3-Month Average of Monthly Migraine Days Across the 12- week Treatment Period in mITT Population

End point title	Number of Subjects With At Least a 50% Reduction in 3-Month Average of Monthly Migraine Days Across the 12- week Treatment Period in mITT Population

End point description:

Data is reported for 50% responders averaged at each 4-week period. 50% responders are subjects with at least a 50% reduction from baseline in 3-month average of 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 are 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. mITT population included all randomised subjects who received at least 1 dose of study treatment, had an evaluable baseline period of eDiary data, and had at least 1 evaluable post-baseline 4-week period of eDiary data during the double-blind treatment period.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo	Atogepant 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	151		
Units: Subjects	27	77		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Atogepant 60 mg
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.02
upper limit	8.79

Notes:

[3] - Odds ratio and p-value are based on logistic regression with treatment group, region, baseline monthly migraine days, and number of classes of failed prior prophylactic treatments (2 and >2) as explanatory variables.

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

End point title	Change From Baseline in Mean Monthly Headache Days Across the 12-week Treatment Period in mITT Population

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 treatment, had an evaluable baseline period of eDiary data, and had at least 1 evaluable post-baseline 4-week period of eDiary data during the double-blind treatment period.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo	Atogepant 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	151		
Units: headache days per month				
least squares mean (standard error)	-1.93 (± 0.424)	-4.21 (± 0.431)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Atogepant 60 mg
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.15
upper limit	-1.42
Variability estimate	Standard error of the mean
Dispersion value	0.44

Notes:

[4] - MMRM=baseline as covariate, treatment group, visit, region, number of classes of failed prior treatments, number of migraine days during baseline period as fixed factors; treatment group and baseline-by-visit with an unstructured covariance matrix.

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

End point title	Change From Baseline in Mean Monthly Acute Medication Use Days Across the 12-week Treatment Period in OTHE Population

End point description:

An acute medication use day is 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. OTHE population consisted of 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 postbaseline 4-week period (Weeks 1 to 4, 5 to 8, 9 to 12) of eDiary data, regardless of whether on study intervention or off study intervention.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo	Atogepant 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	154		
Units: acute medication use days per month				
least squares mean (standard error)	-1.10 (± 0.358)	-3.70 (± 0.361)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Atogepant 60 mg
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.36
upper limit	-1.86
Variability estimate	Standard error of the mean
Dispersion value	0.38

Notes:

[5] - MMRM=baseline as covariate, treatment group, visit, region, number of classes of failed prior treatments, number of migraine days during baseline period as fixed factors; treatment group and baseline-by-visit with an unstructured covariance matrix.

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

End point title	Change From Baseline in Mean Monthly Headache Days Across the 12-week Treatment Period in OTHE Population

End point description:

Subjects recorded daily total duration of a headache in a diary. Headache day : 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. Monthly (4-week) headache days: 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: 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. OTHE 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 postbaseline 4-week period (Weeks 1 to 4, 5 to 8, 9 to 12) of eDiary data, regardless of whether on study intervention or off study intervention.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo	Atogepant 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	154		
Units: headache days per month				
least squares mean (standard error)	-1.91 (± 0.423)	-4.10 (± 0.429)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Atogepant 60 mg
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.05
upper limit	-1.32
Variability estimate	Standard error of the mean
Dispersion value	0.439

Notes:

[6] - MMRM=baseline as covariate, treatment group, visit, region, number of classes of failed prior treatments, number of migraine days during baseline period as fixed factors; treatment group and baseline-by-visit with an unstructured covariance matrix.

