2 Synopsis

Title of Study: 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.

Investigators: [redacted]

Study Sites: This study was conducted at 128 study sites in the US and worldwide.

Publication(s) (Reference): None

Study Period: 30 Nov 2016 (First subject first visit) to 20 Apr 2018 (Last subject last visit)

Phase of Development: 3

Objectives: 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. The secondary study objectives were to: 1) evaluate the safety of repeat doses of ALD403 administered IV compared to placebo in subjects with chronic migraine and 2) evaluate the pharmacokinetics (PK) and immunogenicity of repeat doses of ALD403 administered IV to subjects with chronic migraine.

Methodology: This was a Phase 3, parallel group, double-blind, randomized, placebo controlled study. Eligible subjects were randomly assigned 28 to 30 days after the screening visit into 1 of 2 ALD403 dose levels (100 mg or 300 mg) or placebo in a 1:1:1 ratio. Randomization was stratified by baseline migraine days (<17 days versus ≥17 days during

screening) and prophylactic medication use during the 3 months before screening (prophylactic medication use versus no prophylactic medication use**)**.

The study participation period was approximately 36 weeks, including the screening period. The scheduled visits occurred at screening, randomization (on-site or phone), Day 0, and Weeks 2, 4, 8, 12, 16, 20, 24, and 32. Subjects completed the eDiary daily through Week 24.

The subjects were administered 2 infusions of ALD403 or placebo. Treatment included 2 infusions of ALD403 or placebo administered on Day 0 (within 8 days after randomization) and at the Week 12 (Day 84 ±3 days) visit. Subjects were followed for 20 weeks after the final dose.

Number of Subjects: There were 1072 randomly assigned and treated subjects in this study.

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, and have a history of chronic migraine for ≥12 months before screening. During the 28-day screening period, subjects were to complete the headache eDiary for at least 24 out of 28 days and must have had headaches on ≥ 15 to ≤ 26 days, of which at least 8 must have been migraine days.

Test Product, Dose and Mode of Administration, Batch Numbers: ALD403 Injection, 100 mg/mL (1 mL per 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 following ALD403 lot numbers were used: 1-FIN-2596, 1-FIN-2599, 1-FIN-2600, 1-FIN-2601, and 1-FIN-2602.

Subjects randomly assigned to ALD403 received an IV infusion of ALD403 Injection in 100 mL of 0.9% saline. ALD403 was administered as an IV infusion over a period of 30 (+15) minutes on Day 0 and at the Week 12 (Day 84 ±3 days) visit.

Placebo (lot number 1-FIN-2230) was supplied as a single-use preservative-free solution in 2-mL Type I glass vials formulated with the same excipients as ALD403, without the active ingredient. Subjects randomly assigned to placebo received an IV infusion of placebo in 100 mL of 0.9% saline, administered over a period of 30 (+15) minutes on Day 0 and at the Week 12 (Day 84 ±3 days) visit.

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

Duration of Treatment: Treatment included 2 infusions of ALD403 or placebo administered on Day 0 and at the Week 12 (Day 84 ±3 days) visit. 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.

Criteria for Evaluation:

Primary Endpoint: The primary efficacy endpoint was the change in frequency of migraine days (Weeks 1-12).

Key Secondary Efficacy Endpoints: The key secondary endpoints were as follows:

- 75% migraine responder rate (Weeks 1-4)
- 75% migraine responder rate (Weeks 1-12)
- 50% migraine responder rate (Weeks 1-12)
- Percentage of subjects with a migraine on the day after dosing
- Reduction in migraine prevalence from baseline to Week 4
- Headache Impact Test (HIT-6)[a, b]
- Acute migraine medication usage[a, b]

[a] Applies only to the ALD403 300 mg dose.

[b] The statistical analysis plan (SAP) identified the HIT-6 and Acute Migraine Medication Usage endpoints as key secondary endpoints for the 300 mg dose group only, while the protocol classified these as other secondary endpoints. The SAP called these key secondary endpoints as they were included in the testing algorithm. The SAP was finalized on 08 Nov 2017; unblinding for the 12-week analyses occurred on 05 Jan 2018, and the primary analysis was done on 08 Jun 2018.

Other Secondary Efficacy Endpoints: The other secondary efficacy endpoints were as follows:

- Migraine/headaches with acute medication usage
- Change in frequency of migraine days (Weeks 1-24)
- 100% migraine responder rate (Weeks 1-12)
- Migraine responder rates for time periods other than Weeks 1-12

- Change in frequency of migraine days between baseline and time periods other than Weeks 1-12
- Headache responder rates
- Change in the frequency of headache days
- Percent change in headache or migraine days
- Time to first migraine after dosing
- Migraine/headache hours
- Migraine/headaches with severe intensity
- Patient Global Impression of Change (PGIC)
- Short Form Health Survey (SF-36) v 2.0
- Health-Related Quality of Life (EQ-5D-5L)

Tertiary Efficacy Endpoints: The tertiary efficacy endpoints were as follows:

- Headache episodes/migraine attacks
- Migraine symptom-free days
- Most Bothersome Symptom (MBS)
- Migraine-free days [a]

[a] The SAP included the exploratory endpoint migraine-free days. This endpoint was added as it was believed it may present a clinically meaningful way of viewing the benefit of treatment. The SAP was finalized on 08 Nov 2017; unblinding for the 12-week analyses occurred on 05 Jan 2018, and the primary analysis was done on 08 Jun 2018.

Safety Endpoints: The safety endpoints were:

- Adverse events (AEs) and serious adverse events (SAEs)
- Clinical laboratory assessments

- Vital signs
- Electrocardiogram (ECGs)
- Columbia-Suicide Severity Rating Scale (C-SSRS)

Pharmacokinetic Endpoints:

- Free ALD403 plasma concentrations

Immunogenicity Endpoints: The immunogenicity endpoints were:

- Development of anti-ALD403 antibodies (ADA)
- Characterization of ADA for neutralizing activity and epitope specificity of the ADA response

Statistical Methods: The analysis populations included the full analysis population (FAP), the safety population, and the PK population. The FAP included all randomized subjects who received study drug/placebo and subjects were summarized within the treatment group to which they were randomized. The safety population included all subjects who received study drug/placebo and subjects were summarized within the treatment group for which they actually received treatment, or the highest dose received if multiple doses were administered. The PK population included all subjects who had at least 1 reportable plasma concentration.

Efficacy Endpoints: Multiplicity control was used for the primary and key secondary endpoints. A combination of gate keeping and the Holm's procedure was used to control the study-wide Type I error rate. At a high level, this procedure started with the 300 mg versus placebo comparison for the primary endpoint. If this was significant, testing continued to the first group of key secondary endpoints for 300 mg, at which point Holm's multiplicity procedure was used. Testing then continued to the second group of key secondary endpoints and moved on to the 100 mg group for the primary endpoint and, subsequently, the key secondary endpoints using the same methodology (Holm's within each group).

For all efficacy endpoints, the FAP was used and endpoints were calculated from migraine/headache episodes that were self-reported by subjects in the eDiary. For analysis of migraine/headache days, summary tables for the number of migraine/headache days, change from baseline and the percent change by 4-, 12-, and 24-week intervals and treatment group were summarized in tables. The results from Weeks 1-12 were used for the primary analysis and summary statistics, including confidence intervals (CIs), for the treatment differences were used to summarize the results for the primary endpoint. An analysis of covariance (ANCOVA) model was used to test for a difference between treatment arms. This model included the change from baseline measure as the response variable. Treatment and variables

measuring the stratification factors concepts, baseline migraine days (continuous covariate), and prophylactic medication use (binary covariate: use versus no use) were the independent variables. In addition, model-based estimates including CIs for the treatment differences were used to summarize the results for the primary endpoint.

Key Secondary Efficacy Analyses: Summary statistics including CIs for the treatment differences were used to summarize the results for the key secondary endpoints. Testing of the 75% migraine responder rate (Weeks 1-4), 75% migraine responder rate (Weeks 1-12) and 50% migraine responder rate (Weeks 1-12) endpoints were performed with a Cochran-Mantel-Haenszel (CMH) test controlling for the randomization stratification factors. The percent of subjects with a migraine on the day after dosing was tested with a stratified extended CMH test using the randomization stratification factors. The reduction in migraine prevalence from baseline to Week 4 endpoint was the difference in daily prevalence rates between Week 1 and baseline, Week 2 and baseline, etc. The treatment effect was tested using a repeated-measures approach using the subject level change in migraine rate for Weeks 1, 2, 3 and 4 as the outcome variable. The model specified an unstructured variance/covariance matrix and include the treatment group, week, baseline value of the outcome variable and with treatment group-by-week interaction. The Kenward-Roger approximation was used to estimate the degrees of freedom. The change in HIT-6 total score and acute migraine medication usage between baseline and Weeks 1-12 were tested using an ANCOVA model similar to the one used for the primary endpoint. These models included the HIT-6 change from baseline at the Week 12 visit and the acute migraine medication usage change from baseline as response variables, respectively. Treatment and the stratification factors were the independent variables.

A summary table including CIs for the treatment difference for the 4-, 12-, and 24-week time intervals was produced for the remaining secondary endpoints. The time to first migraine analysis was descriptively summarized based upon Kaplan-Meier methods. Testing of the Weeks 1-24 change from baseline in migraine days was performed using a test identical to the test used for the primary endpoint.

For other efficacy endpoints (SF-36, EQ-5D-5L, PGIC, and MBS), summaries at each scheduled visit by treatment group were produced using descriptive statistics.

Pharmacokinetic Endpoints:

The PK analysis included evaluations of concentration-time profiles for free ALD403 on the following days: predose on Day 0, immediately postdose (within 15 minutes of the end of infusion), and at Weeks 2, 4, 8, 12 (predose), 24, and 32 or ET. 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 Day 0 IV infusion of ALD403. Assuming there was a sufficient number of measurable ALD403 concentrations, the PK parameters including $AUC_{0\text{-last}}$, $AUC_{0\text{-}2016}$, C_{max}, t_{max}, t_{min}, $C_{trough\ 84}$, $C_{trough\ 168}$, R^2, λ_z, λ_{zLower}, and λ_{zUpper}, were determined.

Safety Endpoints: Safety endpoints were summarized with descriptive statistics. All safety summaries and analyses were performed using the safety population. Prior and Concomitant medications were coded by the WHO Drug Dictionary version September 2012. Adverse events and medical history were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.1.

Adverse events were collected from the time of informed consent through the final subject visit. The incidence of all AEs and study drug-related AEs were tabulated by treatment received. These AEs were classified by system organ class (SOC) and preferred term (PT). 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. Events recorded between the time the informed consent form was signed and the first study drug administration were listed. A treatment-emergent AE (TEAE) was an AE with a start date and time on or after the date and time of the first study drug dose.

An overview of AEs, which included subject incidence of TEAEs, study drug-related TEAEs, serious TEAEs, TEAEs leading to study drug interruption, and TEAEs leading to study drug discontinuation, was presented. No deaths were reported during this study. The subject incidence of TEAEs and study drug-related TEAEs were summarized by SOC and PT. Treatment-emergent AEs were also summarized in a table 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 as a listing by subject. This listing included the duration of the AE.

All SAEs 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 AESIs were summarized and listed in the following categories: SOC and PT; SOC, PT, and maximum severity; SOC, PT, and relationship to study drug; action taken of infusion interruption by SOC and PT; action taken of study drug discontinuation by SOC and PT; and assessed as serious by SOC and PT.

Results:

Efficacy Results: In this study, ALD403 300 mg and 100 mg groups both achieved the primary efficacy endpoint and all key secondary endpoints in the prespecified statistical

hierarchy. Both ALD403 doses were associated with a consistent pattern of statistically significant and clinically meaningful efficacy across these endpoints compared with placebo. ALD403 300 mg was generally associated with a numerically greater magnitude of therapeutic effect than ALD403 100 mg. Within the ALD403 treatment groups, migraine reductions were rapidly observed and consistently maintained across both dosing intervals. Reductions in mean monthly headache days and headache responder rates mirrored the reductions in migraine days, suggesting that migraines were being prevented and not simply modified to become non-migraine headaches.

ALD403 300 mg and 100 mg dose groups both demonstrated highly statistically significant reductions from baseline in monthly migraine days (MMD) over Weeks 1-12 compared with placebo. ALD403 300 mg was associated with a mean change from baseline in MMD of -8.2 days and a mean difference of -2.60 days from placebo ($P<0.0001$), and ALD403 100 mg was associated with a mean change from baseline in MMD of -7.7 days and a mean difference of -2.03 days from placebo ($P<0.0001$).

On the first full day after the initial infusion (Day 1), the percentage of subjects with a migraine was 27.8% in the ALD403 300 mg group and 28.6% in the ALD403 100 mg group. Both percentages were statistically significantly lower than the 42.3% observed in the placebo group ($P<0.0001$ for both ALD403 groups). Compared with the average daily percentage of subjects with a migraine during the 28-day baseline period of approximately 58%, both ALD403 doses demonstrated an approximate 50% reduction in the percentage of subjects with a migraine on the day after dosing (Day 1), compared with an approximate 27% reduction in the placebo-treated group. The reduction in migraine prevalence observed on Day 1 was generally maintained each day through Week 1 and, on average, each day over the first 4 weeks after infusion. The average daily prevalence of migraine over Weeks 1-4 was 27.9% and 30.6% in the ALD403 300 mg and 100 mg groups, respectively, compared with 38.9% in the placebo group ($P<0.0001$ for both ALD403 groups). These reductions in daily prevalence of migraine were consistent with the study's primary endpoint over Weeks 1-12, and the 75% and 50% migraine responder rates over Weeks 1-4 and 1-12, respectively. Taken together, these results demonstrate that treatment with ALD403 was associated with establishment of a robust migraine preventive effect as early as the day after infusion, and the magnitude of this therapeutic effect was maintained over the full 12-week dosing interval.

ALD403 300 mg or 100 mg was associated with a 75% or greater reduction in MMD in 36.9% and 30.9% of subjects over Weeks 1-4, respectively, and 33.1% and 26.7% of subjects over Weeks 1-12, respectively. All results were highly statistically significant ($P\leq0.0001$) compared with placebo. For the 50% migraine responder rate, 61.4% of subjects in the ALD403 300 mg group and 57.6% of subjects in the ALD403 100 mg group achieved a 50% or greater reduction in MMD over Weeks 1-12, compared with 39.3% in the placebo group. For both ALD403 dose strength groups, the differences from placebo were highly

statistically significant (P<0.0001). The results were robust in the first month after the initial infusion and were similarly maintained over each month of the first 12-Week dosing interval.

The analysis of reduction in MMD after the second dose of study drug demonstrated persistence of the robust migraine preventive effect associated with ALD403 treatment and differences from placebo that were nominally significant based on the 95% CI. Over the second dosing interval (Weeks 13-24), ALD403 300 mg was associated with a mean change from baseline in MMD of -8.8 days and a mean difference of -2.65 days from placebo (95% CI: -3.62, -1.68) and ALD403 100 mg was associated with a mean change from baseline in MMD of -8.2 days and a mean difference of -1.98 days from placebo (95% CI: -2.94, -1.01). The magnitude of migraine responder rates was either maintained or improved after the second dose and remained nominally significantly greater than placebo.

The efficacy results support the 12-week (ie, quarterly) dosing interval for ALD403 administered by IV infusion. Efficacy for the preventive treatment of migraine was consistently maintained across each 12-week dosing interval in both ALD403 dose groups.

Reductions in migraine days were reflected in reductions of acute migraine medication (ie, triptan or ergotamine) use and were therefore greater in the ALD403 groups compared with observations in the placebo group.

Subjects with medication overuse headache (MOH) not associated with opioid analgesics or barbiturate compounds were eligible for the study. The criteria provided to study investigators to determine presence or absence of MOH at baseline were based on ICHD-3 (beta) criteria; in the randomized study population, 40% of subjects overall met criteria for MOH and numbers of subjects with MOH were well-balanced across the treatment arms. In a subgroup analysis of the primary efficacy endpoint, subjects with MOH who were treated with ALD403 300 mg or 100 mg experienced reductions in MMD that were similar to the group of ALD403-treated subjects with no MOH. The mean differences from placebo in both ALD403 groups regardless of MOH status were nominally statistically significant based on the 95% CI. Differences from placebo were observed to be greater in the MOH subgroups compared with the non-MOH subgroups.

