# Alder BioPharmaceuticals, Inc.

# ALD403-CLIN-011

# 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.

## *8 November 2017*

# Statistical Analysis Plan

# Version *1.0*

| | |
|---|---|
| Indication | Treatment for Prevention of Chronic Migraine |
| Development Stage | Phase III |
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**2017**

**Statistical Analysis Plan Version 1.0**

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| ANCOVA | Analysis of Covariance |
| AUC | Area under the concentration-time curve |
| $AUC0_{-inf}$ | Area under the concentration-time curve from time=0 to infinity |
| $AUC0_{-t}$ | Area under the plasma concentration-time curve |
| CGRP | Calcitonin Gene-Related Peptide |
| CMH | Cochran–Mantel–Haenszel |
| $C_{avg}$ | Average steady-state concentration; computed as AUC(0-Tau)/Tau |
| $C_{max}$ | Peak plasma concentration |
| Cmin | Minimum concentration between 0 and Tau at steady-state |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| ECGs | Electrocardiograms |
| EQ-5D-5L | Health-Related Quality of Life |
| hCG | Human chorionic gonadotropin |
| HIT-6 | Headache Impact Test |
| ICD | International Classification of Diseases |
| ICHD | International Classification of Headache Disorders |
| IHS | International Headache Society |
| IV | Intravenous |
| IWRS | Interactive Web Response System |
| LLOQ | Lower Limit of Quantification |
| MBS | Most Bothersome Symptoms |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PGIC | Patient Global Impression of Change |
| PK | Pharmacokinetic |
| SAE | Serious adverse event |
| SF-36 | Short Form Health Survey |
| Tau | The dosing interval for steady-state data |
| $T_{max}$ | Time to peak plasma concentration |
| TEAE | Treatment-emergent adverse event |
| VAS | Visual Analog Scale |
| WHO | World Health Organization |

# 1. CLINICAL TRIAL DESCRIPTION

Migraine is a highly prevalent paroxysmal neurological disease characterized by recurrent episodes of moderate to severe headache associated with physiological disruptions of neurological, gastrointestinal, and sensory function. Episodes typically last between 4 and 72 hours and recur often without warning over decades of time.

Generally, migraine begins as an episodic disease. Between episodes of migraine the nervous system returns to a normal (premorbid) state of function. However, approximately 2.5% of people with episodic migraine will annually transform from episodic to chronic migraine, meaning they are experiencing migraine on greater than 15 days per month for at least 3 consecutive months.[1] For those with chronic migraine, the headaches are more intense; migraine-associated symptoms, more severe; and the disease-related impact and disability are much greater than observed for episodic migraine. In addition, chronic migraine is associated with more co-morbid diseases such as anxiety, depression, and non-headache pain.[2]

Calcitonin gene-related peptide is a member of the calcitonin family of peptides and is thought to have a multiplicity of actions within the brain, including the facilitation of pain transmission and the induction of the nociceptive state, both of which may contribute to the mechanism of migraine. ALD403 is a humanized anti-(calcitonin gene-related peptide) (CGRP) monoclonal antibody (anti-CGRP) that binds to CGRP and is being developed by Alder BioPharmaceuticals, Inc. for the prophylaxis of migraine.

## 1.1. Objectives

### 1.1.1. Primary Objective

The primary objective is:

- To evaluate the efficacy of repeat doses of ALD403 administered intravenous (IV) compared to placebo in subjects with chronic migraine.

### 1.1.2. Secondary Objectives

The secondary objectives include the following:

- To evaluate the safety of repeat doses of ALD403 administered IV compared to placebo in subjects with chronic migraine.
- To evaluate the pharmacokinetics (PK) and immunogenicity of repeat doses of ALD403 administered IV to subjects with chronic migraine.

## 1.2. Clinical Trial Design

This is a parallel group, double-blind, randomized, placebo-controlled trial of two infusions of ALD403 or placebo in patients with chronic migraine. Subjects who provide informed consent will be evaluated for eligibility based upon the inclusion and exclusion criteria.

Eligible subjects will be randomized 28-30 days after the screening visit and treated (first dose) on Day 0. The Day 0 visit occurs 0-8 days after randomization. Treatment includes two infusions of ALD403 or placebo administered on Days 0 and 84 (Week 12). Subjects will be followed for 20 weeks after the final dose for total study duration of approximately 36 weeks, including the screening period.

Approximately 1050 subjects will be randomized and treated. Efficacy, safety, pharmacokinetic, and immunogenicity assessments will be conducted according to the Schedule of Events presented in Table 1.

## Table 1: Schedule of Events and Assessment

| Assessment | Screen | Rand[1] 28-30 days after Screen | Day 0[2] Tx Within 8 days after RAND | Week 2 Day 14 -3 days | Week 4 Day 28 ± 3 days | Week 8 Day 56 ± 3 days | Week 12 Day 84 ± 3 days Tx | Week 16 Day 112 ± 3 days | Week 20 Day 140 ± 3 days | Week 24 Day 168 +7 days[3] | Week 32 EOS/ET Day 224 ± 7 days |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | | | | | |
| Inclusion/Exclusion Criteria Review | X | X | X | | | | | | | | |
| Demographics | X | | | | | | | | | | |
| Medical History | X | | | | | | | | | | |
| Headache eDiary Data Review and Compliance Check[4] | X | X | X | X | X | X | X | X | X | X | |
| Headache eDiary closeout[5] | | | | | | | | | | X | X |
| Height and Weight[6] | X | | X | | | | X | | | X | X |
| Physical Exam[7] | X | | X | | | | X | | | X | X |
| Patient Global Impression of Change (PGIC) | | | | | X | X | X | X | X | X | X |
| Most Bothersome Symptom (MBS) | X | | X | | X | X | X | X | X | X | X |
| Vital Signs[8] | X | | X | | X | X | X | X | X | X | X |
| C-SSRS[9,10] | X | | X | X | X | X | X | X | X | X | X |
| 12-lead ECG[11] | X | | X | | | | X | | | | X |
| Hematology, Chemistry[12] | X | | X | | | | X | | | | X |
| Serology (HIV, Hepatitis B and C) | X | | | | | | | | | | |
| Urine Drugs Abuse Screen | X | | | | | | | | | | |
| Urine Pregnancy (hCG) Test[10] | X | | X | | | | X | | | | X |
| Plasma ALD403 (PK) [12] | | | X | X | X | X | X | | | X | X |
| Serum Anti-ALD403 Ab[12] | | | X | X | X | X | X | | | X | X |
| SF-36, EQ-5D-5L, and HIT-6 | X | | X | | X | | X | X | | X | X |
| AE Review | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant Medication Review | X | X | X | X | X | X | X | X | X | X | X |
| Randomization | | X | | | | | | | | | |
| ALD403/placebo administration[13] | | | X | | | | X | | | | |

Abbreviations: TX: Treatment, Rand: Randomization, EOS/ET: End of Study/Early Termination
Please refer to next page for footnotes.

[1]Randomization must occur after the subject completes the 28-day eDiary screening period, i.e. 28-30 days after the screening visit, and after confirmation of all eligibility criteria. Every effort should be made to conduct an on-site randomization visit; however a phone visit is acceptable in cases where the subject's schedule will not permit an on-site visit.

[2]Dosing must occur on the day of randomization whenever possible, or within 8 days of randomization.

[3]Week 24 visit must be done on the target day or seven days after. The visit may not be conducted earlier than the target date.

[4]Headache eDiary distributed at the screening visit. eDiary review and compliance check through Week 24.

[5]eDiary closeout must be performed at Week 24, or at the ET visit while the subject is on site.

