2 SYNOPSIS

NAME OF SPONSOR/COMPANY: Alder BioPharmaceuticals, Inc. NAME OF FINISHED PRODUCT: ALD403 injection NAME OF ACTIVE INGREDIENT(S): ALD403	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY US E ONLY)

Protocol No.: ALD403-CLIN-005

Title of Study: A Parallel Group, Double-Blind, Randomized, Placebo Controlled, Dose-Ranging Phase 2 Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of ALD403 Administered Intravenously in Patients with Chronic Migraine

Investigators: Multicenter

Study Center(s): This multicenter study was conducted at 82 sites in the United States, 4 in Australia, 3 in New Zealand, and 3 in Georgia for a total of 92 sites.

Publication (Reference): None

Study Period: Date First Patient Randomized: 08 Dec 2014 Date Last Patient Completed: 22 Dec 2016	**Phase of development:** 2

Objectives: The primary objective was to evaluate the dose response of a single dose of ALD403 administered intravenously (IV) in patients with chronic migraine.

The secondary objectives were:

- To evaluate the safety of ALD403 administered IV compared with placebo in patients with chronic migraine.
- To evaluate the duration of effect of ALD403 administered IV in patients with chronic migraine.
- To determine the pharmacokinetics (PK) and immunogenicity of ALD403 administered IV in patients with chronic migraine.

Methodology: This was a parallel-group, double-blind, randomized, placebo-controlled, dose-ranging study of a single infusion of ALD403 or placebo in patients with chronic migraine. Six hundred patients were to be randomized into 1 of 4 ALD403 dose levels (10 mg, 30 mg, 100 mg, or 300 mg) or placebo in a 1:1:1:1:1 ratio. Randomization was stratified by baseline migraine days (< 20 days and ≥ 20 days) and medication overuse status (medication overuse versus no medication overuse). Patients were to complete a headache eDiary daily for 28 days from the screening visit until randomization to determine certain eligibility criteria and the baseline migraine results. There were no more than 10 days between randomization and dosing. Dosing occurred on Day 0. After dosing, visits occurred approximately every 4 weeks through 3 months post-dose, and approximately every 12 weeks through 49 weeks post-dose. The total study duration was approximately 54 weeks with visits at screening, Day 0, and Weeks 4, 8, 12, 24, 36, and 49. Additionally, phone calls were made by study site staff to patients at Weeks 2, 16, 20, 28, 32, 40, and 44. Patients were asked to continue to complete the headache eDiary daily until the Week 49 visit.

Number of Subjects (planned and analyzed): Assuming the difference in 75% responder rates was greater than 19%, 120 patients per group were planned to provide at least 90% power for each test individually. The number of patients in each group was approximately 130, with a total of 665 patients randomized, 616 in the safety population, 588 in the modified full analysis population (mFAP), and 493 in the PK population.

	ALD403 300 mg n (%)	**ALD403 100 mg n (%)**	**ALD403 30 mg n (%)**	**ALD403 10 mg n (%)**	**Placebo n (%)**	**Overall n (%)**
Randomized	131	133	134	133	134	665
Safety	121 (92.4)	122 (91.7)	122 (91.0)	130 (97.7)	121 (90.3)	616 (92.6)
mFAP	114 (87.0)	118 (88.7)	117 (87.3)	123 (92.5)	116 (86.6)	588 (88.4)
PK Population	120 (91.6)	122 (91.7)	122 (91.0)	129 (97.0)	NA	493 (74.1)

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Diagnosis and Main Criteria for Inclusion:

