



Clinical trial results:

A Parallel Group, Double-Blind, Randomized, Placebo Controlled Phase 3 Trial to Evaluate the Efficacy and Safety of ALD403 Administered Intravenously in Patients with Chronic Migraine

Summary

| | |
|--------------------------|----------------------------|
| EudraCT number | 2016-001306-41 |
| Trial protocol | GB CZ DK DE BE SK HU ES IT |
| Global end of trial date | 18 September 2018 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 21 September 2019 |
| First version publication date | 21 September 2019 |

Trial information

Trial identification

| | |
|-----------------------|-----------------|
| Sponsor protocol code | ALD403-CLIN-011 |
|-----------------------|-----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02974153 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Alder BioPharmaceuticals, Inc. |
| Sponsor organisation address | 11804 North Creek Pkwy S, Bothell, United States, WA 98011 |
| Public contact | Lahar Mehta, Alder BioPharmaceuticals, Inc., 1- 425-205-2900, |
| Scientific contact | Lahar Mehta, Alder BioPharmaceuticals, Inc., 1- 425-205-2900, |

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 | 19 September 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 20 April 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 September 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary study objective was to evaluate the efficacy of repeat doses of ALD403 administered intravenously (IV) compared to placebo in subjects with chronic migraine.

Protection of trial subjects:

Before each subject was admitted to the clinical study, informed consent was to be obtained from the subject (or his/her legally authorized representative) according to the regulatory and legal requirements of the participating country. The informed consent form (ICF) was to be dated and retained by the investigator as part of the clinical study records. The investigator was not to undertake any investigation specifically required for the clinical study until valid consent was obtained. The date consent was obtained was to be documented in the electronic case report form (eCRF). Each subject was to receive a fully signed copy of each consent form that he/she signed for the clinical study.

Background therapy:

Any concomitant therapy used from the time the subject signed the ICF through Week 32 was recorded in the eCRF, including medications required for treatment of any AEs or SAEs. The medication name, dosage, date, and indication for use was recorded.

Evidence for comparator:

There was not an active comparator in this study. To minimize the bias, this clinical study was randomized, double blinded and placebo controlled. Placebo-controlled studies are the gold standard to demonstrate the therapeutic effect of an active treatment intervention.

| | |
|---|------------------|
| Actual start date of recruitment | 30 November 2016 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 5 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Slovakia: 18 |
| Country: Number of subjects enrolled | Spain: 63 |
| Country: Number of subjects enrolled | United Kingdom: 9 |
| Country: Number of subjects enrolled | Belgium: 1 |
| Country: Number of subjects enrolled | Czech Republic: 28 |
| Country: Number of subjects enrolled | Denmark: 7 |
| Country: Number of subjects enrolled | Germany: 12 |
| Country: Number of subjects enrolled | Hungary: 12 |
| Country: Number of subjects enrolled | Italy: 15 |
| Country: Number of subjects enrolled | Georgia: 102 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Russian Federation: 91 |
| Country: Number of subjects enrolled | Ukraine: 114 |
| Country: Number of subjects enrolled | United States: 649 |
| Worldwide total number of subjects | 1121 |
| EEA total number of subjects | 165 |

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) | 1115 |
| From 65 to 84 years | 6 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Subjects were eligible for inclusion if they met all of the inclusion criteria at screening and during the 28-day screening period prior to randomization.

Pre-assignment

Screening details:

The study participation period was approximately 36 weeks. This included a 4-week screening period, a 12-week treatment period, and a 20-week follow-up period.

Period 1

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

Blinding implementation details:

This clinical study was double-blinded, meaning the subjects and site personnel were blinded to treatment assignment, except for the clinical study site's unblinded pharmacist or designee. The study site had a written Blinding Plan in place to ensure blinding was adequately maintained for the study. The study remained blinded until the last subject completed the Week 12 visit.

Arms

| | |
|------------------------------|---------------|
| Are arms mutually exclusive? | Yes |
| Arm title | ALD403 300 mg |

Arm description:

Subjects randomly assigned to ALD403 received an IV infusion of ALD403 in solution with a concentration of 100mg/ml in 1 ml of solution.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ALD403 |
| Investigational medicinal product code | N/A |
| Other name | IV Infusion |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

ALD403 (eptinezumab) is an anti-CGRP humanized monoclonal antibody (anti-CGRP mAb). ALD403 Injection, 100 mg/mL (1 mL per vial), vial) was provided in 2-mL Type I glass vials as a single-use preservative-free solution for IV administration. ALD403 was formulated at a concentration of 100 mg/mL with a pH of 5.8. The eptinezumab solution for infusion is prepared by adding Eptinezumab Injection to pre-filled, sterile, 100 mL normal saline prior to IV infusion.