[6]Height and weight collected at screening visit. Weight only collected on Day 0 (pre-dose) and at Weeks 12 (pre-dose), 24, and 32 or ET.

[7]Physical exam must be done pre-dose on Day 0 and Week 12.

[8]Vital signs measured pre-dose and within 4 hours post-dose on Days 0 and Week 12.

[9]C-SSRS "Baseline/Screening Version" should be used at screening, and C-SSRS "Since Last Visit Version" should be used on Day 0 (pre-randomization), Weeks 2,4, 8, 12 (pre-dose), 16, 20, 24, and 32 or ET.

[10]Inclusion/exclusion criteria review, C-SSRS, and urine pregnancy test must be done prior to dosing on Day 0. C-SSRS and urine pregnancy test must be done prior to dosing at Week 12.

[11]Conduct ECG pre-dose, and within 2 hours post dose on Day 0 and Week 12.

[12]Blood draws obtained pre-dose on dosing days (within 1 hour before dosing). On Day 0, draw additional PK immediately post dose (within 15 minutes of end of infusion). Subjects who test positive for anti-ALD403 antibodies at the last study visit will be asked to provide up to 2 additional blood samples for immunogenicity testing at 3 month intervals for up to 6 months.

[13]Subjects must be monitored for at least 2 hours after the dosing completion to assess for the occurrence of adverse events. Subjects will be requested to stay longer than 2 hours after dosing should the investigator determine this is clinically warranted (e.g., subjects should be observed until all AEs are resolved or clinically stable).

## 1.3. Method of Assigning Subjects to Treatment Groups

Randomization will occur 28-30 days after the screening visit once eligibility assessments are approved by the Medical Monitor and eligibility, including eDiary criteria, are reconfirmed by the investigator. Every effort should be made to conduct an on-site randomization visit, however a phone visit is acceptable in cases where the subject's schedule will not permit an on-site visit. Sites will complete randomization in IWRS, and the randomization assignment will be obtained by the clinical trial site's unblinded pharmacist or designee. Subjects will be randomized in equal ratios to one of the treatment groups. Stratified permuted block randomization will be used. Stratification will be by migraine days during the screening period (<17 days vs. ≥17 days) and prophylactic medication use during the 3 months prior to screening (prophylactic medication use vs. no prophylactic medication use).

Prophylactic medication use for migraine will be determined at screening based upon the subjects' medical history. Stratification for prophylactic medication use will be defined as any migraine preventive therapies, as defined in the protocol, that have been taken as a stable regimen for 3 months prior to screening. Use of other medications taken for migraine prophylaxis will not be considered when determining stratification by prophylactic medication use.

Randomized subjects who terminate their clinical trial participation for any reason, regardless of whether Investigational Product was taken or not, will retain their randomization assignment and subject number.

## 1.4. Blinding

This clinical trial is double-blind, meaning the subjects and site personnel are blinded to treatment assignment, except for the clinical trial site's unblinded pharmacist or Investigational Product consignee. Immediately prior to PK/immunogenicity sample analysis, the bioanalytical laboratory will be unblinded in order to obtain the treatment assignments. Selected sponsor personnel in the Safety and Regulatory groups may be unblinded to individual subject's treatment assignments as required for safety reporting. More details can be found in the blinding plan.

The primary analysis is planned when the last subject randomized and treated has completed the Week 12 visit. The study will remain blinded until the last subject has completed the Week 12 visit at which time limited sponsor representatives will be unblinded. Sites will not be unblinded to treatment assignments for individual subjects.

## 1.5. Sample Size

The planned sample size for this study is 1050 randomized and treated subjects. These subjects will be allocated into 3 treatment groups in a 1:1:1 ratio. Pair-wise testing of each ALD403 group vs. placebo will be performed. Three hundred and fifty subjects per group provides at least 90% power for the primary endpoint for each comparison assuming a treatment effect of at least 1 day and a common standard deviation of 4 days or less. For the key secondary 75% responder rate endpoints 90% power is achieved for the pair-wise comparisons, assuming a placebo responder rate of 20%, and an ALD403 rate of 31%. These sample size calculations have been performed using Pass 2008 and are based upon a t-test and chi-squared test that should approximate the ANCOVA and CMH tests.[3]

# 2. STATISTICAL METHODS

## 2.1. Populations Analyzed

The analysis populations are defined as the following:

- Full Analysis Population (FAP) – Randomized subjects who received Investigational Product/placebo. Subjects will be summarized within the treatment group to which they were randomized. This population will be used for all efficacy analyses.
- Safety Population – Includes all subjects who received Investigational Product/placebo. Subjects will be summarized within the treatment group for which they actually received treatment. If a subject is treated with two different doses they will be summarized in treatment arm of the highest dose received. This population will be used for the safety analyses.
- PK Population - All subjects who have at least one reportable plasma concentration. The PK population will be used for PK analyses.

## 2.2. Clinical Trial Endpoints

The efficacy, safety, pharmacokinetic and immunogenicity of ALD403 will be assessed using the following endpoints. Greater detail concerning these endpoints can be found in Section 2.2.2.

**Primary Efficacy Endpoint**

- Change in frequency of migraine days (Weeks 1-12)

**Key Secondary Efficacy Endpoints**

- 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)
- Acute Migraine Medication Usage

**Other Secondary Efficacy Endpoints**

- Headaches/migraines 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
- Headache/migraine hours
- Headache/migraines 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 Endpoints**

- Headache episodes/migraine attacks
- Migraine symptom-free days
- Most Bothersome Symptom (MBS)
- Migraine Free Days

**Safety Endpoints**

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

**Pharmacokinetic Endpoints**

- Free ALD403 plasma concentrations

**Immunogenicity Endpoints**

- Development of specific anti-ALD403 antibodies
- Characterization of specific anti-ALD403 antibodies for neutralizing activity

### 2.2.1. eDiary

Subjects will complete a daily headache eDiary from the time of screening to Week 24. The diary includes two separate functionalities. The evening report is completed each trial day whether or not the subject had a headache. Among other items this evening report is where

subjects record if they took acute migraine medication on that day. In addition to the evening report the eDiary captures headaches as individual events with a start and end time. It is these headache reports which are used to derive the migraine and headache endpoints. Subjects are allowed to tell the eDiary about headaches that started today and yesterday and are unable to record headaches that started before yesterday. Headaches must be entered in order and at the completion of the headache the subject answers questions about the headache that allow the headache to be classified as a migraine or non-migraine headache as outlined in Section 2.2.2. The eDiary data from the 28 days following screening visit will be used to determine eligibility criteria, and the baseline migraine and headache results.

### 2.2.2. Migraine and Headache Endpoints

In the statistical analysis plan the term headache will encompass both headaches and migraine headaches. Migraine headaches (migraines) are a subgroup of the headaches with the characteristics outlined below. In this way all migraines are headaches but not all headaches are migraines. Migraine and headache data will be collected through Week 24. Headaches (i.e. headache episodes) will be self-reported by the subject. An episode is a single headache event which lasts at least 30 minutes, as defined by the subject reported start and end time. Start and end times are recorded in 15 minute intervals (e.g. 4:00, 4:15, 4:30, …). The migraine and headache endpoints will be summarized in four week, twelve week and the twenty-four week intervals. Specifically, migraine and headache endpoints will be summarized for the four week intervals: Weeks 1-4, 5-8, 9-12, 13-16, 17-20, 21-24, the twelve week intervals 1-12, 13-24, and Weeks 1-24 as outlined in Section 2.3 . The results from Weeks 1 to 12 will be used for the primary analysis.