1. Willing and able to read and understand the consent process and sign an Informed Consent Form for the clinical study approved by the investigator's local Review Board or a central Institutional Review Board or Independent Ethics Committee.
2. Male or female 18 to 55 years of age inclusive (age determined at time of providing informed consent).
3. Diagnosis of migraine at ≤ 35 years of age with history of chronic migraine ≥ 1 year.
4. During the 28 day screening period, must have had ≥ 15 headache days of which ≥ 8 days were assessed as migraine days with at least 5 migraine attacks as recorded in the eDiary.
5. Women of childbearing potential, and males with partners of child-bearing potential had to agree to use adequate contraception throughout study participation. Adequate contraception included oral, transdermal, or injectable (depot) estrogen, and/or progestogen, selective estrogen receptor modulator therapy, intrauterine contraceptive device, double barrier method (e.g., condom and diaphragm or spermicidal gel) or vasectomy. Non-childbearing potential was defined as post-menopausal for at least 1 year or surgical sterilization or hysterectomy at least 3 months before screening.
6. Any hormonal therapy (eg, contraceptives, hormone replacement therapy) use was stable and ongoing for at least 3 months before screening and during the 28 day period from screening to randomization.
7. Willing, committed, and able to comply with scheduled clinic visits and complete all study-related procedures.
8. Headache eDiary was completed on at least 22 of the 28 days before randomization.
9. Any use of prophylactic medications for headaches (with the exception of botulinum toxin) was stable for at least 3 months before screening.
10. Any use of barbiturates (including Fiorinal®, Fioricet®, or any other combination containing butalbital) or prescription opiates was stable for 3 months before screening and dosing did not exceed 4 days per month through Week 24. Drugs containing nonprescription codeine (16 mg or less) were permitted.
11. Patient agreed not to use any approved devices, neuromodulation, neurostimulation, or injectable therapy (trigger point injections, extracranial nerve blocks, facet joint injections) for headache prophylaxis through Week 24.
12. Patient agreed not to use any botulinum toxin administered to the head, face, or neck through Week 24.
13. Patient agreed not to post any personal medical data related to the study or information related to the study on any website or social media site (eg, Facebook, Twitter) during the study.

Test Product, Dose, Mode of Administration, and Batch No.: The doses of ALD403 (total volume of 100 mL mixture with 0.9% saline) were administered IV over a period of 1 hour (± 15 minutes). Those patients randomized to ALD403 were to receive an IV infusion of 100 mL of 0.9% saline with ALD403. Batch No.: 1-FIN-1820.

Reference Product, Dose, Mode of Administration, and Batch No.: Matching placebo, IV infusion of 100 mL of mixture with 0.9% saline. Batch No.: 1-FIN-1745.

Duration of Treatment: The total study duration was approximately 54 weeks.

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Criteria for Evaluation:

Efficacy: The migraine and headache efficacy endpoints were summarized within 4-week intervals (ie, Weeks 1 to 4, 5 to 8, 9 to 12, and so on until Weeks 45 to 48), 12-week intervals (ie, Weeks 1 to 12, 13 to 24, 25 to 36, and 37 to 48), 24-week intervals (ie, Weeks 1 to 24 and 24 to 48), and 48-week intervals, and were derived separately based upon headaches and migraines. For these endpoints, baseline was the 28 days after the screening visit. Migraines were defined as chronic migraines, as outlined in the International Headache Society, ICHD III beta version, 2013. Over Weeks 1 to 12, the 75% migraine responder rate (ie, patients with an average reduction in migraine days of at least 75% over Weeks 1 to 12, as compared with baseline) was evaluated.

Migraine and headache secondary efficacy endpoints:

- 50% and 100% migraine/headache responder rates
- Change from baseline in the frequency of migraine/headache days
- Percent change from baseline in migraine/headache days
- Time to first migraine after dosing
- Migraine attacks/headache episodes
- Migraine/headache hours
- Migraines/headaches with severe intensity
- Migraines/headaches with acute medication usage

Other secondary efficacy endpoints:

- Short-Form (SF-36) Health Survey Version 2.0
- Headache Impact Test (HIT-6) Version 1.0

Other secondary efficacy endpoints:

- Patient Health Questionnaire-9 (PHQ-9)
- Generalized Anxiety Disorder-7 Scale (GAD-7)
- Allodynia Symptom Checklist-12 (ASC-12)
- Brush (dynamic mechanical) Allodynia
- Migraine Healthcare Utilization Measures

