

**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 | v2 (current) |
| This version publication date | 28 October 2023 |
| First version publication date | 19 August 2023 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set Clarifying text describing timeframe related to safety data. |

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 standard deviation | | | 9.3 ± 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 (\pm 0.389) | -4.29 (\pm 0.397) | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|-------------------------------|
| Comparison groups | Atogepant 60 mg v Placebo |
| 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 (\pm 0.358) | -3.70 (\pm 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 (\pm 0.423) | -4.10 (\pm 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 (\pm 0.359) | -3.79 (\pm 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 (\pm 2.078) | 33.09 (\pm 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 (\pm 2.047) | 33.26 (\pm 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 (\pm 0.748) | -7.43 (\pm 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 (\pm 0.795) | -10.56 (\pm 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 reported from enrollment to end of study; median time followed 93.5, 90.0 days (Pbo, Atogepant). TEAEs/SAEs collected from first dose of drug until 30 days after last dose; mean duration on drug 83.7, 81.7 days (Pbo, Atogepant).

Adverse event reporting additional description:

All-cause mortality is reported for all participants enrolled in the study. Serious and other adverse events are reported for Safety population which consisted of all participants 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) | | | |
| 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 | |
| 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 | |
| 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