| | |
|------------------|---------------|
| Arm title | ALD403 100 mg |
|------------------|---------------|

Arm description:

Subjects randomly assigned to ALD403 received an IV infusion of ALD403 in solution with a concentration of 100mg/ml in 1 ml of solution.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ALD403 |
| Investigational medicinal product code | N/A |
| Other name | IV Infusion |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

ALD403 (eptinezumab) is an anti-CGRP humanized monoclonal antibody (anti-CGRP mAb). ALD403 Injection, 100 mg/mL (1 mL per vial), vial) was provided in 2-mL Type I glass vials as a single-use

preservative-free solution for IV administration. ALD403 was formulated at a concentration of 100 mg/mL with a pH of 5.8. The eptinezumab solution for infusion is prepared by adding Eptinezumab Injection to pre-filled, sterile, 100 mL normal saline prior to IV infusion.

| | |
|--|-----------------------|
| Arm title | Placebo |
| Arm description: | |
| Placebo was supplied as a single-use preservative-free solution in 2-mL Type I glass vials formulated with the same excipients as ALD403. Subjects randomly assigned to placebo received an IV infusion of placebo in 100 mL of 0.9% saline. | |
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | N/A |
| Other name | IV Infusion |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Placebo was supplied as a single-use preservative-free solution in a 2-ml Type I glass vial formulated with the same excipients as ALD403 (eptinezumab), without the active ingredient. Those subjects randomly assigned to placebo received an IV infusion of placebo in 100 mL of 0.9% saline. The placebo solution for infusion is prepared by adding Placebo Injection to pre-filled, sterile, 100 mL normal saline prior to IV infusion.

| Number of subjects in period 1^[1] | ALD403 300 mg | ALD403 100 mg | Placebo |
|---|---------------|---------------|---------|
| Started | 350 | 356 | 366 |
| Completed | 335 | 340 | 342 |
| Not completed | 15 | 16 | 24 |
| Consent withdrawn by subject | 5 | 7 | 14 |
| Adverse event, non-fatal | 8 | 3 | 3 |
| Other | - | 3 | 2 |
| Lost to follow-up | 2 | 3 | 5 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Total number of subject enrolled in the study is 1121. There were 1072 randomly assigned and treated subjects in this study.

Baseline characteristics

Reporting groups

| | |
|--|---------------|
| Reporting group title | ALD403 300 mg |
| Reporting group description: Subjects randomly assigned to ALD403 received an IV infusion of ALD403 in solution with a concentration of 100mg/ml in 1 ml of solution. | |
| Reporting group title | ALD403 100 mg |
| Reporting group description: Subjects randomly assigned to ALD403 received an IV infusion of ALD403 in solution with a concentration of 100mg/ml in 1 ml of solution. | |
| Reporting group title | Placebo |
| Reporting group description: Placebo was supplied as a single-use preservative-free solution in 2-mL Type I glass vials formulated with the same excipients as ALD403. Subjects randomly assigned to placebo received an IV infusion of placebo in 100 mL of 0.9% saline. | |

| Reporting group values | ALD403 300 mg | ALD403 100 mg | Placebo |
|---|-----------------|-----------------|-----------------|
| Number of subjects | 350 | 356 | 366 |
| Age categorical Units: Subjects | | | |
| Adults (18-65 years) | 350 | 356 | 366 |
| Age continuous Units: years arithmetic mean standard deviation | 41.0 ± 10.36 | 41.0 ± 11.72 | 39.6 ± 11.28 |
| Gender categorical Units: Subjects | | | |
| Female | 314 | 307 | 325 |
| Male | 36 | 49 | 41 |

| Reporting group values | Total | | |
|---|-------|--|--|
| Number of subjects | 1072 | | |
| Age categorical Units: Subjects | | | |
| Adults (18-65 years) | 1072 | | |
| Age continuous Units: years arithmetic mean standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 946 | | |
| Male | 126 | | |

Subject analysis sets

| | |
|----------------------------|--------------------------|
| Subject analysis set title | Full analysis population |
| Subject analysis set type | Full analysis |

Subject analysis set description:

The full analysis population included all randomized subjects who received eptinezumab and placebo. Subjects were summarized within the group to which they were randomized.

| | | | |
|---|--------------------------|--|--|
| Reporting group values | Full analysis population | | |
| Number of subjects | 1072 | | |
| Age categorical Units: Subjects | | | |
| Adults (18-65 years) | 1072 | | |
| Age continuous Units: years arithmetic mean standard deviation | 40.5 ± | | |
| Gender categorical Units: Subjects | | | |
| Female | 946 | | |
| Male | 126 | | |