Safety: Safety secondary efficacy endpoints

- Adverse events (AEs) and serious adverse events (SAEs) (including physical examination findings)
- Changes in clinical laboratory assessments (serum chemistry and hematology)
- Vital signs
- Electrocardiograms (ECGs)
- Suicidal ideation and behavior, as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS)

Pharmacokinetic endpoints:

- Concentrations in plasma of free ALD403
- PK parameters including maximum observed plasma concentration (C_{max}), time of maximum observed plasma concentration (T_{max}), area under the plasma concentration-time curve from time 0 to the time t of the last quantifiable concentration ($AUC_{0\text{-}tlast}$), and, when possible, terminal elimination rate constant (λ_z), apparent terminal elimination half-life ($T_{½,z}$), area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0\text{-}inf}$), total plasma clearance (CL), and distribution volume in the terminal elimination phase (V_z), were derived from the free ALD403 concentrations in plasma.

Immunogenicity endpoints:

- Development of anti-ALD403 antibodies (ADAs)
- Characterization of ADAs for neutralizing activity

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Statistical Methods: Study results were presented using summary statistics by treatment group.

Primary

The difference in rates and associated confidence interval (CI) were calculated based upon the z-test for 2 independent proportions without CIs. A p-value for the difference in rates was based upon the Cochran-Mantel-Haenszel (CMH) test was performed for the primary efficacy endpoint and the 50% and 100% responder rates for the interval Weeks 1 to 12. The tests were stratified by the randomization stratification factors.

The 75% responder rate for Weeks 1 to 12 and associated counts were summarized for the following subgroups:

- Calculated baseline migraine days (< 20 days versus ≥ 20 days)
- Investigator judgement of medication overuse status (medication overuse versus no medication overuse)
- Sex
- Age group (≤ 35 years versus > 35 years)
- Age group at diagnosis of migraine (≤ 21 years versus > 21 years)
- Duration of migraine at baseline (≤ 15 years versus > 15 years)

Secondary

For migraine/headache days, the treatment difference and associated CI (without stratification) based on normal approximation were calculated. Testing for the treatment difference for the change and percent change endpoints of the interval Weeks 1 to 12 was performed based upon the extended CMH test. Additionally, the change from baseline in migraine/headache days for the three 4-week intervals from Weeks 1 to 12 was analyzed using repeated measures. The model included treatment group, timepoint (Weeks 1 to 4, Weeks 5 to 8, and Weeks 9 to 12), and randomization stratification factors as fixed factors.

The analysis of the time to the first migraine after dosing endpoint was based upon the Kaplan-Meier method. The 25th percentile, 50th percentile (median), and 75th percentile, and their corresponding 95% CIs were reported for each treatment group.

Safety

Only treatment-emergent adverse events (TEAEs) were included in summary tables. All AEs were included in listings. The incidence of all TEAEs was tabulated by treatment received.

Pharmacokinetic analyses

The concentrations of free ALD403 were listed and summarized by visit with descriptive statistics. Non-compartmental PK analysis was carried out to derive the PK parameters. Hummel power analysis was used to assess dose proportionality using C_{max} and $AUC_{0\text{-}inf}$ (if possible). The basic model for the investigation of dose proportionality was a power model that described the functional relationship between the dose and PK endpoints C_{max} and $AUC_{0\text{-}inf}$.

Based on the estimate for slope parameter (β), a 2-sided 90% CI for the slope was computed. Dose-proportionality was rejected if the 90% CI of the estimated slope fell outside the critical interval.

Data for patients developing an antibody response were listed. The effect of possible antibody responses on PK parameters was evaluated descriptively.

Immunogenicity

The Safety Population analysis set was used for immunogenicity analyses. All the immunogenicity data were listed. For patients with pre-existing antibodies at baseline, the number and percent of patients who were positive for anti-ALD403 antibody were summarized. In addition, the number and percent of patients who developed anti-drug antibodies to ALD403 during the study were summarized at each scheduled visit in the same table. Additional testing of confirmed positive ADA for potential neutralizing activity on ALD403 was summarized if these data were available. The summary tables for frequency of anti-drug antibodies, titer, neutralizing potential, and other characteristics were included. Analysis of specific ADAs was restricted to patients who were treated with anti-ALD403.

