2. SYNOPSIS

Title of Study: An open-label phase 3 trial to evaluate the safety of ALD403 administered intravenously in patients with chronic migraine.

Investigators: [redacted]

Study Sites: This study was conducted at 20 study sites by 20 investigators in the United States.

Publications (Reference): None

Study Period: 12 Dec 2016 (first subject first visit) to 07 Mar 2019 (last subject last visit). An interim clinical study report summarizing data collected up to and including a data cutoff date of 11 Apr 2018 was written. Data from all subjects through the primary treatment phase (Week 48) and data from most, but not all, subjects participating in the secondary treatment phase through Week 60 were included in the interim clinical study report. This final clinical study report summarizes cumulative key safety, anti-drug antibodies (ADAs), and health outcomes data from all subjects during both treatment phases through Week 104 and summarizes the pharmacokinetic (PK) analysis results from all subjects during the primary treatment phase through Week 48.

Phase of Development: 3

Objectives: The primary study objective was to evaluate the long-term safety of repeat doses of ALD403 administered intravenously (IV) in chronic migraine subjects. The secondary study objectives were: 1) to evaluate the PK and immunogenicity of repeat doses of ALD403 administered IV to subjects with chronic migraine and 2) to further evaluate the impact of ALD403 on various patient-reported outcomes (PROs).

Methodology: This was an open-label study consisting of 2 treatment phases. The primary treatment phase included 4 ALD403 infusions administered 12 weeks apart. The secondary treatment phase included 4 additional ALD403 infusions administered 12 weeks apart. In the primary treatment phase, visits occurred on Day 0 and at Weeks 2, 4, 8, 12, 24, and 36; eligible subjects received 4 IV infusions of ALD403 on Day 0 and at Weeks 12, 24, and 36. Subjects who received all 4 infusions of ALD403 in the primary treatment phase could have entered the secondary treatment phase. In the secondary treatment phase, subjects received up to 4 additional IV infusions of ALD403 for a total of 8 infusions. Visits and ALD403 IV infusions for the secondary treatment phase occurred at Weeks 48, 60, 72, and 84. Subjects were followed for 20 weeks until Week 104, for a total study duration of approximately 106 weeks, including the screening period. Subjects who did not receive all 4 infusions of ALD403 in the primary treatment phase or did not consent to participate in the secondary treatment phase were to be

followed at Week 48 and Week 56, at which point they would have their end of study visit.

Number of Subjects: There were 128 enrolled and treated subjects in this study.

Overall, 119 subjects (93.0%) completed the primary treatment phase (Week 36) and 101 subjects (78.9%) completed the secondary treatment phase (Week 84). In total, 100 subjects (78.1%) completed the study (Week 104).

Diagnosis and Main Criteria for Inclusion: Males and females between 18 and 65 years of age, inclusive, who were diagnosed with migraines at ≤ 50 years of age with a history of chronic migraine for ≥ 12 months before screening.

Test Product, Dose and Mode of Administration, Batch Numbers:

ALD403 injection, 100 mg/mL (each vial to deliver 1 mL), 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 following ALD403 lot numbers were used: 1-FIN-2348, 1-FIN-2597, 1-FIN-2598, 1-FIN-2600, 1-FIN-2601, 1-FIN-2602, 1-FIN-2874, 1-FIN-2875, and 1-FIN-2876.

Subjects received an IV infusion of ALD403 300 mg injection in 100 mL of 0.9% saline over a period of 30 (+15) minutes. Infusions occurred on Day 0, Week 12 (Day 84 ± 3 days); Week 24 (Day 168 ± 3 days); Week 36 (Day 252 ± 3 days); Week 48 (Day 336 -7/+14 days); Week 60 (Day 420 ± 7 days); Week 72 (Day 504 ± 7 days); and Week 84 (Day 588 ± 7 days).

Reference Therapy, Dose and Mode of Administration, Batch Numbers: None

Duration of Treatment: Treatment included up to 8 IV infusions of ALD403, given approximately 12 weeks apart over an 84-week period. Total study duration was approximately 106 weeks. This included a 2-week screening period, a 48-week primary treatment administration period, a 36-week secondary treatment administration period, and a 20-week follow-up period.