Secondary: Number of Subjects With At Least a 50% Reduction in 3-Month Average of Monthly Migraine Days Across the 12- week Treatment Period in OTHE Population

End point title	Number of Subjects With At Least a 50% Reduction in 3-Month Average of Monthly Migraine Days Across the 12- week Treatment Period in OTHE Population

End point description:

Data is reported for 50% responders averaged at each 4-week period. 50% responders are subjects with at least a 50% reduction from baseline in 3-month average of 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 are 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. OTHE population consisted of 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 postbaseline 4-week period (Weeks 1 to 4, 5 to 8, 9 to 12) of eDiary data, regardless of whether on study intervention or off study intervention.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo	Atogepant 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	154		
Units: subjects	28	78		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Atogepant 60 mg
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.85
upper limit	8.14

Notes:

[7] - Odds ratio and p-value are based on logistic regression with treatment group, region, baseline monthly migraine days, and number of classes of failed prior prophylactic treatments (2 and >2) as explanatory variables.

Secondary: Change From Baseline in Mean Monthly Acute Medication Use Days Across the 12-week Treatment Period in mITT Population

End point title	Change From Baseline in Mean Monthly Acute Medication Use Days Across the 12-week Treatment Period in mITT Population

End point description:

An acute medication use day is 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. mITT population included all randomised subjects who received at least 1 dose of study treatment, had an evaluable baseline period of eDiary data, and had at least 1 evaluable post-baseline 4-week period of eDiary data during the double-blind treatment period.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo	Atogepant 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	151		
Units: acute medication use days per month				
least squares mean (standard error)	-1.11 (± 0.359)	-3.79 (± 0.363)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Atogepant 60 mg
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.43
upper limit	-1.93
Variability estimate	Standard error of the mean
Dispersion value	0.381

Notes:

[8] - MMRM=baseline as covariate, treatment group, visit, region, number of classes of failed prior treatments, number of migraine days during baseline period as fixed factors; treatment group and baseline-by-visit with an unstructured covariance matrix.

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

End point title	Change From Baseline in Migraine Specific Quality of Life Questionnaire (MSQ) v2.1 Role Function-Restrictive Domain Score at Week 12 in mITT Population

End point description:

The MSQ v2.1 is a 14-item questionnaire designed to measure health-related quality of life impairments attributed to migraine in the past 4 weeks. It is divided into 3 domains: Role Function Restrictive (question numbers 1-7, score ranges 7 to 42) assesses how migraines limit one's daily social and work-related activities; Role Function Preventive (question numbers 8-11, score ranges 4 to 24) assesses how migraines prevent these activities; and the Emotional Function (question numbers 12-14, score ranges 3 to 18) domain assesses the emotions associated with migraines. Subjects respond to items using a 6-point scale ranging from none of the time to all of the time. Raw dimension scores are computed as a sum of item responses and rescaled to a 0 to 100 scale, where higher scores indicate better quality of life. MMRM was used for analysis. mITT population. Subjects analysed is the number of subjects available for analysis.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo	Atogepant 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	144		
Units: score on a scale				
least squares mean (standard error)	15.41 (± 2.078)	33.09 (± 2.102)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Atogepant 60 mg
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	17.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.05
upper limit	22.3
Variability estimate	Standard error of the mean
Dispersion value	2.348

Notes:

[9] - MMRM=baseline as covariate, treatment group, visit, region, number of classes of failed prior treatments, number of migraine days during baseline period as fixed factors; treatment group and baseline-by-visit with an unstructured covariance matrix.

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

End point description:

The MSQ v2.1 is a 14-item questionnaire designed to measure health-related quality of life impairments attributed to migraine in the past 4 weeks. It is divided into 3 domains: Role Function Restrictive (question numbers 1-7, score ranges 7 to 42) assesses how migraines limit one's daily social and work-related activities; Role Function Preventive (question numbers 8-11, score ranges 4 to 24) assesses how migraines prevent these activities; and the Emotional Function (question numbers 12-14, score ranges 3 to 18) domain assesses the emotions associated with migraines. Subjects respond to items using a 6-point scale ranging from none of the time to all of the time. Raw dimension scores are computed as a sum of item responses and rescaled to a 0 to 100 scale, where higher scores indicate better quality of life. MMRM was used for analysis. OTHE population. Subjects analysed is the number of subjects available for analysis.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo	Atogepant 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	144		
Units: score on a scale				
least squares mean (standard error)	15.38 (± 2.047)	33.26 (± 2.065)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Atogepant 60 mg
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [10]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	17.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.34
upper limit	22.42
Variability estimate	Standard error of the mean
Dispersion value	2.308

Notes:

[10] - MMRM=baseline as covariate, treatment group, visit, region, number of classes of failed prior treatments, number of migraine days during baseline period as fixed factors; treatment group and baseline-by-visit with an unstructured covariance matrix.

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

End point title	Change From Baseline in Mean Monthly Performance of Daily Activities Domain Score of the Activity Impairment in Migraine - Diary (AIM-D) Across the 12-Week Treatment Period in mITT Population

End point description:

The AIM-D is a 11-item patient-reported outcome (PRO) measure that assesses the impact of migraine on the performance of daily activities which include, 7 items: difficulty with household chores, errands, leisure activities at home, leisure or social activities outside the home, strenuous physical activities, concentrating, and thinking clearly and physical impairment; 4 items: difficulty walking, moving body, bending forward, moving head 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. The raw performance of daily activities domain scores were transformed to 0-100 scale, with higher scores indicating greater impact of migraine (higher disease burden). mITT population. Subjects analysed is the number of subjects available for analysis.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo	Atogepant 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	145		
Units: score on a scale				
least squares mean (standard error)	-4.97 (± 0.800)	-9.68 (± 0.826)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Atogepant 60 mg
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [11]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-4.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.37
upper limit	-3.05
Variability estimate	Standard error of the mean
Dispersion value	0.844

Notes:

[11] - MMRM=baseline as covariate, treatment group, visit, region, number of classes of failed prior treatments, number of migraine days during baseline period as fixed factors; treatment group and baseline-by-visit with an unstructured covariance matrix.

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

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

End point description:

The AIM-D is a 11-item PRO measure that assesses the impact of migraine on the performance of daily activities which includes 7 items: difficulty with household chores, errands, leisure activities at home, leisure or social activities outside the home, strenuous physical activities, concentrating, and thinking clearly and physical impairment; 4 items: difficulty walking, moving body, bending forward, moving head 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. The raw physical impairment domain scores were transformed to 0-100 scale, with higher scores indicating greater impact of migraine (higher disease burden). mITT population. Subjects analysed is the number of subjects available for analysis.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo	Atogepant 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	145		
Units: score on a scale				
least squares mean (standard error)	-3.03 (± 0.748)	-7.43 (± 0.773)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Atogepant 60 mg
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-4.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.94
upper limit	-2.85
Variability estimate	Standard error of the mean
Dispersion value	0.786

Notes:

[12] - MMRM=baseline as covariate, treatment group, visit, region, number of classes of failed prior treatments, number of migraine days during baseline period as fixed factors; treatment group and baseline-by-visit with an unstructured covariance matrix.

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

End point title	Change From Baseline in the Headache Impact Test (HIT-6) Total Score at Week 12 in OTHE Population

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). MMRM was used for the analyses. OTHE population consisted of 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 postbaseline 4-week period (Weeks 1 to 4, 5 to 8, 9 to 12) of eDiary data, regardless of whether on study intervention or off study intervention. Subjects analysed is the number of subjects available for analysis.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo	Atogepant 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	144		
Units: score on a scale				
least squares mean (standard error)	-4.14 (± 0.795)	-10.56 (± 0.804)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Atogepant 60 mg
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [13]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-6.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.22
upper limit	-4.63
Variability estimate	Standard error of the mean
Dispersion value	0.912

Notes:

[13] - MMRM=baseline monthly migraine days as covariate, treatment group, visit, region and number of classes of failed prior treatments as fixed factors; treatment group and baseline by-visit as interaction terms, with an unstructured covariance matrix.