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SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

This ALD403-CLIN-005 study enrolled patients with chronic migraine. The treatment arms were generally well balanced with respect to demographics and baseline characteristics. The population had a mean age of 36.6 years and on average experienced migraine for 17.9 years, was predominantly white (88.8%) and female (86%), and recorded an average of 16.5 migraine days by electronic diary over a 28-day screening period.

Several endpoints aimed at demonstrating the efficacy of a single intravenous infusion of ALD403 for migraine prophylaxis in patients with chronic migraine were analyzed. A consistent pattern of efficacy was seen among these endpoints, some of which are summarized in the table below. For the primary efficacy endpoint, the 75% migraine responder rate over Weeks 1 to12, results for all ALD403 dose groups were greater than that for placebo and results for the 300 mg and 100 mg dose groups were significantly greater than placebo when tested at the pre-specified 10% 2-sided significance level. The 50% migraine responder rates over Weeks 1 to12 were significantly greater in the ALD-403 300 mg, 100 mg, and 30 mg dose groups as compared to placebo. The 75% migraine responder rates over Weeks 1 to 4 were greater than placebo in all ALD403 dose groups. The 50% migraine responder rates over Weeks 1 to 4 were also greater than placebo in all ALD403 dose groups but predominantly in the 300 mg, 100 mg, and 30 mg groups. In these 3 groups, results for the 50% migraine responder rates over Weeks 1 to 4 were similar to that observed over Week 1 to 12 and these results were consistently maintained over the Weeks 5 to 8 and Weeks 9 to 12 assessment intervals. The numbers of patients included in the 100% migraine responder rates over Week 1 to 12 were small but results for all ALD403 dose groups were numerically greater than that for placebo. Reductions in migraine days and percent change in migraine days from baseline over Week 1 to 12 were greater than placebo in all ALD403 dose groups. These differences were greatest in the 300 mg dose group, and differences in the 100 mg and 30 mg dose groups were greater than that observed for the 10 mg group. Similar patterns of results were observed for reductions in headache days and percent change in headache days from baseline. Over Week 1 to 12, patients in all ALD403 dose groups on average experienced greater reductions in the percent of migraine headaches with severe intensity than did placebo-treated patients. In addition, the impact of headaches on ability to function normally in daily life at Weeks 4 and 12, as determined by total score of the 6-Question HIT-6, was reduced to a greater extent on average for patients in all ALD403 dose groups as compared to the placebo group. Taken together, the results of this phase 2 study suggest that ALD403 administered by intravenous infusion is efficacious for the prophylaxis of migraine in patients with chronic migraine.

Summary of Key Results (Modified Full Analysis Population)

Endpoint	300 mg	100 mg	30 mg	10 mg	Placebo
75% Migraine responder rate					
Week 1 to 12	33.3%	31.4%	28.2%	26.8%	20.7%
Weeks 1 to4	36.8%	31.4%	27.4%	25.2%	16.4%
50% Migraine responder rate					
Week 1 to 12	57.0%	55.1%	55.6%	43.9%	40.5%
Weeks 1 to4	52.6%	56.8%	61.5%	42.3%	37.9%
Week 1 to 12 change from baseline - mean (SD)					
Migraine days	-8.2 (7.00)	-7.7 (6.87)	-7.9 (6.38)	-6.7 (6.80)	-5.6 (6.56)
Headache days	-9.6 (6.94)	-8.9 (6.79)	-9.2 (6.33)	-7.5 (6.93)	-6.9 (6.37)
% Severe migraines – mean (SD)					
Week 1 to 12	-20.7% (29.47)	-15.9% (27.38)	-17.2% (26.98)	-16.1% (29.80)	-9.7% (27.32)
HIT-6 % patients with severe impact					
Baseline	90.3%	86.4%	82.9%	86.2%	79.3%
Week 4 (Δ baseline)	31.5% (-58.8%)	41.8% (-44.6%)	45.4% (-37.5%)	46.5% (-39.7%)	50.5% (-28.8%)
Week 12 (Δ baseline)	29.9% (-60.4%)	43.0% (-43.4%)	48.0% (-34.9%)	51.4% (-34.8%)	50.9% (-28.4%)