#### Migraine Day

A migraine day is defined as any day with a headache that meets the chronic migraine definition as outlined in the International Headache Society (IHS) International Classification of Headache Disorders (ICHD, 3rd edition, beta version 2013), Section 1.3 with diagnostic criteria C limited to items 1 and 3.[1] Criteria C defines what characteristics must be present for a headache to be considered a migraine. These characteristics define a migraine as a self-reported headache that:

1. Lasted
    a. 4 hours or more **or**
    b. 30 minutes to 4 hours, and believed by the subject to be a migraine that was relieved by medication
2. Had at least 2 of the following:
    a. Unilateral location
    b. Pulsating quality
    c. Moderate or severe pain intensity
    d. Aggravation by or causing avoidance of routine physical activity
3. Had at least 1 of the following
    a. Nausea and/or vomiting
    b. Photophobia and phonophobia

These characteristics will be summarized for each 4-week interval.

### Frequency, Change and Percent Change of Migraine Days / Headache Days

The frequency of migraine days is the number of migraine days within four week intervals and the average four week frequency in twelve and twenty-four week intervals. Change from baseline is the difference in frequency between baseline and the counts within these four week intervals. The 12 and 24 week change is the difference in the frequency between baseline and the average of the 4 week intervals. The percent change is 100 times the ratio of the change and the baseline frequency. Similar measures will be produced based upon headache frequency.

### Migraine/ Headache Responder Rate

Three responder rates will be utilized: 50%, 75% and 100%. A responder is a subject who achieves a ≥50% reduction, ≥75% reduction, or 100% reduction in migraine days, respectively. These reductions will be evaluated by comparing the baseline frequency of migraine days to the migraine frequency in four week intervals. The same analysis will be conducted for headache days.

Results from the four week intervals will be averaged to produce 12 and 24 week responder endpoints. The Weeks 1-4, 5-8, and 9-12 change from baseline measures are averaged, and the average values are compared to baseline. A 75% migraine responder will be a subject who achieves the specified percent reduction in migraine days within these intervals based upon the average change from baseline measures. Specifically, the 75% 12 weeks responder status is defined as,

$$75\%\ Responder\ Status = \begin{cases} 1\ if\ \dfrac{ave(\Delta_{Month\ 1}, \Delta_{Month\ 2}, \Delta_{Month\ 3})}{Baseline} \leq -0.75 \\ 0\ if\ \dfrac{ave(\Delta_{Month\ 1}, \Delta_{Month\ 2}, \Delta_{Month\ 3})}{Baseline} > -0.75 \end{cases}$$

A 50% migraine responder will be similarly defined.

The 100% migraine responder rate over Weeks 1-12, 13-24, and 1-24 are calculated by averaging the subjects 100% responder status (i.e. 1 if responder and 0 if not). So a subject who is a 100% responder for month 1 but not 2 and 3 will have a 100% responder rate of 33% (1+0+0/3).

### Percentage of Subjects with a Migraine on the Day after Dosing

The percent of subjects with a migraine on the day after dosing will be summarized. For subjects who do not complete the diary on this day the missing data rule outlined in Section 2.7.2 will be used.

### Reduction in Migraine Prevalence from Baseline to Week 4

The average percent of subjects with a migraine on any given day during baseline and the equivalent rate over Weeks 1, 2, 3 and 4 will be evaluated for the treatment arms. These treatment arm rates will be based upon subject rates. The baseline daily rate for a subject will be calculated as the number of migraine days within baseline for that subject divided by 28. The

treatment (e.g. 300 mg) average baseline prevalence is calculated as the average of the subject level rates for baseline. The weekly (i.e. Weeks 1, 2, 3 and 4) subject level rates will be the number of migraine days within the week divided by 7. The difference in rates between these weeks and baseline will be subject level reduction in migraine prevalence which will be averaged to produce treatment level reduction in daily migraine prevalence. The missing data rules outlined in Section 2.7.2 will be used for these calculations.

**Time to First Migraine**

Time to the first migraine after dosing will be analyzed based upon the migraine data entered into the eDiary.

**Migraine Attack / Headache Episode**

A migraine attack is defined as 1 continuously recorded migraine. One attack may result in multiple migraine days. Headache episodes are similarly defined.

**Migraine Hours / Headache Hours**

Migraine hours are the sum of the duration of migraines within four week intervals, and the average four week duration within 12 and 24 week intervals. Headache hours are similarly defined but include all headaches. Subjects with no migraines/headaches will have duration of zero.

**Migraine /Headache Severity**

Headache severity will be collected on a 3 point scale: mild pain, moderate pain, severe pain. The percent of migraines and headaches with severe pain will be summarized. Subjects with no migraines/headaches will be included with a rate of zero.

**Acute Medication Usage**

The percent of migraines and headaches with acute medication usage as recorded in the eDiary will be summarized. Subjects with no migraines/headaches will be included with a rate of zero.

**Acute Migraine Medication Usage**

The number of days that subjects used acute migraine medication (i.e. triptan or ergotamine) will be summarized in 4, 12, and 24 week intervals. The 12 and 24 week results will be the average of the individual 4 week results that make up those wider intervals (e.g. the secondary endpoint of Weeks 1-12 will be the average of the Weeks 1-4, 5-8, and 9-12 results). The change from baseline for these measures will be the difference between the post baseline interval and baseline.

**Migraine Free Days**

The number of days between migraines are classified as migraine free days. Multiple migraine free intervals will exist for each subject. The Migraine Free Days endpoint will measure the length of these intervals. For these calculations all days between recorded migraines will be considered migraine free.

### Patient Global Impression of Change (PGIC)

The PGIC includes a single question concerning the subject's impression of the change in their disease status since the start of the study. Seven responses are possible: Very Much Improved, Much Improved, Minimally Improved, No Change, Minimally Worse, Much Worse, Very Much Worse.

### SF-36 Health Survey (SF-36 v2.0)

The SF-36 v2.0 is a health survey containing 36 questions consisting of eight scaled scores to measure quality of life over the past 4 weeks. The eight sections measured are vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. These domains are combined into the mental component sore and the physical component score. Scoring software utilizing the 2016 norm-based scoring algorithm will be used to calculate the scaled score for each of the eight sections.

### EQ-5D-5L

The EQ-5D-5L is a descriptive system of health-related quality of life states consisting of five dimensions/questions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of five responses. The responses record five levels of severity (no problems/slight problems/moderate problems/severe problems/extreme problems) within a particular EQ-5D dimension. The EQ-5D-5L additionally includes a VAS scale. Each item will be summarized separately.

### Headache Impact Test (HIT-6 v1.0)

The Headache Impact Test (HIT) is a tool used to measure the impact and effect on the ability to function normal in daily life when a headache occurs. The HIT is a 6 question, Likert-type, self-reporting questionnaire with responses ranging from "Never" to "Always" with the following response scores: Never=6, Rarely=8, Sometimes=10, Very Often=11, Always=13. The total score for the HIT is the sum of each response score and will be treated as missing if the response is missing for one or more questions. The HIT total score ranges from 36 to 78, with score ranges having the following life impact:

| Score Range | Life Impact |
|---|---|
| >= 60 | Severe |
| 56-59 | Substantial |
| 50-55 | Some |
| <= 49 | Little to None |

### Migraine symptom-free days

The number of days the subject is free of migraine symptoms (e.g. pulsating, moderate or severe pain, nausea) will be summarized for each 4-week period.

**Most Bothersome Symptom (MBS)**

At screening subjects will identify migraine related symptom that is most bothersome for them. Subjects will be asked to rate the improvement in this symptom from screening on a seven-point scale identical to the scale used for the PGIC.

### 2.2.3. Pharmacokinetics

The concentrations of ALD403 will be measured in plasma from all ALD403-treated subjects using a validated assay. The PK analysis will include evaluations of concentration-time profiles for free ALD403 at the following times: pre-dose on Day 0, immediately post-dose (within 15 minutes of end of infusion) and Weeks 2, 4, 8, 12 (pre-dose), 24, and 32 or ET.

For subjects receiving placebo, selected plasma samples may be analysed for the potential presence of ALD403 using a validated assay.

If a subject terminates early from the clinical trial, all efforts will be made to collect blood samples to analyse for free ALD403 unless consent has been withdrawn.

### 2.2.4. Immunogenicity

Serum blood samples will be taken pre-dose on Day 0, and Weeks 2, 4, 8, 12 (pre-dose), 24, and 32 or ET to test for the development of antibodies to ALD403. The immunogenicity will be assessed in serum from all ALD403-treated subjects using a validated assay. Immunogenicity will not be assessed in placebo subjects.

For any samples that are positive for anti-ALD403 antibody, there may be additional testing to characterize the anti-ALD403 antibody for the potential to neutralize (NAb) ALD403 activity. Subjects who test positive for specific anti-ALD403 antibodies at the time of the last study visit will be asked to provide up to 2 additional blood samples for immunogenicity testing at 3 month intervals for up to 6 months. See the blinding plan for details concerning blinding and the capture of these samples.

## 2.3. Multiple Comparisons/Multiplicity

Multiplicity control will be used for the primary and key secondary endpoints. A combination of gate keeping and the Holm's procedure will be used to control the study wide Type-I error rate. At a high level this procedure will start with the 300 mg vs placebo comparison for the primary endpoint. If this is significant, testing will continue to the first group of key secondary endpoints for 300 mg where Holm's[6] multiplicity procedure will be used. Testing will then continue to the second group of key secondary endpoints and then move 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). Greater detail concerning this testing algorithm is provided below.

Confirmatory efficacy analysis will include testing, within the FAP, of eight endpoints (see below) across the two treatment arms:

- Change in frequency of migraine days (Weeks 1-12)
- 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)
- Acute Migraine Medication Usage (Weeks 1-12)

A hybrid approach will be utilized to control for the experiment wise type-I error rate. The hybrid testing approach will be utilized a fixed sequence of tests and Holm's procedure as follows:

Compute p-value for Change in frequency of migraine days (Weeks 1-12) for the 300 mg dose group. If p-value < 0.05, declare statistical significance and go to step 2 below. Otherwise stop.

Compute p-values key secondary endpoints #1 and follow Holm's testing procedure, see Table 2 for the P-value comparisons. If all endpoints are statistically significant, then go to step 3 below. Otherwise stop.

Compute p-values key secondary endpoints #2 and follow Holm's testing procedure, see Table 2 for the P-value comparisons. If all endpoints are statistically significant, then go to step 4 below. Otherwise stop.

Compute p-value for Change in frequency of migraine days (Weeks 1-12) for the 100 mg dose group. If p-value < 0.05, declare statistical significance and go to step 5 below. Otherwise stop.

Compute p-values key secondary endpoints #3 and follow Holm's testing procedure, see Table 2 for the P-value comparisons. If all endpoints are statistically significant, then go to step 6 below. Otherwise stop.

Compute p-values key secondary endpoints #4 and follow Holm's testing procedure, see Table 2 for the P-value comparisons. If all endpoints are statistically significant, then go to step 7 below. Otherwise stop.

Compute p-values key secondary endpoints #5 and follow Holm's testing procedure, see Table 2 for the P-value comparisons. If all endpoints are met statistically, then declare statistical significance. Otherwise stop.

All other efficacy analyses and associated p-values will be deemed exploratory and no adjustment for multiplicity will be used.

**Table 2: Key Efficacy Analyses and Multiplicity Adjustment**

| Testing Sequence | Endpoint | Population | Declare Significant |
|---|---|---|---|
| Key Secondary #1 | 300 mg Wk1-4 75% responder rate | FAP | $p_{(1)} < 0.0167$<br>$p_{(2)} < 0.025$<br>$p_{(3)} < 0.05$ |
| | 300 mg Wk1-12 75% responder rate | FAP | |
| | 300 mg % subjects with migraine on the day after dosing | FAP | |
| Key Secondary #2 | 300 mg migraine prevalence Day 1-28 Post dose | FAP | $p_{(1)} < 0.025$<br>$p_{(2)} < 0.05$ |
| | 300 mg wk 1-12 50% responder rate | FAP | |
| Key Secondary #3 | 100 mg Wk1-4 75% responder rate | FAP | $p_{(1)} < 0.0167$<br>$p_{(2)} < 0.025$<br>$p_{(3)} < 0.05$ |
| | 100 mg Wk1-12 50% responder rate | FAP | |
| | 100 mg % subjects with migraine on the day after dosing | FAP | |
| Key Secondary #4 | 100 mg migraine prevalence Day 1-28 Post dose | FAP | $p_{(1)} < 0.025$<br>$p_{(2)} < 0.05$ |
| | 100 mg wk 1-12 75% responder rate | FAP | |
| Key Secondary #5 | 300 mg Acute medication usage | FAP | $p_{(1)} < 0.025$<br>$p_{(2)} < 0.05$ |
| | 300 mg Change from baseline in HIT-6 | FAP | |

## 2.4. Trial Day

Trial endpoints will be reported within analysis windows or analysis intervals based upon the actual date of the assessment. Assignment of results to these time points is based upon the trial day. Trial day is defined as:

Trial day = date of assessment - date of treatment

Analysis Windows used to report non-diary endpoints are outlined in Table 3.

**Table 3: Analysis Windows**

| Visit | Range | Target Day | If more than one which one is used for analyses |
|---|---|---|---|
| Screening | < Day 0 | | First value |
| Day 0 | Day 0 to Day 9 | Day 0 | Closest to Target Day |
| Week 2 | Day 10 to Day 21 | Day 14 | Closest to Target Day |
| Week 4 | Day 22 to Day 42 | Day 28 | Closest to Target Day |
| Week 8 | Day 43 to Day 70 | Day 56 | Closest to Target Day |
| Week 12 | Day 71 to Day 98 | Day 84 | Closest to Target Day |
| Week 16 | Day 99 to Day 126 | Day 112 | Closest to Target Day |
| Week 20 | Day 127 to Day 154 | Day 140 | Closest to Target Day |
| Week 24 | Day 155 to Day 203 | Day 168 | Closest to Target Day |
| Week 32 | > Day 204 | Day 224 | Closest to Target Day |

Note: If two observations exist with same distance to target day, use first observation.

For the eDiary data used to produce the migraine and headache endpoints the intervals specified in Table 4 will be used to collapse the daily data into 4, 12, and 24 week intervals. For these data baseline is defined as the 28 days starting on the day of the first diary entry.

**Table 4: eDiary Headache/Migraine Endpoint Analysis Intervals**

| Diary Weeks | Trial Time | Comments | Endpoints |
|---|---|---|---|
| Baseline | The 28 days starting from the first eDiary entry | | All eDiary related endpoints |
| 1-4 | Days: 0-27 | Day 0 = First day of treatment | All eDiary related endpoints |
| 5-8 | Days: 28-55 | | All eDiary related endpoints |
| 9-12 | Days: 56-83 | | All eDiary related endpoints |
| 1-12 | Weeks 1-4, 5-8, and 9-12 | Average of the 4 week intervals after imputation methods are applied | All Primary and Secondary eDiary related endpoints |
| 13-16 | Days: 84-111 | | All eDiary related endpoints |
| 17-20 | Days: 112-139 | | All eDiary related endpoints |
| 21-24 | Days: 140-167 | | All eDiary related endpoints |
| 13-24 | Weeks 13-16, 17-20 and 21-24 | Average of the 4 week intervals after imputation methods are applied | All Primary and Secondary eDiary related endpoints |
| 1-24 | Weeks 1-4, 5-8, 9-12, 13-16, 17-20 and 21-24 | Average of the 4 week intervals after imputation methods are applied | All Primary and Secondary eDiary related endpoints |

## 2.5. Statistical Assessment of the Trial Objectives

### 2.5.1. Primary Endpoint

Hypothesis testing will be performed for the primary endpoint: change in frequency of migraine days (Weeks 1-12). This endpoint will be calculated as outlined in Section 2.2.2 and will utilize the missing data rules provided in Section 2.7.2. Summary statistics including confidence intervals for the treatment differences will be used to summarize the results for the primary endpoint. Testing will also be employed. The hypotheses tested are

$$H_o: \Delta_{plb} = \Delta_{403} \qquad H_a: \Delta_{plb} \neq \Delta_{403}$$

where $\Delta_{403}$ is the change in migraine days for subjects in the ALD403 treatment arm and $\Delta_{plb}$ is similarly defined for the placebo subjects. The change from baseline is expected to be negative as migraines are being reduced. While the test outlined above is two sided, as is the alpha level used for this study (i.e. 5%), clinically relevant results require a larger reduction of migraines on the ALD403 arms.

An ANCOVA model will be used to test for a difference between treatment arms. This model will include 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 vs. no use) will be the independent variables.

### 2.5.2. Key Secondary Efficacy Analyses

Summary statistics including confidence intervals for the treatment differences will be used to summarize the results for the key secondary endpoints. Testing, as outlined below, will be used for the key secondary endpoints.

#### Responder Rates

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 will be performed with a CMH test controlling for the randomization stratification factors baseline migraine days (<17 days, ≥17 days) and prophylactic medication use (use vs. no use). Cumulative distribution of the responder rate will be plotted.

#### Percentage of Subjects with a Migraine on the Day after Dosing

The percent of subjects with a migraine on the day after dosing key secondary endpoint will be tested with a stratified extended CMH test.[4] Randomization stratification factors baseline migraine days (<17 days, ≥17 days) and prophylactic medication use (use vs. no use) will be used for this test. An extended CMH test is used here as subjects with missing data will have a value imputed between 0 and 1 as outlined in Section 2.7.2.

#### Reduction in Migraine Prevalence from Baseline to Week 4

The reduction in migraine prevalence from baseline to Week 4 endpoint will be the difference in daily prevalence rates between Week 1 and baseline, Week 2 and baseline, etc. The treatment effect will be tested using a repeated-measures approach (Mallinckrodt and Lipkovich, 2016),[5]

using the subject level change in migraine rate (see Section 2.2.2) for Weeks 1, 2, 3 and 4 as the outcome variable. The model will specify 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 will be used to estimate the degrees of freedom.

**Headache Impact Test (HIT-6)**

The change in HIT-6 total score will be tested using an ANCOVA model similar to the one used for the primary endpoint. This model will include the HIT-6 change from baseline at Week 12 as the response variable. Treatment and the stratification factors will be the independent variables.

**Acute Migraine Medication Usage**

The change in acute migraine medication usage between baseline and Weeks 1-12 will be tested using an ANCOVA model similar to the one used for the primary endpoint. This model will include the acute migraine medication usage change from baseline as the response variable. Treatment and the stratification factors will be the independent variables.

### 2.5.3. Secondary Efficacy Analyses

Summary statistics will be used to summarize the results for the secondary endpoints. The time to first migraine analysis will be descriptively summarized based upon Kaplan-Meier methods, see Section 3.4.2.3. Testing of the Weeks 1-24 change from baseline in migraine days will be performed using a test identical to the test used for the primary endpoint.

### 2.5.4. Tertiary Efficacy Analyses

Tertiary endpoints will be summarized with descriptive statistics by treatment group. For the Migraine Free Days endpoint the summary measures will be the longest migraine free interval that started within the first two weeks following treatment.

## 2.6. Safety Analyses

Safety endpoints will be summarized with descriptive statistics. All safety summaries and analyses will be performed using the safety population.

Prior and Concomitant medications will be coded by the World Health Organization (WHO) Drug Dictionary version September 2012.

Adverse Events and Medical History will be coded using MedDRA version 20.1.

## 2.7. Additional Statistical Analyses

### 2.7.1. Adjustments for Covariates and Examination of Subgroup Analyses

Summaries with descriptive statistics and frequency counts on the primary endpoint for both dose groups will be provided for the subgroups indicated below. Forest plots will also be created for subgroup analyses and will display treatment differences. The subgroups will be

- Calculated baseline migraine days (<17 days vs. ≥17 days)
- Prophylactic mediation use vs. no prophylactic medication use (based upon a medical review of medications)
- Sex
- Race (groups with minimal subjects will be combined)
- Age Group (≤35 yrs, >35 yrs)
- Age Group at Diagnosis of Migraine (≤21 yrs, >21 yrs)
- Duration of Migraine at Baseline (≤15 yrs, >15 yrs)
- Baseline Medication Overuse (MOH, no MOH)
- Baseline Triptan use (≥33% of days, <33% of days)

### 2.7.2. Handling of Dropouts or Missing Data

Summary statistics will be reported based upon observed data except for the imputation outlined below. Additionally, if the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the infusion of trial medication, except if an incomplete date (e.g., month and year) clearly indicates that the event started prior to treatment.

Subjects who do not complete the eDiary daily will have missing data. It is expected that most missing diary data will be sporadic.

**Missing Headache End Date and Time**

If the end date and time for a headache recorded in the eDiary is missing the headache end date will be set to the earlier of 23:59 on the day before the next reported headache or 23:59 on the last entry reported into the diary (i.e. the last evening report or if no evening report was completed after the start of the headache 23:59 on the day the headache started). Headaches that are not reported as stopped by the subject are missing the answers to the questions that allow for the determination of whether the headache was a migraine or not. In this population most headaches are migraines. Hence, these headaches with missing 'end' information will be classified as migraines.

**Missing Data Rule 1**

If the eDiary has been completed at least 21 days in a 28 day interval, then a normalization procedure will be used. The results will be normalized to 28 days by multiplying the observed results by the inverse of the completion rate (e.g. if a subject does not complete the eDiary on 5 days they will have completed the diary on 82% of the days and the normalized results will be the observed results times 1.22).

For the tertiary endpoints (except migraine free days), only Missing Data Rule 1 will be used and the denominators for will reflect the number of subjects who completed the eDiary 21 or more days in the 28 day interval. For Migraine Free Days no imputation will be used.

**Missing Data Rule 2**

If the eDiary has been completed on less than 21 days in the 28 day interval then the results for the 28 day interval will be a weighted function of the observed data for the current four week interval and the results from the previous interval. The weights will be proportional to how many days the diary was completed and will provide greater weight for higher completion rates. Specifically, the results will be derived as

$$28\,(W\,X_c + (1 - W)\,X_p),$$

where $W$ is the number of days the diary was completed/20, $X_c$ is the available average daily results for the current interval and $X_p$ are the average imputed daily results for the previous interval.

**Missing Data Rule for Prevalence Endpoints.**

For the percentage (prevalence) of subjects with a migraine on the day after dosing and reduction in migraine prevalence from baseline to Week 4 endpoints subjects who did not complete the eDiary on any day following dosing will be included in the calculation based upon their Week 1-4 daily migraine rate. Hence, subjects with a migraine on a given day will have a rate of 1 for that day, subjects who completed the eDiary and did not have a migraine will be included as a 0, and subjects who did not complete the eDiary will be included with a value between 0 and 1 equal to their prevalence rate in Weeks 1-4 (i.e. the number of Weeks 1-4 migraine days divided by 28).

**Missing Data Rule for HIT-6**

If a subject does not complete the HIT-6 at week 12 their Week 12 change from baseline result will be set to imputed values using LOCF. This imputation will only be performed at Week 12.

### 2.7.3. Sensitivity Analyses

A number of sensitivity analyses will be performed. The first group of sensitivity analyses will look at the missing data rules as outlined below.

1. The primary endpoint will be analyzed using a modification to Missing Date Rule 2 to better understand the robustness of the selected algorithm. The analysis replaces $X_p$ with $X_b$, where $X_b$ are the baseline average daily results, if the subject withdrew from the study due to an adverse event, study burden, lack of efficacy or worsening of study indication or if the subject died.
2. The primary endpoint will be analyzed using repeated measures where the individual time periods (Weeks 1-4, 5-8 and 9-12) are included in the model and Missing Date Rule 2 is not used. Hence, subject who do not complete the diary for more than 7 days out of 28 are not included for that 4 week period. The model will specify an unstructured variance/covariance matrix and include the treatment group, timepoint, baseline, and treatment group-by-timepoint interaction. The Kenward-Roger approximation will be used to estimate the degrees of freedom.

The second group of sensitivity analyses change the definition of baseline. Baseline will be redefined using 28-days of headache diary data ending on the day of the first dose. The primary analysis will be repeated using this updated definition of the baseline.

Finally, a repeated measures model will be run that includes all 6 four week intervals and both missing data rules outlined in Section 2.7.2. This model will be identical in structure to the model specified for the missing data sensitivity analysis outlined above but will look at how the primary analysis, based upon the ANCOVA model, compares to a repeated measures analysis.

### 2.7.4. Interim Analyses and Data Monitoring

A Data Monitoring Committee (DMC) will periodically review safety data during the enrollment and treatment phases of this study at regularly scheduled meetings as specified in the DMC Charter. The DMC will advise the Sponsor regarding the continuing safety of trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial. The DMC is not charged with stopping the trial early for efficacy.

### 2.7.5. Multicenter Studies

Data from all sites will be pooled for presentation.

### 2.7.6. Pooling Strategy for Strata

No pooling will be done.

# 3. STATISTICAL SUMMARIES

## 3.1. General Conventions

Unless otherwise stated, summary statistics including the number of subjects (n), mean, standard deviation, median, minimum and maximum will be presented for continuous variables. Generally, the minimum and maximum values will be presented to the same decimal precision as the raw values, the mean and median values to one more, and the standard deviation, to two more decimal places than the raw values. This decimal place convention may be followed for all data elements. For categorical variables, per category, the absolute counts (n) and percentages (%) of subjects with data, and if appropriate, the number of subjects with missing data, will be presented. Percentages will be presented to one decimal place.

For AEs, medical history and concomitant medications reported on a per-subject basis, the denominator for the percentage calculation will be the number of subjects at risk in each treatment group. A subject will be considered at risk if the subject is in the analysis set and in the subgroup of interest.

All p-values will be rounded to 4 decimal places. If a p-value is less than 0.0001 it will be displayed as "< 0.0001".

Unless otherwise specified all summaries will be performed by treatment group, all efficacy analyses will be based upon the full analysis population, all safety as well as demographic and baseline characteristic analyses will be based upon the safety population and all PK analyses will be based upon the PK population.

## 3.2. Definition of Baseline

Baseline assessment for migraine and headache endpoints will be based upon the data recorded in the headache eDiary during the 28 days following screening. For other variables, the baseline assessment will be the latest available valid measurement taken prior to the administration of Investigational Product. This will generally be Day 0.

## 3.3. Clinical Trial Subjects

### 3.3.1. Subject Disposition

The number of subjects randomized, treated, discontinued Investigational Product early, and terminated from the clinical trial early will be summarized. The reason for early discontinuation of Investigational Product or termination from the clinical trial will be summarized. Additionally, the summary of subjects present at each visit will be summarized. Subjects randomized but not included in the full analysis population and the reasons for exclusion will be summarized. The number of subjects screened and summary of screen failure reasons will also be summarized.

A listing of entry criteria that were not met will be produced.

### 3.3.2. Analysis Population

The number of subjects in each analysis population will be summarized.

### 3.3.3. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group.

### 3.3.4. Prior and Concomitant Medications

Medications with a stop date before the study treatment dosing date will be considered prior medications. Medications with a start or stop date on or after the treatment dosing date will be considered concomitant medications. All medications marked as ongoing are concomitant medications.

A medication with an incomplete stop date will be considered concomitant if:

- Month is missing and year is equal to or after the year of treatment dosing date
- Day is missing and year is equal to the year of the treatment dosing date and month is equal to or after the month of the treatment dosing date.

Concomitant medications will be summarized by treatment group. All medications will be provided in a listing.

The headache medications recorded in the eDiary will not be integrated with the concomitant medications as these two data capture tools have distinctly different format, purpose and functionality. These diary-based results will be summarized in a separate series of outputs. For these the percent of days that subjects used headache medication within each 4 week interval and in the trial as a whole will be summarized by treatment group. These summary measures will only include subjects who have completed the eDiary at least 21 days of the 28 days for the selected interval. In addition to the overall summary, descriptive statistics will be provided for each type of medication: Ergotamine, Triptan, Analgesic, Opioid and Combination Analgesic.

### 3.3.5. Medical History

Medical History will be tabulated by system organ class, preferred terms and treatment groups.

Migraine History including age at diagnosis, the average number of headache days, migraine days, and migraine attacks per 28 day period in the 3 months prior to screening, suffers from aura, medication overuse headache diagnosis, length of chronic migraine history, as well as the timing of the start of migraines in relation to puberty/ menarche and hormone migraine history for females will be summarized in a table by treatment groups.

### 3.3.6. Clinical Trial Treatment

Total volume infused, number of infusions and reason for dose interruption will be listed as well as summarized in a table.

### 3.3.7. eDiary Compliance

The rate of missing eDiary data within each four week interval, which is defined as (number of days with missing eDiary data / 28) * 100, will be summarized descriptively. A day will be considered as missing if the subject did not interact with their eDiary and the subject did not experience a headache on that day.

## 3.4. Analysis of Efficacy Endpoints

### 3.4.1. 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 will be produced. The treatment difference and associated confidence interval will also be provided. These confidence intervals will be based on normal approximation. Stratification will not be used for these intervals.

The SAS procedure, Proc Mixed will be used to generate the ANCOVA model outlined in Section 2.5.

Plots of the migraine days, and change from baseline will be produced. These plots will use the four week intervals as the X-axis. A separate set of graphs that provide histograms of the Week 1 to 12 results for these three parameters will also be produced. A plot for the cumulative distribution function of change from baseline migraine days for Weeks 1-12 will be produced.

The change in frequency of migraine days for Weeks 1-12 will be summarized within the subgroups outlined in Section 2.7.1. A forest plot of the treatment difference and associated confidence interval will also be presented.

**Sensitivity Analyses**

Summary statistics for the sensitivity analyses as outlined in Section 2.7.3 will be produced. These summary statistics will include the primary endpoint with the modified Missing Data Rule #2, with the different baseline definition and for the sensitivity repeated measures models. For the repeated measures the estimated treatment difference, for each time point, and associated confidence interval will be estimated using SAS procedure, Proc Mixed. The overall Week 1-12 estimated treatment difference, associated confidence interval and p-value will be reported.

### 3.4.2. Responder Rates

The 50%, 75% and 100% responder rates will be determined as outlined in the missing data Section 2.7.2 and the endpoint definition in Section 2.2.2. The number of subjects who are responders and the rate (full analysis population as the denominator) will be summarized for each treatment group at each 4, 12, and 24 week interval. The difference in rates and associated confidence interval will also be produced. These confidence intervals will be calculated based upon the normal approximation for two independent proportions. Stratification will not be used for these intervals. The SAS procedure, Proc Freq, will be used to calculate these confidence intervals. Any interval for which the normality assumption is questionable (i.e. np <5 or nq <5) will be flagged.

Plots of the percent of responders across time, for each response level, will be produced. These plots will use the four week responder rates.

A p-value for the difference in rates for the key secondary endpoints will be based upon the CMH test outlined in Section 2.5.

Should the as randomized and 'true' values for the stratification factors differ, the as randomized values will be used within these CMH tests. The SAS procedure, Proc Freq, will be used to calculate this p-value. Cumulative distribution of the responder rate will be plotted.

#### 3.4.2.1. Percentage of Subjects with a Migraine on the Day after Dosing

The percentage of subjects with a migraine will be summarized for each treatment group at baseline and each day from Day 0 to Day 7. A p-value for the difference from Placebo in the percentage of subjects with a migraine on the day after dosing (Day 1) will be provided. The average number of migraine hours on each of these days will also be presented.

#### 3.4.2.2. Reduction in Migraine Prevalence

Summary tables for the reduction in migraine prevalence and change from baseline by 1 week intervals for Weeks 1, 2, 3, and 4 and treatment group will be produced. The p-value from the test outlined in Section 2.5.2 will be provided. Plots of the change in the reduction in migraine prevalence from baseline from weeks 1-4, for each response level, will be produced.

#### 3.4.2.3. Time to First Migraine after Dosing

The analysis of the time to the first migraine after dosing endpoint will be based upon Kaplan-Meier method. The 25th percentile, 50th percentile (median), and 75th percentile, and their corresponding 95% confidence intervals will be reported for each treatment group. The percent of subjects who are migraine free at Days 1, 2, 3, 4, 5 and 6 and Weeks 1, 2, 4, 8, 12, 16, 20, 24 and the associated confidence intervals will be summarized for each treatment group. A subject will be censored for the eDiary analysis at the time of their last data entry. Kaplan-Meier plots for time to first migraine will be presented for Weeks 1-12.

#### 3.4.2.4. Acute Migraine Medication Days

Similar outputs will be produced for the Acute Migraine Medications Days as were produced for the primary endpoint. These will include 4 week, 12 week and 24 week summary measures and the p-value from the test outlined in Section 2.5.

#### 3.4.2.5. Health-Related Quality of Life (HIT-6)

The actual score and change from baseline for the total score will be summarized at each scheduled visit by treatment group. A shift from baseline to each scheduled visit by treatment group will be tabulated for each item. The p-value at Week 12 from the test outlined in Section 2.5 will be provided.

### 3.4.3. Remaining Headache and Migraine Secondary Endpoints

A summary table including confidence intervals for the treatment difference for the 4, 12, and 24 week time intervals will be produced for the remaining secondary endpoints.

Missing data rule for both Missing Data Rules provided in Section 2.7.2 will be utilized. For severe intensity and acute medication usage endpoints, the missing data rule will be applied to the numerator and denominator separately before calculating the percent.

### 3.4.4. Tertiary Headache and Migraine Endpoints

A summary table including confidence intervals for the treatment difference for the 4 week time intervals will be produced for headache episodes, migraine attacks, migraine symptom-free days and Most Bothersome Symptoms.

Missing data rule for Missing Data Rule 1 provided in Section 2.7.2 will be utilized for the exploratory analyses.

### 3.4.5. Other Secondary and Tertiary Efficacy Analyses

#### 3.4.5.1. Most Bothersome Symptom (MBS)

The change from baseline will be summarized for MBS using the Full Analysis Population at each scheduled visit by treatment group.

#### 3.4.5.2. Short-Form Health Survey (SF-36 v 2.0)

The actual score and change from baseline in each of the eight sections as well as the two component scores will be summarized using the Full Analysis Population at each scheduled visit by treatment group using descriptive statistics.

#### 3.4.5.3. Health-Related Quality of Life (EQ-5D-5L)

The change from baseline will be summarized separately for each EQ-5D-5L item using the Full Analysis Population at each scheduled visit by treatment group. A shift from baseline to each scheduled visit by treatment group will be tabulated for each item.

#### 3.4.5.4. Patient Global Impression of Change (PGIC)

The change from baseline will be summarized for PGIC using the Full Analysis Population at each scheduled visit by treatment group.

## 3.5. Analysis of Drug Concentrations

The concentrations of Free ALD403 will be measured in plasma from all ALD403-treated subjects using validated assay methods. The PK analysis will include evaluations of concentration-time profiles for Free ALD403 at the following times: pre-dose on Day 0, immediately post-dose (within 15 minutes of end of infusion) and Weeks 2, 4, 8, 12 (pre-dose), 24, and 32 or ET.

The concentrations of Free ALD403 will be listed and summarized by time point and dose group, and descriptive statistics will be provided. In this analysis, concentrations below the lower limit of quantification (LLOQ) will be set to zero.

Plots of the individual concentrations of ALD403 will be presented over time (linear and log scales). Plots of the mean or median concentration will be presented over time (linear and log scales). When the scale is linear, concentrations below the lower limit of quantification will be set to zero. In the log-scaled figures, concentrations below the LLOQ will be imputed as LLOQ/2. Population pharmacokinetic analysis will be performed on the results for ALD403

concentrations obtained during this study in combination with the results from other studies of ALD403 in normal subjects and migraine patients.

## 3.6. Analysis of Safety Endpoints

### 3.6.1. Adverse Events

Adverse events are collected from the time of Informed Consent through the final subject visit. The incidence of all AEs and study drug-related AEs will be tabulated by treatment received. These AEs will be classified by system organ class and preferred term using the MedDRA. For incidence reporting, if a subject reported more than 1 AE that was coded to the same preferred term/system organ class, the subject will be counted only once for that specific preferred term/system organ class. Events recorded between the time the informed consent is signed and the first Investigational Product administration will be listed.

A treatment-emergent AE (TEAE) is an AE with a start date and time on or after the date and time of the treatment.

For the purpose of inclusion in TEAE tables, incomplete AE onset and end dates will be imputed as follows:

Missing onset dates (where UK and UKN indicate unknown or missing day and month respectively):UK-MMM-YYYY: If the month and year are different from the month and year of the first dose of trial drug, assume 01-MMM-YYYY. If the month and year are the same as the first dose of trial drug month and year, and the end date (after any imputation) is on or after the first dose of trial drug, then assume the date of the first dose of trial drug. If the month and year are the same as the first dose of trial drug month, and year and the end date (after any imputation) is prior to the first dose of trial drug, then assume the end date for the onset date.

- DD-UKN-YYYY/UK-UKN-YYYY: If the year is different from the year of first dose of trial drug, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of trial drug year, and the end date (after any imputation) is on or after the first dose of trial drug, then assume the date of the first dose of trial drug. If the year is the same as the first dose of trial drug, and the end date (after any imputation) is prior to the first dose of trial drug, then assume the end date for the onset date.

Missing end dates (where UK and UKN indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: Assume the last day of the month;
- DD-UKN-YYYY/UK-UKN-YYYY: Assume 31-DEC-YYYY.

An overview of AEs, which includes subject incidence of TEAEs, study drug-related TEAEs, Serious TEAEs, TEAEs leading to study treatment interruption, TEAEs leading to study drug discontinuation and deaths will be presented.

The subject incidence of TEAEs and treatment-related TEAEs will be summarized by system organ class and preferred term.

Treatment-emergent AEs will also be summarized in a table by severity. For TEAEs presented by severity, the worst severity for each event during the clinical trial will be presented for each subject.

All AEs will be presented as a listing by subject. This listing will include the duration of the AE.

### 3.6.2. Deaths, Serious Adverse Events and Other Significant Adverse Events

#### 3.6.2.1. Adverse events of special interest

Adverse events of special interest include the following, with additional PTs to be determined at time of database lock;

**Hypersensitivity and Anaphylactic Events**

The subset of adverse events with a MedDRA coded SOC of Immune system disorders and PTs of Hypersensitivity, Anaphylactic reaction and Anaphylactoid reaction.

**Events Associated with C-SSRS**

The subset of adverse events with a MedDRA coded SOC of Psychiatric disorders and PTs of Suicidal behavior, Suicidal ideation, Suicidal attempt and Self injurious behavior.

**Cardiovascular Events**

The subset of adverse events with

- a MedDRA coded SOC of Cardiac disorders and PTs of Atrial fibrillation, Bradycardia, chest pressure, Palpitations, Sinus bradycardia, Sinus tachycardia and Tachycardia, or
- a MedDRA coded SOC of Investigations and PTs of Blood pressure increase, Blood pressure systolic increase, Elevated blood pressure, Heart rate increased, Heart rate decreased, Heart rate irregular, Electrocardiogram abnormal, Electrocardiogram Q wave abnormal, Electrocardiogram QT interval abnormal, and Electrocardiogram QT prolonged, or
- a MedDRA coded SOC of Nervous system disorders and PTs of Seizure and Syncope, or
- a MedDRA coded SOC of Vascular disorders and PTs of Flushing, Hot flush, Hypertension, Hypotension and Ischemia.

**Hepatic Events**

A subset of adverse events with a MedDRA coded SOC of Investigations and PTs of Alanine aminotransferase increased, Aspartate aminotransferase increased, Bilirubin increase, Hepatic enzyme increased, Liver function test abnormal, and Transaminases increased.

**Events Associated with Study Drug Infusion**

A subset of adverse events within one week of dosing with

- a MedDRA coded SOC of Skin and subcutaneous tissue disorders and PTs of Dermatitis bullous, Pruritus, Pruritus generalized, Rash, Rash macular, Rash macular-papular, Rash papular, Rash pruritic and Urticaria.
- a MedDRA coded SOC of General disorders and administration site conditions and PTs of Infusion site erythema, Infusion site extravasation, Infusion site pain, Infusion site paresthesia, Infusion site pruritus, Infusion site rash, Infusion site reaction, and Infusion site swelling.

**Adverse Event of Interest Analysis**

The adverse events of special interest will be summarized and listed in the following categories:

- AESIs by system organ class and preferred term.
- AESIs by system organ class, preferred term, and maximum severity.
- AESIs by system organ class, preferred term, and relationship to study drug.
- AESIs that lead to infusion interruption by system organ and preferred term.
- AESIs with action taken of study drug discontinuation by system organ class and preferred term
- AESIs assessed as serious by system organ class and preferred term.

#### 3.6.2.2. Serious Adverse Events

All SAEs will be listed and summarized in a similar manner to TEAEs.

#### 3.6.2.3. Deaths

A listing of deaths will be presented.

### 3.6.3. Clinical Laboratory Evaluations

Summary statistics for actual values and for changes from baseline will be tabulated for clinical laboratory results by scheduled visit. Subjects with clinical laboratory values outside of the normal reference range at any post-baseline assessment will be summarized. Shifts from baseline clinical laboratory values based upon the normal range and will be tabulated. Subjects developing an antibody response will be listed. A listing of the Immune response laboratory results will be produced.

Plots of average clinical laboratory parameters will be presented over time.

### 3.6.4. Vital Signs, Physical Findings and Other Observations Related to Safety

#### 3.6.4.1. Vital Signs

The observed data at baseline and change from baseline for each measurement day will be summarized with descriptive statistics. A plot of average vital sign parameters will be presented over time.

#### 3.6.4.2. Physical Exam

Physical exam findings at screening will be documented in medical history. Post baseline physical examination findings, including unscheduled visits, may be reported as adverse events using the protocol adverse event definition.

#### 3.6.4.3. Electrocardiogram Results

The observed data at baseline and change from baseline for each measurement day will be summarized with descriptive statistics by treatment group.

The overall ECG assessment based upon PI assessment will be summarized including post treatment ECGs determined to be abnormal clinically significant.

The absolute QTcF values provided by the core lab will be analyzed as a categorical variable. Each QTcF value in a given patient will be grouped into 4 categories:

- QTcF interval < 450 msec
- QTcF interval 450 - 480 msec
- QTcF interval > 480 - 500 msec
- QTcF interval > 500 msec

The changes in QTcF measures will also be analyzed as categorical variables. The change in QTcF in a given patient will be grouped into 2 categories:

- QTcF interval increases from baseline > 30 msec
- QTcF interval increases from baseline > 60 msec

The overall ECG assessment will be summarized along with a summary of how many subject developed a post treatment abnormal clinically significant result. Denominators for percentages will use the number of assessments available at each visit.

### 3.6.5. Immunogenicity Data Analysis

Analyses will be conducted using treatment group that the subjects actually received for safety population. Analysis of specific anti-ALD403 antibodies is restricted to subjects who are treated with anti-ALD403.

For subjects with pre-existing antibodies at baseline, the number and percent of subjects who are positive for anti-ALD403 antibody will be summarized. In addition, the number and percent of subjects who develop anti-drug antibodies to ALD403 during the trial will be summarized at each scheduled visit in the same table. Denominators for percentages will be the total number of samples taken for the specified visit.

All the immunogenicity data will be listed.

#### 3.6.5.1. Anti-ALD403 Antibody Analysis

Subjects with a positive anti-ALD403 antibody result will be listed.

### 3.6.6. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS assesses lifetime suicidality during an initial baseline evaluation, and then monitors suicidal ideation and suicidal behavior at subsequent follow-up assessments. Four constructs are measured. The first and second are the severity and intensity of ideation, rated on a 5-point ordinal scale. The third is the behavior subscale, which is rated on a nominal scale and the fourth is the lethality subscale, which assesses actual attempts. These results will be reported at baseline and post baseline. Results for individual time points will be provided in a listing.

The denominator for percentages will be the number of subjects with a C-SSRS assessment at baseline or at any time post baseline. The post baseline summary will list a subject as yes if they ever selected yes after baseline.

### 3.6.7. Pregnancies

Positive pregnancy test results will be listed.

# 4. DEVIATIONS FROM THE PROTOCOL

1. The SAP identifies the HIT-6 and Acute Migraine Medication Usage endpoints as key secondary endpoints while the Protocol classifies these as secondary endpoints. The SAP calls these key secondary endpoints as they are included in the testing algorithm.
2. The SAP includes the exploratory endpoint Migraine Free Days. This endpoint has been added as it is believed it may present a clinically meaningful way of viewing the benefit of treatment.

# REFERENCES

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4. LaVange L, Durham T, Koch G. Randomization-based Nonparametric Methods for the Analysis of Multicenter Trials. Statistical Methods in Medical Research. 2005; 14:281-301.
5. Mallinckrodt, C., Lipkovich, I. (2016). Analyzing Longitudinal Clinical Trial Data: A Practical Guide. Chapman and Hall/CRC Press, New York.
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