Randomized, double-blind, placebo-controlled trial of ALD403, an anti-CGRP antibody in the prevention of frequent episodic 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 a single intravenous (i.v.) infusion of ALD403 versus placebo in the prevention of frequent episodic 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: NCT01772524). The study was conducted at 26 clinical research centers in the United States of America.

Male and female patients (*n* = 174) age 18 to 55 years with a diagnosis of migraine (ICHD-II, Cephalalgia 2004 ;24[Suppl 1]:1-160), and with between 5 and 14 migraine days per month were randomized to receive either a single infusion of ALD403 (81 dosed) 1000mg or placebo (82 dosed) by a one hour intravenous infusion. Subjects completed an electronic headache (eDiary) daily for 28 days prior to randomization to confirm number migraine days per month were between 5 and 14. The patients who were treated continued to use the eDiary for 24 weeks after randomization. There were a total of 7 visits during the study at screening, dosing, week 2, 4, 8, 12, and 24 post-dose. The pre-specified primary analysis of safety and efficacy was performed using the 12 week post-infusion data.

Safety data included adverse event monitoring, laboratory safety data, vital signs, and 12-lead ECGs. The primary efficacy endpoint was the change in the frequency of migraine days, defined as any day with migraine or probable migraine with or without aura according to ICHD-II (except for duration = 30 mins), from baseline to weeks 5-8. Secondary efficacy endpoints included the change, compared to baseline, in the frequency of migraine days at weeks 1-4 and 9-12; responder rates (subjects achieving a 50%, 75%, or 100% reduction in migraine days); migraine hours; and migraine episodes (defined as one continuously recorded migraine from onset and termination of migraine pain). Other secondary efficacy endpoints included the change in headache day frequency (defined as any headache lasting any duration of time), Headache Impact Test (HIT-6 v1.1) and Migraine Specific Quality of Life Instrument (MSQ v2.1).

The 1000mg dose of ALD403 was chosen as this was shown to be the dose that fully suppressed peripheral CGRP responses in healthy subjects for ≥12 weeks as judged by suppression of capsaicin-induced increases in skin blood flow (Data on file).

Subjects were centrally randomized via an IWRS system in a 1:1 ratio to receive ALD403 or placebo. The sponsor was un-blinded following the completion of the primary endpoint at week 12. The sites and subjects remained blinded through study completion.

Methods

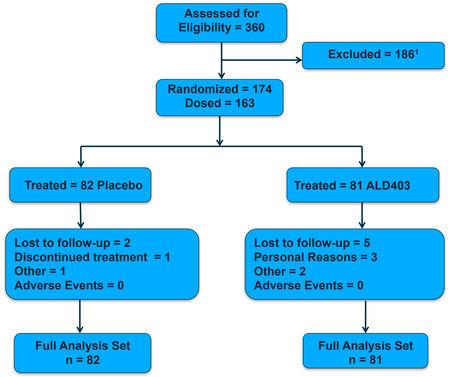
The treatment difference for the primary endpoint was tested with an extended Cochran-Mantel-Haenszel test stratified by baseline migraine days (≤ 9 days, > 9 days). Testing of the weeks 1-4 and 9-12 migraine days endpoints was also performed. Testing was not performed for the other efficacy endpoints. Because of the utility of responder rates as an outcome measure in migraine prevention trials, a *post-hoc* responder endpoint that evaluated overall responder status overall from weeks 1-12 was also included. This endpoint classifies a subject as a 50% responder from Weeks 1-12 if they were a 50% responder for each of the 4 week intervals (Week 1-4, 5-8 and 9-12). Similarly, defined 75% and 100% Week 1-12 responder rates have also been included.

The sample size provided at least 90% power with a 5% one-sided alpha under the assumption that the standard deviation is equal to 2.5 and the treatment difference ≥ 1.2 days (ALD403 reduces migraine days by 1.2 days more than placebo). All p-values reported are one-sided p-values.

Baseline Patient Demographics

	ALD403 1000mg iv (n=81)	Placebo iv (n=82)
Mean ±SD Age (years)	38.6 (10.8)	39.0 (9.6)
Mean ±SD Weight (kg)	75.0 (16.5)	75.4 (14.4)
Gender (M:F)	14 (17%): 67 (83%)	16 (20%): 66 (80%)
Race:		
Caucasian	66 (81.5%)	66 (80.5%)
African American	10 (12.4%)	9 (11.0%)
Asian	4 (5.0%)	3 (3.7%)
Other	1 (1.1%)	4 (4.8%)
Mean ±SD Migraine Days	8.5 (2.5)	8.8 (2.7)
Mean ±SD Headache Days	9.2 (2.6)	9.6 (2.8)
Mean ±SD Migraine Hours	80.1 (49.1)	72.2 (51.0)
Mean ±SD Migraine Episodes	6.0 (2.2)	6.7 (2.4)
Mean ±SD Migraine Severity	3.2 (0.4)	3.2 (0.4)
Mean HIT-6 Score	63.8 (5.21)	64.5 (4.44)

Results - Disposition



[1] Main reasons for exclusion before randomization were too many (>14) or too few (<5) migraine days per month during eDiary run-in and lack of compliance with the eDiary.

Results - Safety

Adverse events were experienced by 52.4% and 56.8% of subjects in the placebo and ALD403 groups, respectively. The most frequent adverse events in the placebo and ALD403 group respectively were; upper respiratory tract infection (7.3% vs 8.6%), urinary tract infection (4.9% vs 1.2%), fatigue (3.7% vs 3.7%), back pain (4.9% vs 3.7%) and arthralgia (4.9% vs 1.2%). Most adverse events were transient and mild to moderate in severity. There were no infusion reactions reported during the study.

There were four serious adverse events reported by three subjects. In the investigator's opinion these events were unrelated to study drug. One subject on placebo suffered a fractured fibula that required hospitalization. One subject on ALD403 experienced pyelonephritis that required hospitalization. One subject on ALD403 experienced an episode of chest pain and shortness of breath and required hospitalization. After a complete cardiac assessment the diagnosis was non-cardiac chest pain. During this admission it was discovered that this subject had experienced a previous admission to a hospital earlier in the study for a possible transient ischaemic attack (TIA) that after a full neurovascular assessment no etiology was found.

There were no significant differences in vital signs or laboratory safety data between subjects treated with ALD403 or placebo at any time during the study.

Results - Efficacy

The study met the primary efficacy endpoint which was the difference in the mean absolute change from baseline in migraine days during weeks 5 to 8 between ALD403 and placebo (Figure 1).

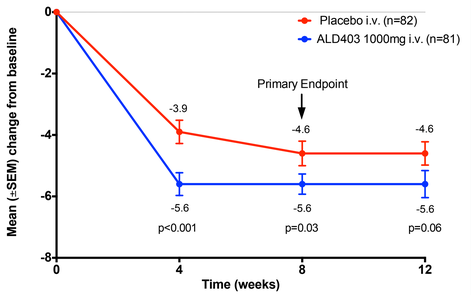


Figure 1

More patients on ALD403 than on placebo achieved a 50%, 75%, and 100% reduction in migraine days per month during weeks 1–4, 5–8, and 9–12. Between 26.0% and 41.1% of the patients receiving ALD403 experienced no migraines during any four-week period (table below).

Time period	Percent reduction migraine days	ALD403 1000mg iv Number (%) n=81	Placebo iv Number (%) n=82	P value
Week 1-4	50	57 (75.0)	40 (50.0)	p=0.0011
	75	39 (51.3)	19 (23.8)	p=0.0003
	100	20 (26.7)	4 (5.0)	p<0.0001
Week 5-8	50	58 (75.3)	43 (53.8)	p=0.0032
	75	34 (44.2)	28 (35.0)	p=0.1347
	100	20 (26.0)	12 (15.0)	p=0.0493
Week 9-12	50	56 (76.7)	52 (66.7)	p=0.1603
	75	39 (53.4)	24 (30.8)	p=0.0039
	100	30 (41.1)	13 (16.7)	p=0.0008

More patients achieved a 50%, 75%, and 100% reduction in migraine days for the entire 12 weeks (1-12) on ALD403 than on placebo (Figure 2).

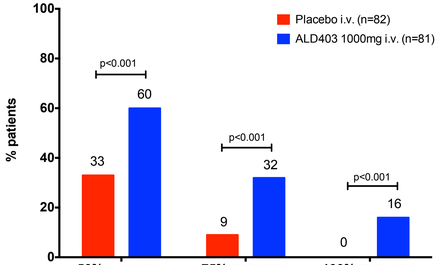


Figure 2

ALD403 patients maintained a high degree of response for the full 24 weeks (1-24) of the study (Figure 3).

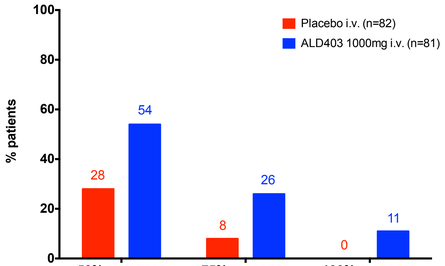


Figure 3

Conclusions

- ALD403 given to subjects with frequent episodic migraine was safe and well tolerated.
- ALD403 appears to be effective in preventing migraine in subjects with frequent episodic migraine.
- There appears to be a substantial subgroup of patients who are responders to CGRP blockade.
- This study supports further phase II studies of ALD403 in the prevention of migraine.