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SAFETY RESULTS:

No dose-response pattern was noted for safety. No significant differences in the frequency or types of AEs reported across the treatment groups were identified. Reported AEs were generally mild to moderate in severity. Overall, 345 (56.0%) patients reported a TEAE, and 101 (16.4%) patients reported a TEAE that was considered related to study drug. There were 11 (1.8%) patients with a severe TEAE, 13 (2.1%) patients with a serious TEAE, and 10 (1.6%) patients with a TEAE that was associated with interruption of the study drug infusion. One patient in the placebo group was reported to have a TEAE associated with discontinuation from the study. No patient in the ALD403 treatment groups discontinued because of an AE. No deaths occurred during this study. The C-SSRS did not identify any patterns to suggest association between the AEs related to C-SSRS responses and ALD403 treatment. Mean ECG values were generally similar across treatment groups at each visit and mean changes over time were generally small and similar across all active and placebo treatment groups. No remarkable laboratory findings were identified. Overall, ALD403 demonstrated an acceptable safety profile.

PHARMACOGENETICS AND IMMUNOGENICITY RESULTS:

The PK profile of free ALD403 at all dose levels demonstrated regular absorption and elimination typical for IV infused monoclonal antibodies. The maximum concentration was observed mainly at the end of infusion.

The elimination half–life for ALD403 was dose-independent and longer than for most therapeutic monoclonal antibodies. The related clearance was slower and consistent with the longer elimination half-life.

The pharmacokinetics of ALD403 after IV infusion for the dose range 10-300 mg was dose-proportional and linear.

A dose-responsive immune response to ALD403 treatment was observed with an overall ADA incidence of 3.1%, 6.6%, 18.9% or 18.2% for subjects receiving 10 mg, 30 mg, 100 mg, or 300 mg ALD403. At the higher dose levels, 100 mg or 300 mg, up to 32% of the ADA positive samples had neutralizing activity with over 50% or 86% (4/7 or 6/7) resolved by the last measurement in the study. The formation of ADA, with or without NAb activity, did not appear to affect the CL of ALD403. Similarly, the exposure to ALD403, C_{max} or AUC_{last}, was not affected by ADA formation. AUC_{last} was slightly lower in ADA/NAb positive subjects receiving 100 mg or 300 mg ALD403.

CONCLUSION:

In conclusion, the ALD403-CLIN-005 phase 2 trial demonstrated that ALD403 in doses of 300 mg, 100 mg, and 30 mg administered by IV infusion had an acceptable benefit-risk profile for the prophylaxis of migraine in patients with chronic migraine. The 10 mg dose generally showed numeric but not statistically significant differentiation from placebo and less efficacy than the other ALD403 doses. Efficacy of ALD403 for migraine prophylaxis was demonstrated over first 4 weeks following a single IV infusion and maintained over the 12 week evaluation period for efficacy. Overall, ALD403 was found to have a high level of effectiveness for migraine prophylaxis with clinically meaningful efficacy across several measures and an acceptable safety profile. The PK profile of free ALD403 at all dose levels demonstrated regular absorption and elimination typical for an IV infused monoclonal antibody. The formation of ADA, with or without NAb activity, was observed in a dose-responsive manner and did not appear to markedly effect the pharmacokinetics for ALD403. Taken together, these results support continued clinical development in phase 3 trials to confirm and further delineate the full extent of the efficacy and safety profiles for ALD403 as a new treatment for the prophylaxis of migraine.

Date of the report: 11 JUL 2017