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	41.0	41.0	39.6
standard deviation	± 10.36	± 11.72	± 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	40.5		
standard deviation	±		
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	Amendment 2 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. 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]). 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. Section 9.4: Added restriction for hormonal therapy during the study (must remain stable through Week 32). 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.
31 August 2017	Amendment 3a 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. 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. 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. Section 5.3.2: Table 5.3 was updated to reflect the status of ALD403 clinical studies Section 5.4: Clarification was made to confirm the safety findings to date.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported