Randomized, double-blind, placebo-controlled trial of ALD403, an anti-CGRP antibody in the prevention of chronic migraine.

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Background

ALD403 is a humanized, IgG1, anti-CGRP antibody being developed for the prevention of migraine.

Objectives

The objectives of this study were to determine the safety, efficacy and tolerability of single intravenous (i.v.) infusions of ALD403 300mg, 100mg, 30mg and 10mg versus placebo in the prevention of chronic migraine.

Methods

This study was performed in compliance with ICH guidelines for clinical trials, was approved by an Institutional Review Board and all patients gave written informed consent prior to enrollment. The trial was registered prior to enrollment (Clinicaltrials.gov Identifier: NCT02275117). The study was conducted at 92 clinical research centers in the United States of America, Republic of Georgia, Australia and New Zealand.

Male and female patients (*n* = 616) age 18 to 55 years with a diagnosis of migraine (ICHD-II, Cephalalgia 2004 ;24[Suppl 1]:1-160), and ≥ 15 headache days per month of which ≥ 8 days were assessed as migraine days with at least 5 migraine attacks were randomized and received either a single infusion of ALD403 300mg, 100mg, 30mg, 10mg or placebo by a one hour intravenous infusion . Subjects completed an electronic headache eDiary daily for 28 days prior to randomization and continue to use the eDiary for 48 weeks after randomization (study still ongoing at present). There are a total of 9 visits during the study at screening, dosing, week 2, 4, 8, 12, 24, 36 and 48 post-dose. The pre-specified primary analysis of safety and efficacy was performed using the 12 week post-infusion data. The study was un-blinded after the week 12 time-point.

Safety data included adverse event monitoring, laboratory safety data, vital signs, and 12-lead ECGs. The primary efficacy endpoint was the percentage of patients who achieved a 75% reduction in migraine days over weeks 1-12. Key secondary endpoints included the change, compared to baseline, in the frequency of migraine days for weeks 1-12; subjects achieving a 50% and 100% reduction in migraine days for weeks 1-12; subjects achieving a 50%, 75%, or 100% reduction in migraine days for weeks 1-4. Other secondary efficacy endpoints included the change in headache days, hours, and frequency; percentage change in migraine days reported as severe by patients.

The treatment difference for the primary endpoint was tested with a Cochran-Mantel-Haenszel, CMH, test controlling for the stratification factors (baseline migraine days and medication overuse status). Multiplicity was controlled using step-down testing, starting with 300mg vs placebo and proceeding down through the dose range. The 50% and 100% responder rate endpoints were tested using the same CMH test and change from baseline in migraine days were tested using an extended CMH test. The week 1-4 responder rates and the percentage of migraines reported as severe by patients were both post-hoc analysis.

The efficacy results are limited to the modified full analysis population. The study was originally designed to use the full analysis population but was amended to remove subjects from the efficacy analysis from one clinical site in the USA. At this site, 75% of subjects (21/28) reported no migraines during the 12 weeks following dosing. For all other sites 6% of subjects were completely migraine free for 12 weeks. Within this site the 75% responder rates were: 100% for the 300mg, 100mg and 10mg groups, 80% for the 30mg group and 60% for placebo. The site was reported to the IRB and FDA for possible misconduct. The subjects from this site were included in the safety analyses.

The target sample size of 120 subjects per group was selected to provide 90% power with a 10% two-sided alpha level or equivalently a 5% one-sided alpha, a placebo 75% response rate of 75% and a ALD403 response rate of 43%. All p-values reported are one-sided p-values.

Baseline Patient Demographics

	ALD403 300mg (n=121)	ALD403 100mg (n=122)	ALD403 30mg (n=122)	ALD403 10mg (n=130)	Placebo (n=121)
Mean ±SD Age (years)	37.4 (10.1)	37.0 (9.5)	36.0 (9.4)	36.6 (10.4)	37.4 (9.3)
Mean ±SD Weight (kg)	77.4 (16.6)	77.3 (17.5)	75.0 (17.6)	75.8 (15.4)	77.0 (18.0)
Female Gender	98 (81%)	104 (85%)	111 (91%)	113 (87%)	109 (90%)
Mean ±SD Migraine Days	16.5 (4.8)	16.9 (4.8)	16.2 (5.1)	16.4 (5.4)	16.4 (5.1)
Mean ±SD Headache Days	21.1 (3.8)	21.7 (3.9)	21.0 (3.8)	21.0 (4.2)	21.1 (4.1)
Mean ±SD Migraine Episodes	12.1 (4.4)	12.6 (4.2)	12.6 (5.0)	12.6 (5.0)	12.2 (5.4)
Mean ±SD % severe migraines	47% (25%)	49% (24%)	54% (26%)	48% (29%)	43% (27%)

Results - Safety

Serious Adverse Events:

Treatment	Event Preferred Term	Days Post-Dose	Investigator Relatedness
ALD403	Affective Disorder	103	Not Related
ALD403	Atrial Fibrillation*	0	Not Related
Placebo	Bronchitis	167	Not Related
ALD403	Cholelithiasis	129	Not Related
ALD403	Viral Gastroenteritis	112	Not Related
ALD403	Pelvic pain	86	Not Related
ALD403	Respiratory Distress	115	Not Related
ALD403	Seizure	121	Not Related
Placebo	Suicidal Ideation	39	Not Related
ALD403	Vaginal Abscess	142	Not Related

* = Present at pre-dose

Adverse Events Occurring in ≥ 5% subjects in any group:

	ALD403 300mg (n=121)	ALD403 100mg (n=122)	ALD403 30mg (n=122)	ALD403 10mg (n=130)	Placebo (n=121)
Upper Respiratory Tract Infection	12 (10%)	6 (5%)	6 (5%)	5 (4%)	6 (5%)
Dizziness	2 (2%)	10 (8%)	3 (3%)	10 (8%)	9 (7%)
Nausea	7 (6%)	8 (7%)	2 (2%)	6 (5%)	8 (7%)
Nasopharyngitis	8 (7%)	7 (6%)	2 (2%)_	5 (4%)	6 (5%)
Sinusitis	6 (5%)	3 (2%)	5 (4%)	7 (5%)	5 (4%)
Bronchitis	2 (2%)	2 (2%)	1 (1%)	3 (2%)	7 (6%)

Other safety data:

There were no significant changes or trends in laboratory safety data, vital sign, or \12 lead ECG parameters at any time-point in the study

Results - Efficacy

Responder Analysis (weeks 1-12):

Time period	Reduction in Migraine days per month	ALD403 300 mg (n=114)	ALD403 100 mg (n=118)	ALD403 30 mg (n=117)	ALD403 10 mg (n=123)	Placebo (n=116)
Weeks 1-12	50%↓	65 (57%)**	64 (54%)*	64 (55%)*	54 (44%)	47 (41%)
	75%↓	38 (33%)*	37 (31%)*	33 (28%)	33 (27%)	24 (21%)
	100%↓	9 (8%)	6 (5%)	5 (4%)	10 (8%)	3 (3%)

* One sided p-value versus placebo < 0.05, ** one sided p-value versus placebo < 0.01

The study met the primary efficacy endpoint which was the difference in the percentage patients achieving a 75% reduction in migraine days from baseline for ALD403 300mg and 100mg versus placebo (weeks 1-12). In addition there was a significant difference in the numbers of patients achieving a 50% reduction in migraine days from baseline for ALD403 300mg, 100mg and 30mg versus placebo (weeks 1-12).

Responder Analysis (weeks 1-4):

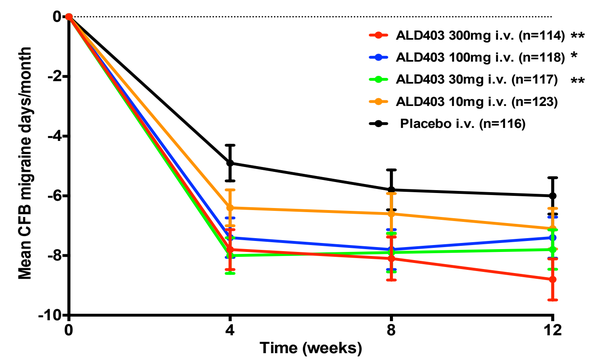
There was a rapid onset of action with regard to prevention as demonstrated by separation from placebo for the 75% responder analysis over the first month after dosing for the ALD403 300mg, 100mg, 30mg, and 10mg groups.

Time period	Reduction in Migraine days per month	ALD403 300 mg (n=114)	ALD403 100 mg (n=118)	ALD403 30 mg (n=117)	ALD403 10 mg (n=123)	Placebo (n=116)
Weeks 1- 4	50%↓	60 (53%)*	67 (57%)**	72 (62%)***	52 (43%)	44 (38%)
	75%↓	42 (37%)***	37 (31%)***	32 (27%)*	31 (25%)*	19 (16%)
	100%↓	9 (8%)	9 (8%)	7 (6%)	11 (9%)	6 (5%)

*** = p<0.0005, ** = p<0.005, * = p<0.05 one sided p value versus placebo (post hoc analysis)

Mean Change from Baseline in migraine days (weeks 1-12):

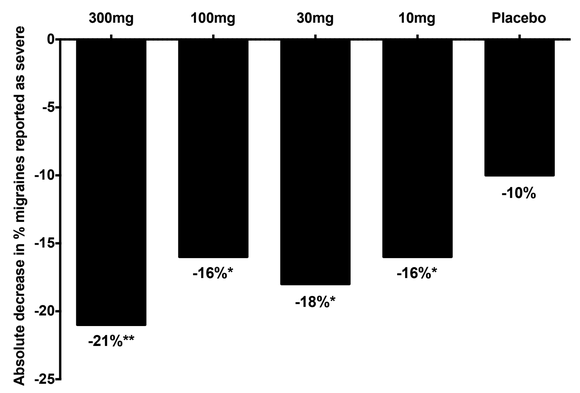
There was a significant difference in the decrease of mean migraine days per month for ALD403 300mg, 100mg and 30mg versus placebo. The 10mg dose appeared to be sub-therapeutic. As with the responder analysis the onset of action was rapid with most of the difference between placebo and active occurring in the first month after dosing.



** = one sided p value <0.005 * = one sided p value <0.01

Change from baseline in percentage of migraines reported as severe by patients (weeks 1-12):

The percentage of remaining migraines that were reported by patients as being severe after dosing was significantly reduced for all doses of ALD403 versus placebo.



** = p< 0.005, * = < 0.05 one sided p value versus placebo (post-hoc analysis)

Conclusions

- ALD403 given to patients with chronic migraine as a single intravenous dose of 300mg, 100mg, 30mg and 10mg was safe and well tolerated.
- ALD403 300mg i.v. and 100mg i.v. met the primary endpoint with a significant number of patients achieving a ≥ 75% reduction in their migraine days (weeks 1-12) versus placebo.
- ALD403 had a rapid onset of action as demonstrated by significant separation from placebo in the first month (weeks 1-4) after dosing for the 50% and 75% responder rates.
- ALD403 300mg, 100mg, and 30mg i.v. demonstrated a significant difference from placebo for mean change from baseline in migraine days per month (weeks 1-12).
- ALD403 300mg, 100mg, 30mg, and 10mg significantly reduced the number of severe migraines reported by patients relative to placebo (weeks 1-12).
- This efficacy and safety data supports the progression of ALD403 into phase 3 clinical trials for chronic migraine.