End points

End points reporting groups

| | |
|--|--------------------------|
| Reporting group title | ALD403 300 mg |
| Reporting group description: Subjects randomly assigned to ALD403 received an IV infusion of ALD403 in solution with a concentration of 100mg/ml in 1 ml of solution. | |
| Reporting group title | ALD403 100 mg |
| Reporting group description: Subjects randomly assigned to ALD403 received an IV infusion of ALD403 in solution with a concentration of 100mg/ml in 1 ml of solution. | |
| Reporting group title | Placebo |
| Reporting group description: Placebo was supplied as a single-use preservative-free solution in 2-mL Type I glass vials formulated with the same excipients as ALD403. Subjects randomly assigned to placebo received an IV infusion of placebo in 100 mL of 0.9% saline. | |
| Subject analysis set title | Full analysis population |
| Subject analysis set type | Full analysis |
| Subject analysis set description: The full analysis population included all randomized subjects who received eptinezumab and placebo. Subjects were summarized within the group to which they were randomized. | |

Primary: Change in frequency of migraine days (Weeks 1-12)

| | |
|--|---|
| End point title | Change in frequency of migraine days (Weeks 1-12) |
| End point description: For the study's primary efficacy endpoint, the change in frequency of migraine days from Weeks 1-12 was measured in ALD403 groups at 300 mg and 100 mg, compared with placebo. This primary efficacy endpoint was calculated as the number of migraine days within 4-week intervals that were then averaged up to Week 12. The difference of this estimate from baseline was calculated as the change from baseline in the frequency of migraine days over Weeks 1-12. | |
| End point type | Primary |
| End point timeframe: The primary efficacy endpoint was evaluated over the 12-week period following the first administration of study drug. | |

| End point values | ALD403 300 mg | ALD403 100 mg | Placebo | |
|--|------------------|------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 350 | 356 | 366 | |
| Units: days | | | | |
| arithmetic mean (full range (min-max)) | -8.3 (-23 to 11) | -7.8 (-22 to 10) | -5.8 (-25 to 9) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis Plan, Ver 1.0 dated 08 Nov 17 |
| Statistical analysis description: Full Analysis Population (FAP) – Randomized subjects who received Investigational Product/placebo. | |

Migraine and headache data were collected through Week 24. Hypothesis testing was performed for the primary endpoint: change in frequency of migraine.

| | |
|---|--------------------------------|
| Comparison groups | ALD403 100 mg v ALD403 300 mg |
| Number of subjects included in analysis | 706 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | < 0.0001 ^[2] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.45 |
| upper limit | -1.74 |
| Variability estimate | Standard deviation |

Notes:

[1] - Taken together and based on the decision rule, the results for the study's primary efficacy endpoint were statistically significant in both the ALD403 300 mg and 100 mg groups compared with placebo.

[2] - With a mean difference of -2.60 days (95% CI: -3.45, -1.74), the ALD403 300 mg dose demonstrated a statistically significant improvement ($P < 0.0001$) from placebo.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Event reporting extended from the time the informed consent was signed until completion of the final visit.

Adverse event reporting additional description:

An overview of AEs, which included subject incidence of TEAEs (Treatment-Emergent Adverse Events), study drug-related TEAEs, serious TEAEs, TEAEs leading to study drug interruption, and TEAEs leading to study drug discontinuation, was presented. The subject incidence of TEAEs and study drug-related TEAEs were summarized by SOC and PT.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | ALD403 300 mg |
|-----------------------|---------------|

Reporting group description: -

| | |
|-----------------------|---------------|
| Reporting group title | ALD403 100 mg |
|-----------------------|---------------|

Reporting group description: -

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events | ALD403 300 mg | ALD403 100 mg | Placebo |
|---|-----------------|-----------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 350 (1.14%) | 3 / 356 (0.84%) | 3 / 366 (0.82%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 356 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 356 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tibia fracture | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 356 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Migraine | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 356 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Migraine with aura | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 356 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 356 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 356 (0.28%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 356 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 356 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Menometrorrhagia | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 356 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Psychiatric disorders | | | |
| Depression suicidal | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 356 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicide attempt | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 356 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 356 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 356 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events | ALD403 300 mg | ALD403 100 mg | Placebo |
|---|--------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 182 / 350 (52.00%) | 154 / 356 (43.26%) | 169 / 366 (46.17%) |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 9 / 350 (2.57%) | 5 / 356 (1.40%) | 4 / 366 (1.09%) |
| occurrences (all) | 9 | 5 | 4 |
| Migraine | | | |
| subjects affected / exposed | 8 / 350 (2.29%) | 5 / 356 (1.40%) | 16 / 366 (4.37%) |
| occurrences (all) | 8 | 5 | 16 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 6 / 350 (1.71%) | 8 / 356 (2.25%) | 7 / 366 (1.91%) |
| occurrences (all) | 6 | 8 | 7 |