The ALD403 300 mg group was associated with statistically significant improvement from baseline in the total HIT-6 score over Weeks 9-12 compared with placebo (P<0.0001). In the ALD403 300 mg group, the mean change of the HIT-6 score from baseline over Weeks 9-12 was -7.3 and the between-group mean difference compared with placebo was -2.88 (95% CI: -3.91, -1.84; P<0.0001). Overall, the within-group mean change and between-group mean difference (versus placebo) of HIT-6 scores at the Week 12 visit demonstrate a clinically meaningful therapeutic effect of ALD403 treatment. The ALD403 100 mg group was associated with clinically meaningful and nominally significant improvement from baseline in the total HIT-6 score over Weeks 9-12 compared with placebo (P=0.0010). In the ALD403 100 mg group, the mean change of the HIT-6 score from baseline over Weeks 9-12 was -6.2

and the between-group mean difference compared with placebo was -1.73 (95% CI: -2.76, -0.70; P=0.0010).

Similarly, subject-reported outcomes such as the SF-36 and EQ-5D-5L generally demonstrated improvements from baseline over time in the ALD403 groups. Improvements in all 8 scale scores of the SF-36 were observed in both ALD403 treatment groups that were numerically greater than those observed in the placebo group. Similarly, modest shifts from baseline indicated general improvements in the Usual Activities and Pain/Discomfort domains of the EQ-5D-5L that were numerically greater in both ALD403 groups compared with placebo, and generally greater in the ALD403 300 mg group than in the ALD403 100 mg group. In concordance with these results, the percentages of subjects who rated their migraine condition as "very much improved" or "much improved" on the PGIC were consistently greater in the ALD403 300 mg and 100 mg groups than in the placebo group and were of greater magnitude in the 300 mg group.

Taken together, these findings demonstrate the following:

- ALD403 administered every 12 weeks by IV infusion in either the 300 mg or 100 mg dose strength is efficacious for the preventive treatment of migraine in adult subjects with chronic migraine as demonstrated by the statistically significant and clinically meaningful reductions in MMD.

- The 12-week dosing interval of ALD403 in both dose groups was effective in establishing a statistically significant and clinically meaningful reduction in migraine after the first infusion for a full 3 months and maintenance or improvement in the magnitude of the therapeutic effect for the next 3 months after a second infusion.

- ALD403 treatment established a robust and clinically meaningful migraine preventative effect on the day after the first infusion as demonstrated by the percentage of subjects with a migraine on the day after dosing (Day 1). The magnitudes of the Day 1 reductions in migraine day prevalence were on average maintained over the first 4 weeks postdose and were consistent with results of the primary efficacy endpoint over the 3 months after the first infusion.

- In both ALD403 dose strength groups, substantial 50% and 75% migraine responder rates were achieved in the first month and consistently maintained in each month over the 3 months after the first infusion, and the magnitude of these results were either maintained or improved over the next 3 months after a second infusion.

- The reductions in migraine were reflected in a significant reduction in the use of acute migraine medications (ie, triptans and ergotamines) in the ALD403 300 mg group and a nominally significant reduction in the ALD403 100 mg group.

- Subjects with MOH not associated with opioid analgesics or barbiturate compounds were enrolled in the study. Similar reductions in migraine were observed in both subgroups of subjects with and without MOH at baseline.

- A statistically significant and clinically meaningful reduction in HIT-6 score over Weeks 9-12 was observed in the ALD403 300 mg group, and a nominally significant and clinically meaningful reduction in the HIT-6 score was observed in the ALD403 100 mg group.

- Clinically meaningful changes in subject-reported outcomes and assessments of health-related quality of life assessments were observed in the ALD403 300 mg and 100 mg treatment groups.

- As a global assessment of the subject's perceived change in activity limitations, symptoms, emotions, and overall quality of life after the first study drug infusion, the percentages of subjects who rated their condition as "very much improved" or "much improved" on the PGIC were consistently greater in the ALD403 300 mg and 100 mg groups than in the placebo group.

Pharmacokinetic Results: Overall, the PK of free ALD403 was predictable and consistent across doses. Mean total and peak exposure for the ALD403 100 mg to 300 mg dose levels ranged from 19798 to 61821 h*µg/mL, from 19916 to 62302 h*µg/mL, and from 37.7 to 126 µg/mL for $AUC_{0\text{-last}}$, $AUC_{0\text{-}2016}$, and C_{max}, respectively. Median t_{max} ranged from 0.67 to 0.71 hours. Steady state was achieved by Week 12 according to a visual assessment of the predose levels over time.

Safety Results: In this study, subjects were randomized equally to 1 of 3 groups that included 2 dose strengths of ALD403 (either ALD403 300 mg or ALD403 100 mg) or placebo. The majority of subjects (1020 subjects [95.1%]) received a total of 2 doses of ALD403 or placebo during the course of the study.

The percent of subjects with any TEAE was similar across all groups (between 43.5% to 52.0%). Incidence of subjects with severe TEAEs was reported in 3.0% of the placebo group, followed by 2.3% in the ALD403 300 mg group, and 1.1% in ALD403 100 mg group. The incidences of subjects with any serious TEAEs were similar across all groups. Incidences of subjects with a TEAE leading to study drug interruption were reported as 1.7% in the ALD403 300 mg group and < 1% in both the ALD403 100 mg and placebo groups. The incidence of subjects with TEAEs leading to study drug withdrawal was 2.3% in the ALD403 300 mg group and < 1% in both the ALD403 100 mg and placebo groups. No

deaths were reported during the conduct of this study. Overall, 122 subjects (11.4%) had at least 1 study drug-related TEAE. The ALD403 300 mg group had the highest number of subjects with study drug-related TEAEs (53 subjects [15.1%]) and the placebo group had the fewest number of subjects with study drug-related TEAEs (29 subjects [7.9%]).

Severe TEAEs were reported in 2.1% of subjects overall; most TEAEs were mild or moderate in severity. The distribution of mild, moderate, and severe TEAEs was similar across groups.

Within the group of most frequently reported TEAEs (≥2% of subjects), no definitive dose-response was identified.

The most frequently reported TEAEs were nasopharyngitis, upper respiratory tract infection, sinusitis, and migraine. Of these TEAEs, the ALD403 300 mg group had a higher incidence rate of nasopharyngitis (9.4%) as compared with both ALD403 100 mg treatment (5.3%) or placebo (6.0%). Incidence rates of sinusitis and migraine were found to be higher in the placebo group (4.1% and 4.4% respectively) as compared to the ALD403 300 mg group (2.6% and 2.3%, respectively) or ALD403 100 mg group (2.0% and 1.7%, respectively).

Overall, 13 subjects (1.2%) presented with a TEAE leading to study drug withdrawal: 11 subjects (1.6%) in the ALD403 groups and 2 subjects (< 1%) in the placebo group. The ALD403 300 mg group had the highest number of subjects with TEAEs leading to study drug withdrawal (8 subjects [2.3%]). Reported TEAEs leading to study drug withdrawal occurred in < 1% of subjects in both the ALD403 100 mg and placebo groups.

The most frequently reported TEAE leading to study drug withdrawal was hypersensitivity (6 subjects; < 1%). All occurred in the ALD403 300 mg group. Four of these subjects also had a TEAE of hypersensitivity leading to study drug interruption. All events of hypersensitivity were mild to moderate in severity, occurred on the day of infusion, and were considered related to study drug.

Overall, 11 subjects (1.0 %) had a TEAE leading to study drug interruption, 9 subjects (1.3%) in the ALD403 groups and 2 subjects (< 1%) in the placebo group.

