Alder BioPharmaceuticals, Inc.

ALD403-CLIN-013

An Open Label Phase 3 Trial to Evaluate the Safety of ALD403 Administered Intravenously in Patients with Chronic Migraine.

05FEB2018

Statistical Analysis Plan

Version *1.1*

Indication	Treatment for Prevention of Chronic Migraine
Development Stage	Phase III
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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
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BMI	Body Mass Index
BP	Blood pressure
CGRP	Calcitonin Gene-Related Peptide
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EQ-5D-5L	Health-Related Quality of Life
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIT-6	Headache Impact Test
IB	Investigator's Brochure
ICD	International Classification of Diseases
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICHD	International Classification of Headache Disorders
IHS	International Headache Society
IgG1	Immunoglobulin G1
IP	Investigational Product
IRB	Institutional Review Board
IV	Intravenous
Kg	Kilogram
LLOQ	Lower Limit of Quantification
M	Molarity

m2	Meter squared
mAb	Monoclonal antibody
MAOI	Monoamine oxidase inhibitor
MBS	Most Bothersome Symptom
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MIDAS	Migraine Disability Assessment
mL	Milliliter
mm	Millimeter
MRM	Menstrually-related migraine
NOAEL	No-observed-adverse-effect-level
NSAID	Non-steroidal anti-inflammatory drug
PI	Principal Investigator
PK	Pharmacokinetic
PGIC	Patient Global Impression of Change
PRO	Patient Reported Outcome
QTcF	QT corrected using Fridericia formula
RBC	Red blood cell
SAE	Serious adverse event
SF-36	Short Form Health Survey
TMD	Temporomandibular Disorder
WBC	White blood cell

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.[2] In addition, chronic migraine is associated with more co-morbid diseases such as anxiety, depression, and non-headache pain.[3]

Calcitonin gene-related peptide (CGRP) 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[4, 5]. ALD403 is a humanized anti-(calcitonin gene-related peptide) 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 Safety Objective

The primary objective is:

- To evaluate the long term safety of repeat doses of ALD403 administered intravenous (IV) in patients with chronic migraine.

1.1.2 Immunogenicity and Patient Reported Outcomes Objectives

The secondary objectives include the following:

- To evaluate the pharmacokinetics (PK) and immunogenicity of repeat doses of ALD403 administered IV to patients with chronic migraine.

- To further evaluate the impact of ALD403 on various patient reported outcomes.

1.2 Clinical Trial Design

This is an open label trial which will include two treatment phases. The primary treatment phase will include four intravenous infusions of 300mg ALD403 in patients with chronic migraine. Infusions will be 12 weeks apart. The secondary treatment phase will include four additional 300mg ALD403 infusions 12 weeks apart. Subjects who provide informed consent will be evaluated for eligibility based upon the inclusion and exclusion criteria.

Eligible subjects will receive 4 IV infusions of 300mg ALD403 in the primary treatment phase on Days 0 (11-14 days after the screening visit), 84 (Week 12), 168 (Week 24) and 252 (Week 36). Subjects who receive all 4 infusions in the primary treatment phase may enter the secondary treatment phase, where subjects will receive up to 4 additional infusions for a total of 8 infusions. The infusions in the secondary treatment phase will occur on Days 336 (Week 48), 420 (Week 60), 504 (Week 72) and 588 (Week 84). Subjects will be followed for 20 weeks until Week 104 for a total study duration of approximately 106 weeks, including the screening period. Subjects who don't receive all 4 infusions of ALD403 in the primary treatment phase or don't consent for participation in the secondary treatment phase will be followed at Week 48 and Week 56, at which point they will have their End of Trial visit.

Approximately 120 subjects will be enrolled and treated. Study specific assessments will be conducted according to the Schedule of Events presented in Table 1: Schedule of Events and Assessment.

1.3 Sample Size

The planned sample size for this study is 120 treated subjects. It is assumed that over 75% of these subjects will complete the primary treatment phase resulting in at least 90 subjects with one year of safety data collection.

TABLE 1: SCHEDULE OF EVENTS AND ASSESSMENT

Assessments	Screening Day -14 to -11	Day 0	Wk 2 Day 14 ± 3 days	Wk 4 Day 28 ± 3 days	Wk 8 Day 56 ± 3 days	Wk 12 & 24 & 36 Day 84 / 168 / 252 ± 3 days	Wk 48 Day 336 -7/+14 days	Wk 60 & 72 & 84 Day 420 / 504 / 588 ± 7 days	Wk 56[9] or 104 EOT / Early Withdrawal Day 392 or 728 ± 7 days
Informed Consent, Demographics, Medical History, Height	X								
In/Ex Criteria	X	X							
Weight	X	X				X			X
Physical Exam[1]	X	X				X	X[11]	X	X
Vital Signs[3]	X	X				X	X	X	X
C-SSRS[4,1]	X	X	X	X	X	X	X	X	X
PGIC[2]				X	X	X	X	X	X
SF-36, HIT-6[1]	X	X		X		X	X	X	X
EQ-5D-5L[12]	X	X		X		X	X		X[10]
MBS	X	X		X	X	X	X		X[10]
MIDAS[1]		X				X	X	X	X
AE/ Con Med Review	X	X	X	X	X	X	X	X	X
ALD403 infusion[5]		X				X	X[11]	X	
12-lead ECG[7]	X	X				X	X	X	X
Hematology, Chemistry[1]	X	X				X	X	X	X
HIV/Hepatitis B and C	X								
Plasma PK[6,8]		X	X	X	X	X	X		X
Serum Anti-ALD403[6]		X	X	X	X	X	X		X
Urine Drugs of Abuse[1]	X								
Urine Pregnancy Test	X	X		X	X	X	X	X	X

[1] Conduct assessment pre-dose on Day 0 and Week 12, 24, 36, 48, 60, 72, and 84.
[2] Conduct assessment pre-dose on Week 12, 24, 36, 48, 60, 72, and 84.
[3] Conduct assessments pre-dose and up to 2 hours (+ 30 min) post-dose on Day 0 and Week 12, 24, 36, 48, 60, 72, and 84.
[4] Conduct **C-SSRS Baseline/Screening Version** at screening and **C-SSRS Since Last Visit Version** at remaining visits where C-SSRS required.
[5] Monitor subjects for at least 2 hours after the end of each dosing to assess for the occurrence of adverse events.
[6] Collect samples pre-dose on Day 0 and Week 12, 24, 36, 48, and 72. 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.
[7] Conduct assessment pre-dose, and within 2 hours (+ 30 min) post dose on Day 0 and Week 12, 24, 36, 48, 60, 72, and 84.
[8] On Day 0, collect additional sample immediately post-dose (within 15 minutes of end of infusion).
[9] Subjects who don't received all 4 infusions of ALD403 in the primary treatment phase or don't consent to participate in the secondary treatment phase will have the End of Trial/Early Withdrawal visit at Week 56.
[10] Only for subjects who have the End of Trial/Early Withdrawal visit at Week 56.
[11] Only for subjects who participate in secondary treatment phase.
[12] Conduct assessment pre-dose on Day 0 and Week 12, 24, 36, and 48.

2 STATISTICAL METHODS

2.1 Populations Analyzed

The analysis populations are defined as the following:

- Safety Population – Includes all subjects who received at least one dose of treatment.
- 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 safety, pharmacokinetic and immunogenicity of ALD403 will be assessed using the following endpoints. Greater detail concerning these endpoints can be found in Section 2.2.1.

Safety Endpoints

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

Patient Reported Outcomes:

- Patient Global Impression of Change (PGIC)
- Short-Form Health Survey (SF-36)
- Health-Related Quality of Life (EQ-5D-5L)
- Headache Impact Test (HIT-6)
- Most Bothersome Symptom (MBS)
- The Migraine Disability Assessment (MIDAS)

Pharmacokinetic and Immunogenicity Endpoints

- Free ALD403 plasma concentrations
- Development of specific anti-ALD403 antibodies
- Characterization of specific anti-ALD403 antibodies for neutralizing activity

2.2.1 Questionnaires

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. 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

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.

The Migraine Disability Assessment (MIDAS)

The MIDAS questionnaire measures the effect headaches have on the subject's daily functioning. Midas is composed of five questions that ask about the subject's performance over the past 3 months. The response to each question is provided in number of days which are totaled to determine the level of disability:

Score Range	Level of Disability
0-5	Grade I, Little or no disability
6-10	Grade II, Mild disability
11-20	Grade III, Moderate disability
21+	Grade IV, Severe disability

2.2.2 Pharmacokinetics

The concentrations of ALD403 will be measured in plasma from all treated subjects using a validated assay. The PK analysis will include evaluations of concentration-time profiles for free ALD403 on Day 0 (pre-dose and immediately post-dose (within 15 minutes of end of infusion)),

and Weeks 2, 4, 8, 12 (pre-dose), 24 (pre-dose), 36 (pre-dose), 48 (pre-dose), 72 (pre-dose) and 104 or ET.

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.

2.2.3 Immunogenicity

Serum blood samples will be taken pre-dose on Day 0, and Weeks 2, 4, 8, 12 (pre-dose), 24 (pre-dose), 36 (pre-dose), 48 (pre-dose), 72 (pre-dose), and 104 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.

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.

2.3 Trial Day

Trial endpoints will be reported within analysis windows 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 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	Closest to Target Day
Week 2	Day 8 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 126	Day 84	Closest to Target Day
Week 24	Day 127 to Day 204	Day 168	Closest to Target Day

Week 36	Day 205 to Day 288	Day 252	Closest to Target Day
Week 48	Day 289 to Day 378	Day 336	Closest to Target Day
Week 60	Day 379 to Day 462	Day 420	Closest to Target Day
Week 72	Day 463 to Day 546	Day 504	Closest to Target Day
Week 84	Day 546 to Day 630	Day 588	Closest to Target Day
Week 104	> Day 630	Day 728	Closest to Target Day

Note: If two observations are equidistant to the target day, the first observation is used.

2.4 Pooling Strategy for Strata

No pooling will be done.

2.5 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.

2.6 Statistical/Analytical Issues

2.6.1 Handling of Dropouts or Missing Data

Summary statistics will be reported based upon observed data. 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 ALD403, except if an incomplete date (e.g., month and year) clearly indicates that the event started prior to treatment.

2.6.2 Multicenter Studies

Data from all sites will be pooled for presentation.

2.6.3 Interim Analyses

This study will include a formal interim analysis after all subjects have completed the primary treatment phase (i.e. approximately a year after the last subject enters the study).

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. A subject will be considered at risk if the subject is in the analysis set and in the subgroup of interest.

Unless otherwise specified 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

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, 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 enrolled but not included in the safety 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, baseline characteristics, migraine history and concomitant medications (coded by the World Health Organization Drug Dictionary) will be summarized descriptively.

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. All medications will be provided in a listing.

3.3.5 Medical History

Medical History will be tabulated by system organ class and preferred terms using MedDRA coded terms.

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.

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.

3.4 Efficacy Analyses

The secondary endpoints of patient reported outcomes (PROs) 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 PROs collected at each visit since not all subjects will complete PROs at all visits.

3.4.1 Most Bothersome Symptom (MBS)

The change from baseline will be summarized for MBS using the Safety Population at each scheduled visit.

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

The actual score and change from baseline in each of the eight sections will be summarized using the Safety Population at each scheduled visit using descriptive statistics. Testing of the change from baseline results will be performed at Weeks 12, 24, 36, 48, 60, 72, 84 and Week 104. T-tests will be performed for the change in the Mental Component and Physical Component scores. Scoring software utilizing the 2016 norm-based scoring algorithm will be used to calculate the actual score for each of the eight sections.

3.4.3 Health-Related Quality of Life (EQ-5D-5L)

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

3.4.4 Patient Global Impression of Change (PGIC)

The change in disease status since the start of the study will be summarized for PGIC using the Safety Population at each scheduled visit.

3.4.5 Headache Impact Test (HIT-6)

The actual score and change from baseline in the total score will be summarized using the Safety Population at each scheduled visit. A shift from baseline to each scheduled visit will be tabulated. Testing of the change from baseline results will be performed at Weeks 12, 24, 36, 48, 60, 72, 84 and Week 104. T-tests will be performed based upon the change in total score.

3.4.6 The Migraine Disability Assessment (MIDAS)

The actual score and change from baseline in the total score will be summarized using the Safety Population at each scheduled visit. A shift from baseline to each scheduled visit will be tabulated. Testing of the change from baseline results will be performed at Weeks 12, 24, 36, 48, 60, 72, 84 and Week 104. T-tests will be performed based upon the change in total score.

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, immediately post-dose (within 15 minutes of end of infusion) and Weeks 2, 4, 8, 12 (pre-dose), 24 (pre-dose), 36 (pre-dose), 48 (pre-dose), 72 (pre-dose) and 104 or ET.

The concentrations of Free ALD403 will be listed and summarized by time point 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. A separate PK analysis plan with additional analyses will be created.

Population pharmacokinetic analysis will be performed, outside of this analysis plan, 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. 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 initial 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 treatment withdrawal, TEAEs leading to treatment interruption, TEAEs leading to discontinuation and deaths will be presented.

The subject incidence of TEAEs and study drug-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 and additional PTs to be determined at time of database lock;

Hypersensitivity and Anaphylactic Events

A 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 CSSRS

A 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

A 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.

A subset of adverse events with 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.

A subset of adverse events with a MedDRA coded SOC of Nervous system disorders and PTs of Seizure and Syncope.

A subset of adverse events with 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 subset of adverse events within one week of dosing with 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, maximum severity, relationship to study drug and infusion interruption status.
- 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.

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. The immune response lab results will be provided in a listing.

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.

The overall ECG interpretation based on investigator interpretation 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

3.6.5 Immunogenicity Data Analysis

Analyses will be conducted for safety population. Analysis of specific anti-ALD403 antibodies is restricted to subjects who are treated with 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 results available for the specified visit.

All the immunogenicity data 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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