Criteria for Evaluation:

Safety endpoints: The safety endpoints were the following:

- Adverse events (AEs) and serious adverse events
- Clinical laboratory assessments
- Vital signs
- Electrocardiograms
- Columbia-Suicide Severity Rating Scale (C-SSRS)

Patient-reported outcomes: The PROs were the following:

- Patient Global Impression of Change
- Short-Form Health Survey
- Health-Related Quality of Life (EQ-5D-5L)
- Headache Impact Test (HIT-6)
- Most Bothersome Symptom
- The Migraine Disability Assessment (MIDAS)

Pharmacokinetic and immunogenicity endpoints:

The PK endpoint and immunogenicity endpoints were the following:

- Free ALD403 plasma concentrations, non-compartmental PK analysis including AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, $t_{½}$, CL, and V_{ss}
- Development of anti-ALD403 antibodies
- Characterization of anti-ALD403 antibodies for neutralizing activity and epitope specificity of the ADA response

Statistical Methods:

The analysis populations included the safety population and the PK population. The safety population included all subjects who received at least 1 dose of study drug. The PK population included all subjects who had at least 1 reportable plasma concentration of ALD403.

Safety Endpoints: Adverse events were collected from the time of informed consent through the final subject visit. The incidences of all AEs and treatment-related AEs were tabulated. The AEs were classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities, Version 20.1. For incidence reporting, if a subject reported more than 1 AE that was coded to the same PT/SOC, the subject was counted only once for that specific PT/SOC. A treatment-emergent AE (TEAE) was an AE with a start date and time on or after the date and time of the initial study drug infusion.

An overview of AEs, which included subject incidence of TEAEs, study drug-related TEAEs, serious TEAEs, TEAEs leading to study drug withdrawal, TEAEs leading to study drug interruption, TEAEs leading to subject discontinuation from the study, and deaths was presented. The subject incidences of TEAEs and study drug-related TEAEs was summarized by SOC and PT. Treatment-emergent AEs were also summarized by severity. For TEAEs presented by severity, the worst severity for each event during the clinical study was presented for each subject. All AEs were presented in a by-subject listing.

All serious adverse events were listed and summarized in a similar manner to TEAEs.

Treatment-emergent adverse events of special interest (AESIs) included the following: immune system events, events associated with C-SSRS, cardiovascular events, nervous system disorders, hepatic events, and events associated with study drug infusion. The treatment-emergent AESIs were summarized and listed in the following categories: SOC and PT; SOC, PT, and maximum severity; SOC, PT, and relationship to study drug; led to infusion interruption by SOC and PT; action taken of study drug discontinuation by SOC and PT; and assessed as serious by SOC and PT.

Pharmacokinetic Endpoints: The PK analysis was to include evaluations of concentration-time profiles for free ALD403 at the following timepoints: predose and immediately postdose (within 15 minutes of end of infusion) on Day 0; Weeks 2, 4, 8, 12 (predose), 24 (predose), 36 (predose), 48 (predose), 72 (predose), and 104 or end of study.

The concentrations of free ALD403 were listed and summarized by timepoint, and descriptive statistics were provided. In this analysis, concentrations below the lower limit of quantification were set to zero. The concentrations of free ALD403 were listed and summarized by timepoint and dose group, and descriptive statistics were provided. All ALD403 PK calculations were performed using actual timepoints calculated relative to the start of the Day 0 IV infusion of ALD403. Assuming there was a sufficient number of measurable ALD403 concentrations, the PK parameters including AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, $t_{½}$, CL, and V_{ss}, were determined.

Immunogenicity Endpoints: Immunogenicity analyses were conducted using the safety population.

Analysis of anti-ALD403 antibodies was restricted to subjects who were treated with ALD403.

The number and percent of subjects with pre-existing antibodies at baseline and subjects who developed ADAs to ALD403 during the study were summarized at the following timepoints: Day 0 (predose); Weeks 2, 4, 8, 12 (predose), 24 (predose), 36 (predose), 48 (predose), 72 (predose), and 104 or end of study. The ADA analysis for subjects who did not consent to participate in the secondary treatment phase included evaluations up to Week 48, then Week 56 or end of study.

In addition, the overall incidence of ADA-positive subjects and the incidence of neutralizing antibody were presented in the same table. Denominators for percentages for each were the total number of results available for the specified visit and the total number of results for the overall incidence. All the immunogenicity data were presented in by-subject listings.

Results:

Patient-Reported Outcomes: Overall, the majority of subjects reported PGIC as "much improved" or "very much improved". The percentages of subjects reporting "very much improved" generally increased after each of the quarterly infusions.

- The percentage of subjects reporting "very much improved" increased from 26/126 subjects (20.6%) at Week 4 to 47/96 subjects (49.0%) at Week 104.
- The percentage of subjects reporting "much improved" decreased from 51/126 subjects (40.5%) at Week 4 to 33/96 subjects (34.4%) at Week 104.
- The percentage of subjects reporting "no change" decreased from 15/126 subjects (11.9%) at Week 4 to 5/96 subjects (5.2%) at Week 104.
- The percentage of subjects reporting "minimally improved" decreased from 31/126 subjects (24.6%) at Week 4 to 11/96 subjects (11.5%) at Week 104.
- The percentage of subjects reporting "minimally worse" decreased from 3/126 subjects (2.4%) at Week 4 to no subjects at Week 104.

The SF-36 generally demonstrated improvements in the mean scores of all 10 parameters at all assessment times from Week 4 to Week 104. At baseline, subjects were most impacted (ie, mean score < 50) in the SF-36 parameters of bodily pain, physical component, role physical, and social functioning. Post-treatment improvements in the mean scores of these 4 most impacted parameters compared to baseline were all nominally significant by Week 24 ($p<0.05$). Results at Week 36 through Week 104 were consistent with these results.

For EQ-5D-5L, modest shifts from baseline within the safety population indicated general improvements in the Usual Activities and Pain/Discomfort domains; however, no consistent patterns of change were observed with the EQ-5D-5L overall.

The mean HIT-6 score decreased from baseline (mean HIT-6 score = 65.2) beginning with the Weeks 1 through 4 assessment (57.1 [±8.15]) and further improved over the Weeks 101 through 104 assessment (56.1 [±9.07]). The reductions from baseline in mean HIT-6 score were generally similar with each measurement through Week 104 and all reductions compared to baseline were nominally significant ($p<0.0001$). Almost all (92.2% [118 subjects]) of the subjects at baseline reported severe life impact based on HIT-6 scores. The percentage of subjects with severe life impact then decreased and remained < 44% throughout the study with 38.5% (37 of 96 subjects) reporting severe life impact over the Weeks 101 through 104 assessment.

Most bothersome symptoms reported by subjects at baseline were nausea, vomiting, sensitivity to light, sensitivity to sound, mental cloudiness, fatigue, pain with activity, mood changes, and other symptoms. Of these, the most commonly reported (> 5% of

subjects) migraine-related symptoms included sensitivity to light (24.2%), nausea (10.9%), sensitivity to sound (7.8%), and pain with activity (7.8%).

- The percentage of subjects reporting "very much improved" increased from 27/126 subjects (21.4%) at Week 4 to 40/112 subjects (35.7%) at Week 48.
- The percentage of subjects reporting "much improved" increased from 47/126 subjects (37.3%) at Week 4 to 44/112 subjects (39.3%) at Week 48.
- The percentage of subjects reporting "no change" decreased from 19/126 subjects (15.1%) at Week 4 to 11/112 subjects (9.8%) at Week 48.
- The percentage of subjects reporting "minimally improved" decreased from 32/126 subjects (25.4%) at Week 4 to 17/112 subjects (15.2%) at Week 48.
- The percentage of subjects reporting "minimally worse" decreased from 1/126 subjects (< 1%) at Week 4 to no subjects at Week 48.

The MIDAS mean total score decreased over time starting at the first assessment at Week 12 (mean score = 20.0 [±40.23] and mean change from baseline of -36.3 [±51.85]). Additional reductions in total MIDAS scores were observed throughout the course of the study and was (-36.7 [±71.51]) at Week 104. Compared to baseline, all reductions in the total MIDAS scores at Weeks 12, 24, 36, 48, 60, 72, 84, and 104 were nominally significant ($p<0.0001$). At baseline, the MIDAS total score indicated that 84.4% of subjects had severe disability compared to 5.5% of subjects that had little to no disability. At Week 104, the percentage of subjects with severe disability reduced to 20.8% while the percentage of subjects with little to no disability increased to 59.4%. These results were generally maintained throughout the course of the study. Overall, the majority of subjects (approximately 60%) reported little or no disability or mild disability over the Week 12 through to Week 104 assessments.

Pharmacokinetics Results: Following a single dose, after reaching peak levels, mean concentration values of free ALD403 declined with a relatively slow elimination phase over an approximate 12-week period. Overall, the mean plasma predose concentrations of free ALD403 appeared to achieve steady state within approximately 12 weeks after dosing. After the single dose administration of ALD403 at 300 mg, mean plasma ALD403 $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$ were 53163 h*µg/mL and 60135 h*µg/mL, respectively. Mean plasma ALD403 C_{max} was 106 µg/mL, mean $t_{½}$ was 674 hours, and median t_{max} was 0.72 hours. Intersubject variability of $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$ and C_{max} ranged from 38.7% to 71.6%.

Safety Results: No deaths were reported in this study. Three subjects (3.9%) had a serious TEAE. Overall, 91 subjects (71.1%) had at least 1 TEAE and 18 subjects (14.1%) had a TEAE that was considered related to study drug. Most TEAEs associated with ALD403 treatment were mild or moderate in severity. There were 13 subjects (10.2%) who had a

severe TEAE. There were 8 subjects (6.3%) with a TEAE that led to study drug withdrawal and 10 subjects (7.8%) with a TEAE leading to study drug interruption.

The most frequently reported TEAEs by PT were nasopharyngitis (18 subjects [14.1%]), upper respiratory tract infection (10 subjects [7.8%]), sinusitis (10 subjects [7.8%]), and influenza (8 subjects [6.3%]).

All TEAEs of hypersensitivity occurred during the time of infusion, were mild or moderate in severity, and either resolved without treatment or were effectively managed with standard medical care at the investigational site. The single TEAE of investigator-reported anaphylactic reaction did not have clinical evidence of respiratory distress or cardiovascular compromise, which are currently required for clinical presentations to be classified as anaphylaxis.

Overall, 10 subjects (7.8%) had a TEAE leading to study drug interruption. The most frequently reported TEAE leading to study drug interruption was infusion site extravasation (6 subjects [4.7%]). All incidences of infusion site extravasation leading to study drug interruption were mild in severity, considered not related to study drug, and resolved on the same day without concomitant treatment.

Overall, 8 subjects (6.3%) had a TEAE leading to study drug withdrawal. The most frequently reported TEAE leading to study drug withdrawal was hypersensitivity (3 subjects [2.3%]).

Overall, 21 subjects (16.4%) had a treatment-emergent AESI. The most frequently reported treatment-emergent AESIs by PT were infusion site extravasation (6 subjects [4.7%]) and hypersensitivity (5 subjects [3.9%] each). The most frequently reported study drug-related treatment-emergent AESI by PT was hypersensitivity (5 subjects [3.9%]). All other study drug-related treatment-emergent AESIs by PT were reported in < 1% of subjects.

Throughout the study, no clinically relevant trends in clinical laboratory, vital sign, or electrocardiograms results were identified. None of the subjects were reported with a QT corrected using Fridericia formula (QTcF) interval > 500 ms or QTcF interval increases from baseline > 60 ms. One subject was reported to have an electrocardiogram with a QTcF interval > 480 ms to 500 ms. This subject's electrocardiograms had QTcF intervals of 469 ms at Screening, 482 ms at Week 12, and 483 ms at Week 36 postdose, which were considered not clinically significant by the investigator

Immunogenicity Results: Anti-drug antibodies developed in 18.0% (23/128) of subjects receiving study drug, with 39.1% (9/23) of these subjects having ADA with neutralizing potential. The number of subjects with positive ADA results increased over time up to Week 24 and decreased thereafter until Week 104. Of the subjects who developed ADA, 5.3% (6/113) remained positive at Week 48, 4.0% (4/101) remained positive at Week 72, and all subjects were ADA negative by Week 104. Characterization of the epitope specificity showed 47.5% (28/59) of the ADA positive responses are directed toward the

complementarity determining regions of ALD403, and 5.1% (3/59) had reactivity directed toward the antibody framework.

Conclusions: ALD403 300 mg administered every 12 weeks by IV infusion for the preventive treatment of migraine in subjects with chronic migraine demonstrated an acceptable safety profile and clinically meaningful reductions in migraine-related life impact and improvements in measures of health-related quality of life for up to 2 years in the ALD403-CLIN-013 study. The results of this open-label clinical study demonstrated that ALD403 is associated with clinically meaningful treatment effects over several PRO measures that are relevant to migraine and its preventive treatment. The establishment of robust and clinically meaningful reductions in migraine-related burden and improvement in measures of quality of life was observed within the first month of treatment and was, on average, sustained or improved over each of the 7 subsequent quarterly infusions that comprised 2 years of treatment. There were no new safety signals identified and the overall safety profile of ALD403 was consistent with that observed in randomized, placebo-controlled studies of ALD403 in migraine subjects and throughout the ALD403 clinical development program overall. A small number of subjects experienced mild to moderate infusion day events that are described in the discussion above.

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