| | | | |
|---|------------------|------------------|------------------|
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 12 / 350 (3.43%) | 6 / 356 (1.69%) | 7 / 366 (1.91%) |
| occurrences (all) | 12 | 6 | 7 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 7 / 350 (2.00%) | 4 / 356 (1.12%) | 1 / 366 (0.27%) |
| occurrences (all) | 7 | 4 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 11 / 350 (3.14%) | 5 / 356 (1.40%) | 3 / 366 (0.82%) |
| occurrences (all) | 11 | 5 | 3 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 4 / 350 (1.14%) | 7 / 356 (1.97%) | 8 / 366 (2.19%) |
| occurrences (all) | 4 | 7 | 8 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 33 / 350 (9.43%) | 19 / 356 (5.34%) | 22 / 366 (6.01%) |
| occurrences (all) | 33 | 19 | 22 |
| Sinusitis | | | |
| subjects affected / exposed | 9 / 350 (2.57%) | 7 / 356 (1.97%) | 15 / 366 (4.10%) |
| occurrences (all) | 9 | 7 | 15 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 19 / 350 (5.43%) | 15 / 356 (4.21%) | 20 / 366 (5.46%) |
| occurrences (all) | 19 | 15 | 20 |
| Urinary tract infection | | | |
| subjects affected / exposed | 12 / 350 (3.43%) | 8 / 356 (2.25%) | 6 / 366 (1.64%) |
| occurrences (all) | 12 | 8 | 6 |
| Influenza | | | |
| subjects affected / exposed | 10 / 350 (2.86%) | 1 / 356 (0.28%) | 9 / 366 (2.46%) |
| occurrences (all) | 10 | 1 | 9 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|--|
| 20 March 2017 | Amendment 1.1 - Applicable for Germany only, incorporating changes requested by German regulatory authorities. All changes made were incorporated into Amendment 2 for all countries. |
| 20 March 2017 | <p>Amendment 2</p> <p>Schedule of Events and Assessments: Clarified the window for randomization as 28 to 30 days after screening and clarified the window for treatment as within 8 days after randomization. Schedule of Events and Assessments footers: Further clarified the process and requirement of review by the medical monitor prior to randomization, clarified the window within which dosing must occur due to drug not typically being onsite at time of randomization, updated the timeframe of postdose vital sign measurement from 4 hours postdose to 2 hours postdose to be consistent with a shorter postdose observation period, updated timeframe of postdose the ECG procedure from 4 hours postdose to 2 hours postdose to be consistent with shorter postdose observation period, and postdose observation period after dosing completion was shortened from 4 hours to 2 hours based on review of safety data.</p> <p>Section 8.2: Clarified that exclusion of temporomandibular disorders must be acute or active. Added clarification to exclusionary headache and migraine types (unusual migraine subtypes such as hemiplegic migraine [sporadic and familial], ophthalmoplegic migraine and migraine with neurological accompaniments that are not typical of migraine aura [eg, diplopia, altered consciousness, or long duration]).</p> <p>Section 8.4.1: Added that study treatment must be discontinued with pregnancy or suicidal ideation or behavior and specified the action to be taken for subjects discontinued due to suicidal ideation and/or suicidal behavior.</p> <p>Section 9.4: Added restriction for hormonal therapy during the study (must remain stable through Week 32).</p> <p>Section 10.2.4: Clarified the scope of the screening physical examination to be comprehensive and appropriate to determine the overall physical health of each subject and clarified that examination of the genitourinary system and rectum may be deferred by the investigator if the subject's related medical history and review of systems are negative.</p> |
| 31 August 2017 | <p>Amendment 3a</p> <p>Protocol Synopsis: Changes were made to update the following key secondary endpoints (50% migraine responder rate [Weeks 1-12], percentage of subjects with a migraine on the day after dosing, and reduction in migraine prevalence from baseline to Week 4) and other secondary endpoints (acute migraine medication usage and change in frequency of migraine days [Weeks 1-24]) to ensure consistency across the development program for ALD403 and to ensure endpoints that were important in understanding the efficacy of ALD403 were appropriately highlighted.</p> <p>Protocol Synopsis: A change was made to the sample size section to clarify that 350 subjects per group provides at least 90% power for the primary endpoint and not for the change from baseline tests.</p> <p>Protocol Synopsis: Changes were made to the statistical analysis section to ensure the text addressed the primary and additional key secondary endpoints. It was clarified that statistical inferential testing of the primary efficacy endpoint and key secondary endpoints will be performed while maintaining a study-wide type I error rate of 2-sided 5%, and not just a testing of the change from baseline in migraine days and responder rate.</p> <p>Section 5.3.2: Table 5.3 was updated to reflect the status of ALD403 clinical studies</p> <p>Section 5.4: Clarification was made to confirm the safety findings to date.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported