Alder BioPharmaceuticals, Inc.

ALD403-CLIN-006

A Parallel Group, Double-Blind, Randomized, Placebo Controlled, Trial to Evaluate the Efficacy and Safety of ALD403 Administered Intravenously in Patients with Frequent Episodic Migraines.

18MAY2017

Statistical Analysis Plan

Version *1.4*

Indication	Treatment for Prevention of Frequent Episodic Migraine Headaches
Development Stage	Pivotal
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Upon review of this document, including table, listing, and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable, and the table, listing, and figure production can begin.

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LIST OF ABBREVIATIONS

AE	Adverse event
ASC-12	Allodynia Symptom Checklist
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
BDI-II	Beck Depression Inventory
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
EQ-5D-5L	Health-Related Quality of Life
hCG	Human chorionic gonadotropin
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
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
SAE	Serious adverse event
SAP	Statistical Analysis Plan
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
Vz	Apparent volume of distribution during the terminal elimination phase
WHO	World Health Organization

1 CLINICAL TRIAL DESCRIPTION

According to the International Classification of Headache Disorder (ICHD)[1], migraine is a common disabling primary headache disorder manifesting in attacks lasting 4 to 72 hours. Migraine frequency is divided into episodic migraine and chronic migraine. Frequent Episodic migraine (FEM, 4 to 14 migraines days per month) affects approximately 17 percent of women and 6 percent of men.

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[2, 3]. ALD403 is a humanized anti- 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 FEM.

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 FEM.
- To evaluate the pharmacokinetics (PK) and immunogenicity of repeat doses of ALD403 administered IV to subjects with FEM.

1.2 Clinical Trial Design

This phase 3, is a parallel group, double-blind, randomized, placebo-controlled trial of multiple infusions of ALD403 or placebo in subjects with FEM. Subjects who provide informed consent will be qualified based upon the inclusion and exclusion criteria and compliance with the eDiary. The key entry criteria are that the subject has FEM, which will be determined from the first 28 days of eDiary data following the screening visit. During this time the subject must experience ≥4 and ≤14 headache days of which at least 4 have to be migraine days and must have completed the eDiary at least 25 of the 28 days to be eligible.

The subject will be instructed to complete the eDiary daily from the screening visit through Week 48. Subjects will return to the site on Day 0 for randomization and first treatment, which should occur at least 29 days but no more than 35 days after the screening visit. Subject eligibility will be re-confirmed on Day 0, prior to randomization. Subjects will be randomized into one of three ALD403 dose levels (30 mg, 100 mg, and 300 mg) or placebo. Any subject found to be no longer eligible for the trial on Day 0, will not be randomized nor dosed. The subjects randomized and dosed will continue the study for 56 weeks. These 56 weeks are divided into two periods, i.e., a primary efficacy and safety period (Weeks 1-24) and a long term safety period (Weeks 25-56). Subjects will complete the eDiary daily through Week 48.

Approximately 800 subjects will be randomized and treated. Efficacy, safety, pharmacokinetic, and immunogenicity assessments will be conducted according to the Schedule of Events in Table 1.

Table 1: Schedule of Events and Assessment

			Primary Efficacy and Safety Period						Long Term Safety Period			
Assessment	**Screen D-35 to -29**	**Rand/ D0 Tx**	**Wk 4 D28 ±3**	**Wk 8 D56 ±3**	**Wk 12 D84 ±3 Tx**	**Wk 16 D112 ±3**	**Wk 20 D140 ±3**	**Wk 24[8] D168 +3 Tx**	**Wk 28 D196 ±7**	**Wk 36 D252 ±3 Tx**	**Wk 48[9] D336 +7**	**Wk 56 EOT/ET D392 ±7**
Informed Consent	X											
In/Ex Criteria	X	X										
Demographics, Medical History, BDI-II	X											
Headache eDiary Review[1]	X	X	X	X	X	X	X	X	X	X	X	
Physical Exam Height and Weight[2]	X	X						X		X		X
Brush Allodynia Test		X	X		X	X	X	X				
Vital Signs[3]	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS[4]	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[3]	X	X	X	X	X			X	X	X	X	X
Hematology, Chemistry[5]	X	X	X		X			X	X	X	X	X
HIV/Hepatitis B and C Urine Drug Screen	X											
Urine Preg (hCG) Test	X	X			X			X		X	X	X
Plasma ALD403 Serum Anti-ALD403[6]		X	X	X	X	X	X	X		X	X	X
SF-36		X	X	X	X	X	X	X		X		X
EQ-5D-5L, ASC-12		X	X	X	X	X	X	X				
AE and Con Meds Review	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X										
ALD403/placebo administration[7]		X			X			X		X		

Abbreviations: TX: Treatment, Rand: Randomization, EOT/ET: End of Trial/Early Termination

[1]Headache eDiary distributed at screening. eDiary review and compliance check through Week 48.
[2]Physical exam must be done pre-dose on Day 0, Week 24, 36. Height and Weight on Screening visit. Weight only on Day 0, Weeks 24, 36, 56
[3]Vital signs, 12-lead ECG pre-dose and 4 hours post-dose (± 30 minutes) on Day 0 and Weeks 12, 24 and 36
[4]C-SSRS Baseline/Screening Version at screening, C-SSRS Since Last Visit Version Day 0 (pre-dose), Weeks 4, 8, 12, 16, 20, 24, 28, 36, 48 and 56
[5]All blood draws obtained pre-dose on dosing days
[6]Sample for Plasma Free ALD403 and anti-ALD403 antibody drawn pre-dose on dosing days (within 1 hour prior to dosing)
[7] Subjects must be monitored for at least 4 hours after the dosing completion.
[8]Week 24 must be done on the target day or 3 days after. Three days earlier than target date is not allowed.
[9]Week 48 must be done on the target day or seven days after. Seven days earlier than target date is not allowed.

1.3 Method of Assigning Subjects to Treatment Groups

Randomization will occur 29 to 35 days after the screening visit when the eligibility assessments are completed and eligibility verified. Sites will complete the randomization using an Interactive Web Response System (IWRS) and the randomization assignment will be obtained by the clinical trial site's unblinded pharmacist or Investigational Product consignee. Subjects will be randomized in equal ratios to one of the four 4 treatment groups (30 mg, 100 mg, or 300 mg of ALD403 or Placebo). Stratified permuted block randomization will be used. Stratification will be by migraine days during the screening period (≤9 days vs. >9 days).

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 study will remain blinded until the last subject has completed the Week 24 visit at which time the sponsor will be unblinded.

1.5 Sample Size

The planned sample size for this trial is 800 randomized and treated subjects. These subjects will be allocated into 4 treatment groups in a 1:1:1:1 ratio. Pair-wise testing of each ALD403 group vs. placebo will be performed. Two hundred subjects per group provides at least 95% power for each change in frequency of migraine days (Weeks 1-12) test individually assuming a treatment effect of at least 1 day and a common standard deviation of 2.7 days or less. Ninety percent power is retained for standard deviations up to 3 days. For the key secondary 75% responder

rates endpoints 95% power is achieved for the pair-wise comparisons assuming rates of 24% for placebo and 42% for ALD403. For the 50% responder rate endpoints 95% power is achieved for the pair-wise comparisons assuming rates of 50% for placebo and 68% for ALD403. For the percentage of subjects with a migraine on the day after dosing endpoint, 95% power is achieved for pair-wise comparisons assuming rates of 15% for placebo and 4% for ALD403.

These sample size calculations have been performed using Pass 2008 and are based upon t-tests and Chi-squared tests that should approximate the ANCOVA and CMH tests, respectively.[4]

2 STATISTICAL METHODS

2.1 Populations Analyzed

The analysis populations are defined as the following:

- Full Analysis Population – 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 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

Other Secondary Efficacy Endpoints

- Change in acute migraine medication days (Weeks 1-12)
- Headaches/Migraines with acute medication usage
- 100% migraine responder rates (Weeks 1-12)
- Short-Form Health Survey (SF-36 v 2.0)
- Health-Related Quality of Life (EQ-5D-5L)
- Allodynia Symptom Checklist-12 (ASC-12)
- Brush (dynamic mechanical) Allodynia
- 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/migraine days
- Time to first migraine after dosing
- Headache/Migraine hours
- Headache/migraines with severe intensity

Tertiary Endpoints

- Headache episodes/migraine attacks

Exploratory Endpoints

- Headache/Migraine characteristics
- Headaches/Migraines with type of acute medication usage
- Headache episode/Migraine attack average length

Safety Endpoints

- Adverse events (AEs) and serious adverse events (SAEs)
- Changes in clinical laboratory assessments
- Vital Signs
- ECGs
- Suicidal ideation and behavior as measured by the 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 48. The diary is to be completed each trial day whether or not the subject had a headache. These daily entries record if the subject took acute migraine medication on that day.

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 48. 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. 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, … 44-48, the twelve week intervals 1-12, 13-24, 25-36, 37-48, and Weeks 1-24, 25-48 as outlined in Section 2.3. The results from Weeks 1 to 12 will be used for the primary analysis.

For this trial, migraines are defined using the definition of migraine without aura and probable migraine without aura as outlined by the International Headache Society. These definitions do not take the presence of aura into account. Subjects will report if they experienced aura with their headache. Hence, in the rare case of aura that does not develop into a migraine, this will not be classified as a migraine but a headache that meets the definition of a migraine without aura will be considered a migraine regardless of if aura was present or not.

Migraine Day

A migraine day is defined as any day with a headache that meets the migraine or probable migraine characteristics as outlined in the International Headache Society (IHS), ICHD II 2004-II, Section 1.1 and 1.6. Specifically, a migraine is defined as a self-reported headache that:

1. Lasted 4-72 hours
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

A probable migraine is a headache that meets only 2 of the above criteria. 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.

Results from the four week intervals will be averaged to produce 12 and 24 week responder endpoints. A responder will be a subject who achieves the specified percent reduction in migraine headache days when response rates for each of the four week intervals are averaged.

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 a duration of zero.

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 / 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 within 4 week intervals 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 baseline and post baseline interval.

Percentage of subjects with a migraine on the day after dosing

The percent of subjects with a migraine on the day after first dose will be summarized.

eDiary Reported Medication Usage

The percent of days per 28 days with medication usage will be summarized overall and by the type of medication used.

Average Migraine / Headache Length

The length of each migraine attack is the average of the duration of each migraine attack within a four week intervals. Headache hours are similarly defined but include all headaches. Subjects with no migraines/headaches will have a duration of zero.

Time to First Migraine

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

2.2.3 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.

2.2.4 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.

2.2.5 Allodynia Symptom Checklist (ASC-12)

The ASC-12 includes 12 questions about the frequency of various allodynia symptoms in association with headache attacks. For individuals with more than one type of headache, questions are directed to the "most severe type of headache." Each item is measured on a Likert type scale option with response categories: "Does not apply to me", "never," "rarely," "less than half the time," and "half the time or more". ASC items were scored as 0 (i.e., never, rarely, or does not apply to me), 1 (less than half the time), and 2 (half the time or more), yielding scores that ranged from 0 to 24. In this trial if a single item is missing it will be scored as a zero. If

more than one item is missing the total score will be missing. The interpretation of the total score is provided below.

Score Range	Allodynia
0-2	None
3-5	Mild
6-8	Moderate
≥9	Severe

2.2.6 Brush Allodynia

Dynamic mechanical brush allodynia will be tested by lightly brushing a 10 by 10 cm gauze pad bilaterally, 1-2 cm over each eyebrow at a rate of 2/second, for a total of 10 times. For each side of their forehead, subjects will be asked to assess the degree of pain elicited by the gauze on a scale of 0 to 10 with 0 being no pain and 10 being the worst imaginable pain.

2.2.7 Pharmacokinetics

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, and Weeks 4, 8, 12, 16, 20, 24, 36, 48, and 56.

Plasma collected at Week 4 from all placebo-treated subjects will be analyzed for the potential presence of Free ALD403 using validated assay methods.

2.2.8 Immunogenicity

Serum blood samples to test for antibodies to ALD403 will be taken pre-dose on Day 0, and Weeks 4, 8, 12,16, 20, 24, 36, 48, and 56. The immunogenicity will be assessed in serum from all ALD403-treated subjects using validated assay methods. 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 potential for neutralizing (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 approximately 3 month intervals for up to 6 months. See the blinding plan for details concerning blinding and the capture of these samples.

2.3 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 2.

Table 2: 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 7	Day 0	Day 0
Week 4	Day 8 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 182	Day 168	Closest to Target Day
Week 28	Day 183 to Day 210	Day 196	Closest to Target Day
Week 36	Day 211 to Day 273	Day 252	Closest to Target Day
Week 48	Day 274 to Day 357	Day 336	Closest to Target Day
Week 56	> Day 357	Day 392	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 3 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 3: 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
25-28	Days: 168-195		All eDiary related endpoints
29-32	Days: 196-223		All eDiary related endpoints
33-36	Days: 224-251		All eDiary related endpoints
25-36	Weeks 25-28, 29-32 and 33-36	Average of the 4 week intervals after imputation methods are applied	All Primary and Secondary eDiary related endpoints
37-40	Days:252-279		All eDiary related endpoints
41-44	Days: 280-307		All eDiary related endpoints
45-48	Days: 308-335		All eDiary related endpoints
37-48	Weeks 37-40, 41-44 and 45-48	Average of the 4 week intervals after imputation methods are applied	All Primary and Secondary eDiary related endpoints
25-48	Weeks 25-28, 29-32, 33-36, 37-40, 41-44 and 45-48	Average of the 4 week intervals after imputation methods are applied	All Primary and Secondary eDiary related endpoints

2.4 Pooling Strategy for Strata

No pooling will be done.

2.5 Statistical Assessment of the Trial Objectives

Hypothesis testing will be performed for the primary endpoint: change from baseline in migraine days from 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. The hypotheses tested are

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

where Δ_{403} is the change in migraine days for subjects in the ALD403 treatment arm and Δ_{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 the stratification variable: baseline migraine days (continuous covariate) will be the independent variables.

In addition, model based estimates including confidence intervals for the treatment differences will be used to summarize the results for the primary endpoint.

A sensitivity analysis of the change from baseline in migraine days will be performed using the sensitivity missing data rule provided in Section 2.7.2.

Secondary Efficacy Analyses

Summary statistics including confidence interval for the treatment differences will be used to summarize the results for the secondary endpoints. Testing will be performed for the key secondary endpoints and for the change in acute migraine medication days endpoint. For the key secondary endpoints (responder rates and percentage of subjects with a migraine on the day after dosing) this testing will utilize a CMH/extended CMH test. The tests will be stratified by the randomization stratification factor. The change in acute migraine medication day endpoints will be tested using an ANCOVA model similar to the one used for the primary endpoints: change from baseline measure as the response, treatment and baseline acute migraine medication days as independent variables. The time to first migraine analysis will be descriptively summarized based upon Kaplan-Meier methods.

Exploratory Analyses

Exploratory endpoints will be summarized with descriptive statistics by treatment group.

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 15.1.

2.7 Statistical/Analytical Issues

2.7.1 Adjustments for Covariates and Examination of Subgroup Analyses

Summaries with descriptive statistics and frequency counts for change in migraine days will be provided for the subgroups indicated below. A forest plot will also be created for subgroup analyses and will display treatment differences. The subgroups will be

- Calculated baseline migraine days (<9 days vs. ≥9 days)
- Sex
- Race (White, Black or African American, Other)
- 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)

2.7.2 Handling of Dropouts or Missing Data

Summary statistics will be reported based upon observed data except for the diary data, which will utilize 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 intake 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).

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.

Unless it is stated otherwise all primary and secondary analyses will use both Missing Data Rules 1 and 2, as appropriate. For the exploratory analyses, 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.

Sensitivity Rule

The primary endpoint and key secondary endpoints will also 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.

2.7.3 Interim Analyses and Data Monitoring

A DMC, guided by a charter, will review safety data during the enrollment and treatment phases of this study. 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.

The primary analysis is planned when the last subject randomized and treated has completed the week 24 visit. The trial will remain blinded until the last subject has completed the Week 24 visit.

The final analysis will be repeated when the final subject has completed the Week 56 visit. A comparison of the Week 24 and Week 56 analyses will be performed to identify any changes in the database that occurred between unblinding and the final analysis.

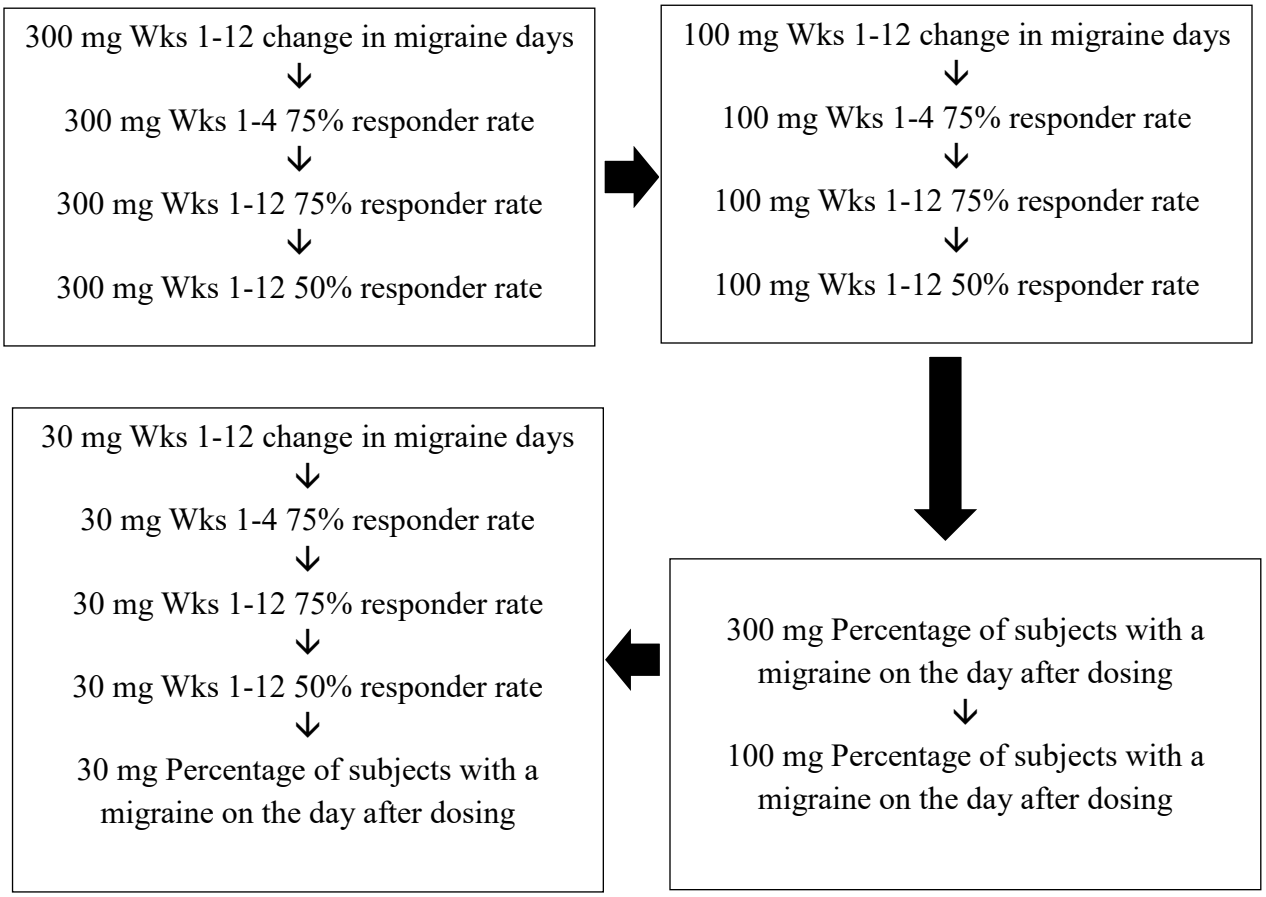
2.7.4 Multicenter Studies

Data from all sites will be pooled for presentation.

2.7.5 Multiple Comparisons/Multiplicity

A serial procedure will be used to account for multiplicity of dose level for the primary endpoint and the secondary endpoints. This procedure will start with the 300 mg vs placebo comparison for the primary endpoint. If this is significant, testing will continue to a subset of the key secondary endpoints for 300 mg (first the Weeks 1-4 75% responder endpoint, then the Weeks 1-12 75% responder endpoint, and then the Weeks 1-12 50% responder endpoint). The procedure will then move on to the primary endpoint for the 100 mg group and subsequently to the same subset of key secondary endpoints as tested for the 300 mg dose. The procedure will then move on to the remaining key secondary endpoint for 300 mg and 100 mg (i.e., percentage of subjects with a migraine on the day after dosing). Only if all of these secondary endpoints reach statistical significance will the 30 mg group be tested.

Statistical testing will be conducted at the 5% alpha level.



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 PK data the following applies:

Concentration values for free ALD403 will be presented as received from the Bioanalytical Laboratory.

Values for all PK parameters and for mean concentrations will be presented in three or four significant digits, as appropriate, i.e., 3 significant digits for minimum and maximum, 4 significant digits for mean, SD and median; % CV is given to 1 decimal point.

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 signed informed consent, randomized, treated, discontinued Investigational Product early, and terminated from the clinical trial early will be summarized. The reason for early termination of Investigational Product or 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 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.

Prophylactic and acute headache medications, identified by a clinical review of the coded concomitant medications data, will be summarized by treatment group.

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, Simple Analgesic, Opioid, Combination Analgesic and Other.

3.3.5 Medical History

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

For females, menstrual medical history will be summarized by 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, 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 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 Headache/Migraine Days and Acute Migraine Medication 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. Similar tables will be produced for acute migraine medication days and the change from baseline acute migraine medication days. 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.

Additionally, the SAS procedure, Proc Mixed using the ANCOVA model controlling for the effects of baseline migraine days outlined in Section 2.5, will be used to calculate the estimated treatment difference from placebo, the change from baseline and the associated confidence intervals for Weeks 1-12. The ANCOVA model will also be used to test for a treatment difference in the primary endpoint change from baseline in migraine days for Weeks 1-12 and for the change from baseline days of acute migraine medication use for Weeks 1-12. Significant p-values based on the formal decision rule criteria outlined in Section 2.7.5 will be clearly noted.

Plots of the migraine days and change from baseline and for days of acute migraine medication use 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.

The change from baseline in migraine days for the six, 4 week intervals from Weeks 1 to 24 will also be analyzed using repeated measures. The model will include treatment group, timepoint (Weeks 1-4, 5-8 9-12, 13-16, 17-20, 21-24), and baseline migraine days as fixed factors. Estimated treatment difference, for each timepoint, and associated confidence interval will be estimated using SAS procedure, Proc Mixed. The unstructured (UN) covariance structure will be specified. If the model fails to converge, an alternative covariance structure will be specified. The timepoint variable will be categorical and baseline migraine days will be continuous. The repeated measures analysis will be repeated for weeks 1-12 using the same subjects and a subset where only subjects/four week intervals where the eDiary was completed a minimum of 21 days and applying Missing Data Rule 1 described in Section 2.2.2. Only the overall week 1-12 estimated treatment difference, associated confidence interval and p-value will be reported for this analysis.

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

3.4.2 Responder Rates

The 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 and 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. Significant p-values based on the formal decision rule criteria outlined in Section 2.7.5 will be clearly noted in the footnotes.

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.

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

The missing data rules provided in Section 2.7.2 will be used for the key secondary endpoints except for the percentage of subjects with a migraine (prevalence) on the day after dosing endpoint. Subjects who did not complete the eDiary on the day following dosing will be included in to the prevalence rate calculation based upon their month 1 daily migraine rate. Hence, subjects with a migraine will be included in the rate calculation as a value of 1, subjects who completed the diary and did not have a migraine will be included as a zero and subjects who did not complete the diary will be included with a value between 0 and 1 equal to the number of month 1 migraine days / 28.

The percentage of subjects with a migraine (full analysis population as the denominator) 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) key secondary endpoint will be based upon the extended CMH test stratified by the randomization stratification factor. Significant p-values based on the formal decision rule criteria outlined in Section 2.7.5 will be clearly noted in the footnotes.

3.4.3.2 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, 4, 8, 12 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. A Kaplan-Meier plot for time to first migraine will be presented for weeks 1-12.

3.4.4 Remaining Headache and Migraine Secondary Endpoints

The following summarizations will be produced for headache episodes, migraine attacks, headache and migraine hours, headaches and migraines with severe intensity and headaches and migraines with acute medication usage. A summary table including confidence intervals for the treatment difference for the 4, 12, and 24-week time intervals will be produced.

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 nominator and denominator separately before calculating the percent.

3.4.5 Tertiary and Exploratory Headache and Migraine Endpoints

The following summarizations will be produced for headache and migraine characteristics, the average length of a headache episode and migraine attack, and headaches and migraines summarized by **type** of acute medication usage. A summary table including confidence intervals for the treatment difference for the 4-week time intervals will be produced.

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

3.4.6 Other Secondary Efficacy Analyses

The secondary endpoints will be summarized with descriptive statistics by time point. These summary measures will be based upon the observed results and where appropriate the change from baseline results. The denominator for percentages will be the total number of assessments collected at each visit.

3.4.6.1 Short-Form Health Survey (SF-36 v 2.0)

The actual scores and change from baseline in each of the eight sections will be summarized using the Full Analysis Population at each scheduled visit by treatment group using descriptive

statistics. Scoring software utilizing the 2009 norm-based scoring algorithm will be used to calculate the actual score for each of the eight sections.

3.4.6.2 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.

3.4.6.3 Allodynia Symptom Checklist-12 (ASC-12)

The ASC-12 total score and change from baseline will be summarized using the Full Analysis Population at each scheduled visit by treatment group using descriptive statistics. In addition, allodynia severity will be summarized using frequency counts for each scheduled visit.

3.4.6.4 Brush (dynamic mechanical) Allodynia

Brush allodynia will be summarized as a continuous measure and binary (does or does not have brush allodynia). The result for each side of forehead will be reported separately. The actual brush allodynia score will be summarized using the Full Analysis Population at each scheduled visit using descriptive statistics. The percent of subjects with brush allodynia (i.e. a score >0) will be summarized at each scheduled visit along with the percent of subjects with a score >2.

3.5 Pharmacokinetic Analyses

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, and Weeks 4, 8, 12, 16, 20, 24, 36, 48, and 56.

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 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.

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 treatment-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 on or after the date 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, treatment-related TEAEs, Serious TEAEs, TEAEs leading to treatment withdrawal, TEAEs leading to treatment interruption, TEAEs leading to 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 Serious Adverse Events

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

3.6.2.2 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.

Additional blood specimens using the immune response lab kit will be collected for subjects who experience a potential systemic allergic reaction that the Investigator believes is related to ALD403.

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

Clinically significant physical exam findings at screening will be documented in medical history. Post baseline physical examination findings, including unscheduled visits, will be reported as adverse events.

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 ALD403. 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.

For subjects with pre-existing antibodies at baseline, the number and percent of subjects with positive anti-ALD403 antibody samples 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. Additional efficacy and safety analyses based upon the immunogenicity results will be performed.

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.

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