Within the predefined PTs of treatment-emergent AESIs, overall incidences were low. In this study, all hypersensitivity events occurred in the ALD403 300 mg group. Among other AESIs, no dose-response patterns were identified. Overall, 30 subjects (2.8%) had a study drug-related treatment-emergent AESI (27 subjects [3.8%] in the ALD403 groups and 3 subjects [< 1%] in the placebo group).

Throughout the study, no clinically concerning trends in clinical laboratory, vital signs, or ECG results were identified, nor was any dose-response trend identified that affected these measurements. There were no QTcF >500 msec values reported and QTcF values between

450 and 500 msec were few, transient, and not clinically significant. Increases in QTcF values of >30 msec were observed in subjects in both ALD403 groups and placebo at various timepoints and no dose-response pattern was observed. Increases in QTcF values of >60 msec were observed in 1 subject each in the ALD403 100 mg group and placebo group at the Week 12 visit postdose and in 1 subject each in the ALD403 300 mg group and the placebo group at the Week 32 visit.

These data demonstrate that:

- ALD403 IV infusion was generally well tolerated and had an acceptable safety profile when administered in repeat doses for migraine preventive treatment in adults with chronic migraine.
- Overall, 508 subjects (47.4%) had at least 1 TEAE, and 122 subjects (11.4%) had at least 1 TEAE that was considered related to study drug.
- Most TEAEs associated with ALD403 treatment were mild or moderate in severity.
- No dose-response patterns were identified across the ALD403 groups for any TEAE (except for the PT hypersensitivity) or serious TEAE.
- In this study, the 6 cases of hypersensitivity treatment-emergent AESIs all occurred in the ALD300 mg group. Among the other AESIs, no dose-response patterns were identified.
- In 4 of the 6 subjects with hypersensitivity TEAEs, 4 subjects (< 1%) had a TEAE of hypersensitivity initially leading to study drug interruption. Study drug was permanently discontinued in all 6 subjects. All incidences of hypersensitivity were mild to moderate in severity, occurred on the day of infusion, were considered related to study drug, and resolved the same day, with the exception of one AE of rash that resolved within 2 days.
- The majority of treatment-emergent AESIs that occurred during the infusion were mild or moderate in severity and were either resolved without treatment or effectively managed with standard medical treatment.
- For subjects receiving ALD403 treatment, the majority of treatment-emergent ADA development was observed 8 weeks post infusion and the incidence peaked to approximately 17.1% in subjects around Week 24 in the study and the incidence decreased thereafter. Approximately 35.2% of these ADA-positive subjects had antibody with neutralizing potential. The ADA titers were low across all groups with no trend of increasing titer related to dose.

Conclusions: ALD403 in a dose strength of either 300 mg or 100 mg administered every 12 weeks by IV infusion for the preventive treatment of migraine in subjects with chronic migraine demonstrated a favorable benefit-risk profile for up to 6 months (2 doses) in the ALD403-CLIN-011 study. The PK of ALD403 was predictable and consistent across doses. The study demonstrated that ALD403 is associated with statistically significant and clinically meaningful treatment effects for migraine prevention over multiple efficacy measures. The establishment of robust and clinically meaningful prevention of migraine was observed as early as the day after dosing and was, on average, sustained over the first 4 weeks and consistently maintained over the initial and subsequent 12-week dosing interval following 2 doses administered every 12 weeks. ALD403 300 mg and 100 mg both demonstrated statistically significant and clinically meaningful efficacy results across the primary and all key secondary efficacy endpoints. There was no clinically meaningful difference in the safety profiles observed across the 2 ALD403 groups except for 6 subjects in the 300 mg group who experienced mild to moderate infusion day events (hypersensitivity) that resulted in withdrawal of study drug treatment. The robust therapeutic effects observed after the initial dose of ALD403 were maintained or improved with a second quarterly infusion. Taken together, the robust reductions in migraine, meaningful reductions in the use of acute migraine medications, consistent efficacy in subjects with non-opiate or barbiturate MOH, reduction in migraine-related life impact, improvements in measures of health-related quality of life, and positive benefit-risk profile demonstrate that ALD403 is associated with a significant and clinically meaningful profile for effectiveness in the preventive treatment of migraine in adults with chronic migraine.

Date of Report: 19 Sep 2018