Secondary: Number of Subjects Experiencing Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Subjects Experiencing Treatment-Emergent Adverse Events (TEAEs)

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. The investigator assesses the relationship of each event to the use of study drug. TEAEs were defined as any AE with the onset that was after the first dose of study intervention. Safety population consisted of all subjects who received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

From first dose of study drug until 30 days after last dose of study drug (up to Week 12)

End point values	Placebo	Atogepant 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	156		
Units: subjects	84	81		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality: from enrollment to end of study; TEAEs and serious AEs (SAEs): from first dose of study drug until 30 days after last dose of study drug; mean duration on study drug: 93.5 days and 90.0 days for Placebo and Atogepa, respectively.

Adverse event reporting additional description:

All-cause mortality is reported for all subjects enrolled in the study. Serious and other adverse events are reported for safety population which consisted of all subjects who received at least 1 dose of study intervention.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Atogepant 60 mg

Reporting group description:

Subjects received atogepant 60 mg, orally, QD for up to 12 weeks in a DB treatment period.

Reporting group title	Placebo

Reporting group description:

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

Serious adverse events	Atogepant 60 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 156 (2.56%)	0 / 157 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BREAST CANCER STAGE II			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INVASIVE BREAST CARCINOMA			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
VENTRICULAR TACHYCARDIA			

subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
ABORTION INDUCED			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Atogepant 60 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 156 (25.64%)	34 / 157 (21.66%)	
Gastrointestinal disorders			
NAUSEA			
subjects affected / exposed	11 / 156 (7.05%)	5 / 157 (3.18%)	
occurrences (all)	12	5	
CONSTIPATION			
subjects affected / exposed	16 / 156 (10.26%)	4 / 157 (2.55%)	
occurrences (all)	18	4	
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	8 / 156 (5.13%)	12 / 157 (7.64%)	
occurrences (all)	10	12	
COVID-19			
subjects affected / exposed	13 / 156 (8.33%)	15 / 157 (9.55%)	
occurrences (all)	13	15	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 April 2020	The following changes were implemented with Amendment 1: - Clarified the study rationale. - Added the diagnosis of "medication overuse headache" in key exclusion criteria and synopsis. - Added "region" to the analysis model. - Updated the study design by clarifying the block randomisation procedure.
01 December 2020	The following changes were implemented with Amendment 2: -Removed the atogepant 30 mg QD treatment arm from the study and reduced the total number of subjects from 627 to 300 subjects. - Define the number of scheduled study visits. - Updated section with the results from the recently completed Phase 3 studies (Study 3101-301-002 and Study 3101-302-002) in Background section. – Revised the first 3 secondary objectives and endpoints. - Added text to clarify the previous secondary objective and endpoints of evaluating the effect of atogepant versus placebo on functioning and activity impairment by specifying the AIM-D domains of Performance of Daily Activities and Physical Impairment. Revised exploratory objectives and endpoints. - Clarification of stratification strategy. - Adjusted block size for block randomisation to accommodate the deletion of the atogepant 30 mg QD treatment arm. - Reference to Subpopulation A removed. - Added that approximately 50% of randomised subjects will have failed >2 classes of prior migraine prophylactic medications. - Defined the number of scheduled study visits for subjects who will roll over into Study 3101-312-002 (long-term extension study) and those who do not. – Updated the justification for dose section by adding results from Study 3101-301-002. – Simplified the enrolment requirements. – Revised the Exclusion criteria to clarify the use of barbiturate containing and opioid-containing analgesics on a monthly basis in the 3 months prior to Visit 1; Clarified that the use of any investigational or approved CGRP-RA is excluded. - Clarified that prior use of ubrogepant or rimegepant is not exclusionary. – Clarified possibilities for rescreening in pandemic situations (eg, COVID-19). - Added text related to the subgroup analyses. - Added text related to an Offtreatment Hypothetical Estimand. – Clarified prohibited concomitant medication. - Clarified the Schedule of Activities for remote visits.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported