Alder BioPharmaceuticals, Inc.
Clinical Trial Protocol

Clinical Trial Title	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
Protocol Number	ALD403-CLIN-006
Investigational Product	ALD403
Indication	Treatment for Prevention of Frequent Episodic Migraine Headaches
Sponsor	Alder BioPharmaceuticals, Inc. 11804 North Creek Pkwy S Bothell, WA 98011 USA Phone: +1 425-205-2900 Fax: +1 425-205-2901
Sponsor's Medical Monitor	[redacted] Alder BioPharmaceuticals, Inc. Phone: [redacted]
Clinical Trial Compliance	This clinical trial will be conducted in accordance with standards of Good Clinical Practice, as defined by the International Conference on Harmonisation and all applicable federal and local regulations.
Date of Protocol (original release)	30-June-2015
Date of Amendment 1	05-February-2016
Date of Amendment 2	14-June-2016
Date of Amendment 3	22-Nov-2016
Date of Amendment 4	24-Apr-2017

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SIGNATURE PAGE

Declaration of Sponsor

Title: 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

This clinical trial protocol was subject to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the Investigational Product, with moral ethical and scientific principles governing clinical research and in accordance with Good Clinical Practice and applicable federal and local regulations.

[redacted]

[redacted]
Date

VP, Clinical Development
Alder BioPharmaceuticals, Inc.

Declaration of the Principal Investigator

Title: 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

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Principal Investigator

_____ _____

<Name> Date
<Title>
<Institution>

1 Protocol Synopsis

Title	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
Sponsor	Alder BioPharmaceuticals, Inc.
Investigational Product	ALD403, a humanized anti-(calcitonin gene-related peptide) (CGRP) monoclonal antibody
Primary Objective	To evaluate the efficacy of repeat doses of ALD403 administered intravenously (IV) compared to placebo in patients with Frequent Episodic Migraine (FEM).
Secondary Objectives	To evaluate the safety of repeat doses of ALD403 administered IV compared to placebo in patients with FEM. To evaluate the pharmacokinetics (PK) and immunogenicity of repeat doses of ALD403 administered IV to patients with FEM.
Methodology	This is a phase 3, a parallel group, double-blind, randomized, placebo-controlled trial. Subjects will be randomized into one of three ALD403 dose levels (30 mg, 100 mg, and 300 mg) or placebo. Randomization will be stratified by migraine days during screening (≤9 days vs. >9 days). Subjects will be allocated equally to each treatment group. The total study duration is 60 weeks with 12 scheduled visits. The visits will occur on Screening, Day 0, and Weeks 4, 8, 12, 16, 20, 24, 28, 36, 48 and 56. Following the screening visit, subjects will be followed for four weeks to confirm eligibility. Once subjects are eligible, they will be randomized and treated on Day 0, which is 29-35 days after the screening visit. Patients must complete eDiary from Screening through Week 48. Study drug treatment includes four infusions of ALD403 or placebo on Days 0, 84 (Week 12), 168 (Week 24) and 252 (Week 36) with 20 weeks follow up after the final dose. 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.
Number of Subjects Planned	Approximately 800 subjects will be randomized and treated at approximately 85 centers in the US and Republic of Georgia.
Subject Selection Criteria	Males and females between 18 and 75 years of age inclusive, who were diagnosed with migraines at ≤ 50 years of age, and have a history of migraine for ≥ 12 months at a frequency of ≤ 14 headache days of which at least 4 have to be migraine days (migraine days count as headache days) per 28 day period, and have met eDiary compliance criteria during the screening period.
Investigational Product, Dose and Schedule	There will be 4 treatment groups. 1. 30 mg ALD403 administered IV on Day 0 and Week 12, 24, and 36. 2. 100 mg ALD403 administered IV on Day 0 and Week 12, 24, and 36. 3. 300 mg ALD403 administered IV on Day 0 and Week 12, 24, and 36. 4. Placebo administered IV on Day 0 and Week 12, 24, and 36.
Duration of Treatment	Four doses of ALD403/placebo will be given 12 weeks apart.
Duration of Clinical Trial Participation	The trial participation period will be 60 weeks, which will include a 4 week screening period, randomization and the start of treatment on Day 0, dosing at Week 12, 24 and 36 with 20 weeks of post-dose follow-up at Week 56.
Clinical Trial Endpoints	Primary Efficacy Endpoint • Change in frequency of migraine days (Weeks 1-12) Key Secondary 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 Endpoints

- Change in acute migraine medication days (Weeks 1-12)
- Headache/migraines with acute medication usage
- 100% migraine responder rates (Weeks 1-12)
- Short-Form Health Survey (SF-36)
- 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

Safety Endpoints

- Adverse events (AEs) and serious adverse events (SAEs)
- Changes in Clinical laboratory assessments
- Vital Signs
- Electrocardiogram (ECGs)
- Suicidal ideation and behavior as measured by the C-SSRS

Pharmacokinetic and Immunogenicity Endpoints

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

Concomitant Medications	• Concomitant medications must be recorded in the Case Report Form (CRF) through Week 56. The following medications are restricted through Week 24: Any prophylactic headache medication is prohibited and its regular use (greater than 7 days) is not allowed within 2 months prior to screening through randomization (medication details in Section 15.1). • Short-term (no more than 7 days in a month) menstrual migraine prophylactics are allowed. • Additional restriction applies to the following medications: barbiturates and opiates are allowed for ≤ 4 days per month through Week 24, provided the subject does not meet the criteria for Medication Overuse Headache overall and has been on a stable regimen (≤ 4 days per month) for at least 2 months prior to screening. • Any botulinum toxin injections for migraine or for any other medical/cosmetic reasons requiring injections in the head, face, or neck are prohibited within 4 months prior to screening and through Week 24. • Devices, neuromodulation, neurostimulation, or injectable therapy (trigger point injections, extracranial nerve blocks, facet joint injections) for headache prophylaxis are prohibited within 2 months prior to screening and through Week 24.
Sample Size	The planned sample size for this study 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. Testing will be at the 5% alpha level. Two hundred subjects per group provides at least 95% power for the change from baseline tests individually assuming a treatment effect of at least 1 day and a common standard deviation of 2.7 days or less. For the key secondary 75% responder rate endpoints 95% power is achieved for the pair-wise comparisons, the 75% responder rates are 24% for placebo and 42% for ALD403.
Statistical Analysis	The primary periods for efficacy and safety for this study are through Week 12 and 24, respectively. The primary efficacy

evaluations will encompass results from Weeks 1-12. Following Week 24, the study will continue so that long term safety data can be captured. The efficacy analyses are based upon migraine days. A migraine day is defined as any day with a migraine or probable migraine as outlined in the IHS classification ICHD-II. (migraine without aura, Section 1.1[11]). Specifically, a migraine is defined as a self-reported headache which meets each of the following conditions:

1) lasted 4 to 72 hours
2) had at least 2 of the following: unilateral location, pulsating quality, moderate or severe pain intensity and/or aggravation by or causing avoidance of routine physical activity, and
3) had at least 1 of the following: nausea and/or vomiting and/or photophobia and phonophobia.

A probable migraine is defined as a headache that meets only 2 of the 3 criteria listed above. The migraine days reported during the initial 28-days following screening will be used as baseline. Following treatment, migraine data will be summarized and analyzed in 4 week intervals, 12 week intervals and a 24 week interval. A 75% responder for a given four week interval will be a subject with at least a 75% reduction in migraine days during that interval. A 75% responder over a 12 week interval will be a subject who achieves an average reduction of 75% over the twelve weeks. The 50% and 100% responder rates are similarly defined. The 12 weeks average change from baseline in frequency of migraine days is the average change from baseline in each of the 4 weeks intervals that make up weeks 1-12. Subjects who do not complete their migraine eDiary will have their missing data imputed.

Efficacy and safety endpoints will be summarized with descriptive statistics. Testing of the key secondary responder rate endpoints and the primary Weeks 1-12, change from baseline in migraine day endpoint will be performed. The testing of the primary endpoint will be with an ANCOVA. The key secondary responder rate and percentage of subjects with a migraine on the day after dosing endpoints will be tested

	with a Cochran Mantel Haenszel (CMH) test controlling for the randomization stratification factor.
Pharmacokinetic and Immunogenicity Analyses	The concentrations of Free ALD403 will be measured in plasma from all ALD403 treated subjects using validated assay methods. The PK analysis of plasma will include determination of the Free ALD403 concentrations at the following times: Day 0 Weeks 4, 8, 12, 16, 20, 24, 36, 48 and 56. The PK plasma samples will be collected pre-dose within 1 hr before dosing on Day 0, and Weeks 12, 24 and 36. For subjects receiving placebo, selected samples will be analysed. Blood will be taken for the detection of anti-ALD403 antibody, and when appropriate neutralizing anti-ALD403 antibody, at the following times: Day 0, Weeks 4, 8, 12 16, 20, 24, 36, 48 and 56. Subjects who test positive for specific anti-ALD403 antibodies at the time of the last study visit will be asked to provide additional blood samples for immunogenicity testing. The anti-ALD403 antibody blood samples will be collected pre-dose within 1 hour before dosing on Day 0, and Weeks 12, 24 and 36.

2 Schedule of Events and Assessments

		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[11] D168 + 3 Tx**	**Wk 28 D196 ± 7**	**Wk 36 D252 ± 3 Tx**	**Wk 48[12] D336 +7**	**Wk 56 EOS/ET D392 ± 7[13]**
Informed Consent	X											
In/Ex Criteria	X	X										
Demographics	X											
Medical History	X											
Headache eDiary Review and Compliance Check[1]	X	X	X	X	X	X	X	X	X	X	X	
Hgt/Wgt[2]	X	X						X		X		X
Physical Exam[3]	X	X						X		X		X
Brush Allodynia Test		X	X		X	X	X	X				
Vital Signs[4]	X	X	X	X	X	X	X	X	X	X	X	X
BDI-II	X											
C-SSRS[5]	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[4]	X	X	X	X	X			X	X	X	X	X
Hem/Chem[6]	X	X	X		X			X	X	X	X	X
HIV/Hepatitis B and C	X											
Urine Drugs Abuse Screen[7]	X											
Urine Preg (hCG) Test	X	X			X			X		X	X	X
Plasma ALD403 (PK)[8]		X	X	X	X	X	X	X		X	X	X
Serum Anti-ALD403 Ab[9]		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 Review	X	X	X	X	X	X	X	X	X	X	X	X
Con Meds Review	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X										
ALD403/placebo administration[10]		X			X			X		X		

Abbreviations: TX: Treatment, Rand: Randomization, EOS/ET: End of Study/Early Termination

Please refer to next page for footnotes.

[1]Headache eDiary distributed at screening. eDiary review and compliance check through Week 48.

[2]Height and Weight on Screening visit. Weight only on Day 0, Weeks 24, 36 and 56.

[3]Physical exam must be done pre-dose on Day 0, Week 24, and 36.

[4]Vital signs and 12-lead ECG pre-dose and 4 hours post-dose (± 30 minutes) on Day 0, Weeks 12, 24 and 36.

[5]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.

[6]All blood draws obtained pre-dose on dosing days.

[7]"International Classification of Diseases (ICD)". World Health Organization. Retrieved 23 November 2010.

[8]Sample for Plasma Free ALD403 drawn pre-dose on dosing days (within 1 hour prior to dosing).

[9]Sample for anti-ALD403 antibody drawn pre-dose on dosing days (within 1 hour prior to dosing).

[10] Subjects must be monitored for at least 4 hours after the dosing completion.

[11]Week 24 must be done on the target day or 3 days after. Three days earlier than target date is not allowed.

[12]Week 48 must be done on the target day or seven days after. Seven days earlier than target date is not allowed.

[13]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 approximately 3 month intervals for up to 6 months.

3 List of Abbreviations

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of Covariance
ASC-12	Allodynia Symptom Checklist
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0\text{-inf}}$	Area under the concentration-time curve from time=0 to infinity
$AUC_{0\text{-tlast}}$	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
BDI-II	Beck Depression Inventory
BMI	Body Mass Index
CGRP	Calcitonin Gene-Related Peptide
CMH	Cochran–Mantel–Haenszel
Cavg	Average steady-state concentration; computed as $AUC_{(0\text{-Tau})/Tau}$
C_{max}	Peak plasma concentration
C_{min}	Minimum concentration between 0 and Tau at steady-state
CL	Total body clearance
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
DNA	Deoxyribonucleic acid
EC	Ethics Committee
EQ-5D-5L	Health-Related Quality of Life
FDA	Food and Drug Administration
FEM	Frequent Episodic Migraine
hCG	Human chorionic gonadotropin
IB	Investigator Brochure
ICD	International Classification of Diseases
ICHD	International Classification of Headache Disorders
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IHS	International Headache Society
IgG1	Immunoglobulin G1
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
L	Liter

LLOQ	Lower Limit of Quantification
M	Molarity
m^2	Meter squared
mAb	Monoclonal antibody
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
mm	Millimeter
mM	Millimolar
msec	Milliseconds
NAb	Neutralizing antibody
NOAEL	No-observed-adverse-effect-level
NSAID	Non-steroidal anti-inflammatory drug
OTC	Over-The-Counter
PK	Pharmacokinetic
QTcF	QT corrected using Fridericia formula
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SF-36	Short Form Health Survey
SOP	Standard Operating Procedure
Tau	The dosing interval for steady-state data
$t_{½}$	Elimination half-life during the terminal elimination phase
T_{max}	Time to peak plasma concentration
TEAE	Treatment-emergent adverse event
TMD	Temporo-mandibular Disorders
TMF	Trial Master File
ULN	Upper limit of normal
Vz	Apparent volume of distribution during the terminal elimination phase
WBC	White blood cell
WHO	World Health Organization
µg	Micrograms

4 Table of Contents

5 Introduction

5.1 Investigational Product

ALD403 is a humanized anti-(calcitonin gene-related peptide) (CGRP) monoclonal antibody (anti-CGRP) that is being developed by Alder BioPharmaceuticals, Inc. for the prophylaxis of migraine.

5.2 Background

According to the International Classification of Headache Disorder, migraine is a common disabling primary headache disorder manifesting in attacks lasting 4 to 72 hours. Migraine headaches range from moderate to very severe and are debilitating. Episodic migraine affects 17 percent of women and 6 percent of men. Migraine frequency is divided into episodic and chronic episodic migraine is characterized by <15 migraine days and chronic migraine by ≥15 headache days per month of which 8 or more must be migraine days. All migraine types significantly affect the physical, psychological, and social well-being of patients, and can impose serious lifestyle restrictions. Each year lost work time and diminished productivity from migraine costs American employers $225.8 billion. Forty percent of adults with episodic migraine and all patients with chronic migraine might benefit from preventive medication; yet, only about 12 percent of adults with migraines take preventive medication. This is largely due to poor tolerability and/or lack of efficacy of currently marketed drugs for the prevention of migraine. There is therefore a need for new therapeutic alternatives[1].

CGRP is a member of the calcitonin family of peptides, which in humans exists in two forms, α-CGRP and β-CGRP. α-CGRP is a 37-amino acid peptide and is formed from the alternative splicing of the calcitonin/CGRP gene located on chromosome 11. The less-studied β-CGRP differs in three amino acids (in humans) and is encoded in a separate gene in the same vicinity of the genome.

CGRP is one of the most abundant peptides produced in both peripheral and central neurons. It is the most potent peptide vasodilator and can function in the transmission of pain. In the spinal cord, the function and expression of CGRP may differ depending on the location of synthesis. CGRP is derived mainly from the cell bodies of motor neurons when synthesized in the ventral horn of the spinal cord and may contribute to the regeneration of nervous tissue after injury.

Conversely, CGRP is derived from dorsal root ganglion when synthesized in the dorsal horn of the spinal cord and may be linked to the transmission of pain. In the trigeminal vascular system, the cell bodies on the trigeminal ganglion are the main source of CGRP where it is thought to have a role in cardiovascular homeostasis and nociception.[2]

CGRP 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. [3, 4]

During migraine attacks, there is an increase in the plasma levels of CGRP in the external jugular vein. [5] In addition, intravenous (IV) infusion of CGRP causes migraine and headache in patients with migraine, suggesting that the increase in CGRP observed during spontaneous migraine attacks plays a causative role.[6]

CGRP is thought to play an important role in migraine by facilitating the transmission of migraine pain, thereby contributing to the induction of the pronociceptive stage through modulation of the central nervous system (CNS).[4, 5] Studies in animals and humans indicate that the trigeminal ganglion and the trigeminal nucleus caudalis are likely to be sites of action of CGRP in migraine. In addition, CGRP is expressed in many locations within the CNS, including regions that may be relevant to migraine pain. [7, 8]

CGRP dilates intracranial and extracranial blood vessels, and can additionally activate adjacent mast cells, which leads to the secretion of vasoactive, proinflammatory, and sensitizing mediators, thereby contributing to migraine pathogenesis. [9, 10]

5.3 Investigational Product

ALD403 is a genetically engineered humanized immunoglobulin G1 (IgG1) antibody that binds to human-α-CGRP with an affinity of 1.5E-11 M and human-β-CGRP with an affinity of 5.7E-11 M.

5.3.1 Summary of Nonclinical Studies

A nonclinical testing program has been conducted supporting the use of ALD403 in clinical trials. More detailed discussion is provided in the current version of the ALD403 Investigator's Brochure (IB).

ALD403 is a genetically engineered humanized IgG1 antibody that binds to α- and β- forms of human, cynomolgus monkey, and rat CGRP. The amino acid sequence for α- and β-CGRP is identical in cynomolgus monkeys and humans (data on file); therefore the *in vitro* binding characteristics of cynomolgus monkey and human CGRP to ALD403 would be indistinguishable. Rat α-CGRP is one amino acid different from human α-CGRP and rat β-CGRP is 3 amino acids different from human β-CGRP. Based on comparable binding affinity and *in vitro* potency for rat, cynomolgus monkey, and human α- and β-CGRP, the rat and cynomolgus monkey were selected for nonclinical safety assessments.

Pharmacodynamic activity by ALD403 in the species selected for toxicological investigations (rats, rabbits, and monkeys) was confirmed in vivo by conducting studies to determine the ability of ALD403 to inhibit CGRP-mediated neurogenic dermal vasodilation. In rats, changes in dermal blood perfusion were measured using Laser Doppler, while in rabbits and monkeys a Laser Speckle Contrast Analysis (LASCA) imaging system was utilized. The parenteral administration of ALD403 inhibited increases in dermal blood perfusion induced by topical capsaicin in rats and cynomolgus monkeys, and intravenous ALD403 administration in rabbits inhibited increased dermal blood perfusion secondary to intradermal β-CGRP challenge.

The toxicokinetic profile for ALD403 has been evaluated following single and once weekly repeated-dose IV administrations for four weeks in rats and cynomolgus monkeys, and following administration once every two weeks for 6-months in cynomolgus monkeys.

The plasma concentration profiles for ALD403 following single or repeated-dose IV administrations in rats or cynomolgus monkeys were characterized by an apparent mono-exponential decline. The plasma half-life for ALD403 ranged between 102-155 hours following single administration in rats, and 142 to 323 hours following single or multiple weekly administrations in cynomolgus monkeys. The distribution for ALD403 appeared limited to the vascular compartment, and the systemic exposure was dose proportional from 10 to 150 mg/kg/dose. No gender differences were observed among any of the toxicokinetic parameters evaluated.

In the single-dose nonclinical toxicology studies, the no-observed-adverse-effect-level (NOAEL) for IV administration of ALD403 to rats and cynomolgus monkeys was 100 mg/kg.

Toxicological investigations in rats and monkeys indicated that repeated-dose IV administration of ALD403 at 10, 30, or 100 mg/kg once weekly for four weeks was well tolerated, with no signs of adverse effects related to treatment. Under the conditions of these studies, the no-observed-adverse-effect-level (NOAEL) for once weekly IV administration of ALD403 to rats or monkeys for four weeks was 100 mg/kg.

A chronic multiple-dose toxicology study in cynomolgus monkeys was conducted to evaluate the potential effects by ALD403 following 6-months administration via slow bolus injection once every two weeks (a total of fourteen dosing occasions) at 0, 20, 50, or 150 mg/kg/dose followed by a three month recovery period in select animals.

The following parameters were evaluated in this study: clinical signs, body weights, food consumption, blood pressure, heart rate, and body temperature, ophthalmology, electrocardiology, clinical pathology parameters (hematology, coagulation, clinical chemistry, and urinalysis), insulin analysis, flow cytometry parameters, toxicokinetic parameters and anti-drug antibody (ADA) formation, gross necropsy findings, organ weights, and histopathologic examinations.

Following the sixth dosing occasion on study day 71, one low-dose (20 mg/kg/dose) female animal exhibited an anaphylactoid-like reaction and died within approximately 30 minutes. Collectively, the clinical, gross, and microscopic findings were consistent with an ADA-mediated anaphylactoid event as the cause of death. Humanized monoclonal antibodies are known for their potential to illicit severe immunologic reactions in monkeys and therefore, the death of one animal was considered a class effect and was not included in the determination of the no-adverse-effect-level (NOAEL).

There were no ALD403-related clinical signs or changes in body weight, food consumption, ophthalmology, electrocardiology, blood pressure, heart rate, body temperature, clinical pathology, insulin, or flow cytometry parameters. There were no ALD403-related effects on organ weights or organ weight ratios. Additionally, there were no ALD403-related macroscopic or microscopic changes.

The presence of ADA was confirmed in 5/10 (50%) animals from the 20 mg/kg group, 5/10 (50%) animals from the 50 mg/kg group, and 11/14 (79%) animals from the 150 mg/kg group.

Considering that the ALD403 exposure did not decrease after repeated administration and that the exposure of ADA positive animals was not notably or consistently different from ADA negative animals, the presence of ADA did not appear to impact exposure.

Administration of ALD403 via intravenous (slow bolus) injection once every 2 weeks for approximately 6-months (for a total of 14 doses) did not result in any treatment-related effects upon the parameters evaluated in this study. The NOAEL for ALD403 following chronic administration in monkeys was considered to be 150 mg/kg/dose (Day 183 mean C_{max} of 19,600/6,160 µg/mL; mean $AUC_{(0\text{-}2wk)}$ of 1,610,000/904,000 µg·h/mL for males/females, respectively).

ALD403 is not expected to interact directly with DNA or other chromosomal materials, and genotoxicity assessments have not been conducted. The carcinogenic potential for ALD403 has not been thoroughly investigated. The results of toxicological and clinical investigations to date with ALD403 have provided no indications of effects with the potential to support or induce the proliferation of malignant cells.

Range-finding embryo-fetal development studies with ALD403 have been completed to support the selection of dosages for use in definitive studies. The administration of ALD403 by intravenous (slow bolus) injection to pregnant female rats on Days 6, 12 and 18 post coitum or pregnant female New Zealand White rabbits on Days 7, 13 and 20 post coitum, at 75 or 150 mg/kg/dose was well tolerated, and there was no evidence of embryo-fetal mortality (embryolethality), alterations in growth (fetotoxicity), or structural abnormalities (teratogenicity) in either species. The definitive embryo-fetal development studies with ALD403 in pregnant rats and rabbits are currently in progress.

The local tolerance of ALD403 was assessed following repeated-(once weekly) dose studies in rats and cynomolgus monkeys utilizing ALD403 administered IV. Following the end-of-treatment, no gross or microscopic lesions were observed in the ALD403 injection sites excised from rats. In the injection sites obtained from cynomolgus monkeys, only procedure-related findings were observed and included (in order of decreasing incidence) minimal and/or mild superficial perivascular infiltrates, fibroplasia/fibrosis, myointimal hyperplasia of the injected vein, hemorrhage, and sporadic observations in the epidermis and skeletal muscle.

5.3.2 Summary of Clinical Trials

Detailed descriptions of the relevant clinical findings for ALD403 are provided in the Investigator's Brochure (IB).

A summary of completed and ongoing ALD403 clinical trials is shown in Table 5.3

Table 5.3 ALD403 Clinical Trials

Trial ID	Phase/Objective	Trial Subject Population	Total Number of Subjects in the Trial	Number of Subjects Randomized to ALD403	Number of Subjects Randomized to Placebo
ALD403-CLIN-001 (completed)	Phase 1 Safety	Healthy Volunteer[1]	104	67	37
ALD403-CLIN-002 (completed)	Phase 1b Safety & Efficacy	Frequent Episodic Migraine	163	81	82
ALD403-CLIN-003 (completed)	Phase 1 Safety	Healthy Volunteer	60	36	24
ALD403-CLIN-007 (ongoing)	Phase 1 (Safety)	Healthy Volunteer	60	49	11
ALD403-CLIN-009 (ongoing)	Phase 1 (Safety)	Healthy Volunteer	36	24	12
ALD403-CLIN-005[2] (ongoing)	Phase 2 Safety & Efficacy	Chronic Migraine	616		
ALD403-CLIN-006[2] (ongoing)	Phase 3 Safety & Efficacy	Frequent Episodic Migraine	800 (planned)		
ALD403-CLIN-011 (ongoing)	Phase 3 Safety & Efficacy	Chronic Migraine	1050 (planned)		
ALD403-CLIN-013 (ongoing)	Phase 2 Safety	Chronic Migraine	128	128	NA

[1] ALD403-CLIN-001 included a subset of seven migraine subjects.

[2] Enrollment in this blinded clinical trial has been completed and subjects are in the follow-up phase of the trial.

5.3.3 Dose Justification

In study ALD403-CLIN-002, a single intravenous infusion of 1000 mg ALD403 produced sustained efficacy in terms of mean change from baseline in migraine days and the responder analysis. The mean Free ALD403 (ALD403 available for binding to the CGRP ligand) plasma concentrations observed at weeks 12 and 24 in subjects receiving 1000 mg ALD403 were

25.6 and 3.4 µg/mL, respectively. Results from a prior study, ALD403-CLIN-001, demonstrated marked suppression of capsaicin-induced skin blood flow at doses ranging from 30-1000 mg ALD403 given as a single intravenous infusion. Prolonged suppression of capsaicin-induced skin blood flow for 12 weeks was observed following IV infusion of ≥ 100 mg ALD403.

The ALD403-CLIN-006 study design will explore ALD403 given by repeat IV administration at doses of 30, 100, and 300 mg every 12-weeks.

For subjects participating in ALD403-CLIN-006 at the highest dose level, 300 mg ALD403 administered by IV infusion every 12-weeks, the estimated systemic exposure to Free ALD403 following the last (fourth) administration is C_{max} = 110.2 µg/mL and $AUC_{(0\text{-}12wk)}$ = 46,648 µg*hr/mL. These ALD403 exposure levels are at least 56- and 19-fold less than the mean C_{max} and $AUC_{(0\text{-}2Wk)}$ systemic exposures, 19,600 µg/mL in males and 6,160 µg/mL in females, and 1,610,000 µg*hr/mL in males and 904,000 µg*hr/mL in females, respectively, observed in cynomolgus monkeys following a chronic 6-month evaluation of ALD403 administered IV at the no-observed-adverse-effect-level (NOAEL) of 150 mg/kg once every 2-weeks.

The high dose of 300 mg administered during ALD403-CLIN-006 is expected to provide efficacious treatment in FEM. The low and mid doses, 30 and 100 mg ALD403, respectively, were selected to explore the potential for dose-related efficacy following ALD403 treatment.

5.4 Risks and Benefits

ALD403 may prevent migraine from occurring in patients treated in this trial. No specific toxicities or adverse effects related to the blockade of CGRP by ALD403 have been identified in either the nonclinical toxicology program or the clinical trials with ALD403 that have been completed to date.

There may be unknown adverse effects and unforeseeable risks associated with study drug administration or unexpected interactions with another drug that have not yet been identified.

As with all protein therapeutics, there is a risk of a serious allergic reaction. In completed ALD403 trials conducted to date, no serious allergic reactions have been observed with the administration of ALD403 in humans.

In the completed ALD403 clinical trials with headache patients, the most common observed adverse events (>5%) with receiving ALD403 or placebo included upper respiratory tract infection, back pain, dizziness, arthralgia, urinary tract infection, and headache. The majority of these adverse events were categorized as mild to moderate.

Long term data with ALD403 is limited.

- Healthy volunteer trials have included limited dosing, short duration of follow up and have not include long term follow-up.
- Trials in migraine patients have also included limiting dosing. These trials are currently ongoing and no new significant findings have been noted during the follow-up period to date.

The safety findings to date indicate that ALD403 Injection is well tolerated, with ALD403 demonstrating a favorable benefit-risk profile based on review of nonclinical, clinical, and scientific literature data.

The sponsor will continue to monitor for significant new information and suspected adverse reactions associated with the use of ALD403.

5.5 Compliance Statement

This clinical trial will be conducted in accordance with standards of Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and all applicable federal and local regulations.

6 Objectives

6.1.1 Primary Objective

The primary objective is:

- To evaluate the efficacy of repeat doses of ALD403 administered IV compared to placebo in patients with FEM.

6.1.2 Secondary Objectives

The secondary objectives include the following:

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

7 Trial Design

7.1 Clinical Trial Endpoints

More detail regarding the clinical trial endpoints and their derivation can be found in Section 12.1. Migraine headaches for the efficacy endpoints are defined as migraines or probable migraines as outlined in the International Headache Society (IHS), International Classification of Headache Disorders (ICHD II 2004-II), Section 1.1 and 1.6.[11] The presence or absence of aura will not impact the classification of a headache as a migraine.

7.1.1 Primary Efficacy Endpoint

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

7.1.2 Key Secondary 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

7.1.3 Other Secondary Endpoints

- Change in acute migraine medication days (Weeks 1-12)
- Headache/migraines with acute medication usage
- 100% migraine responder rates (Weeks 1-12)
- Short-Form Health Survey (SF-36)
- 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

7.1.4 Tertiary Endpoints

- Headache episodes/migraine attacks

7.1.5 Safety Endpoints

- Adverse events (AEs) and serious adverse events (SAEs)
- Changes in clinical laboratory assessments
- Vital signs
- Electrocardiogram (ECGs)
- Suicidal ideation and behavior as measured by the C-SSRS

7.1.6 Pharmacokinetic Endpoints

- Free ALD403 plasma concentrations

7.1.7 Immunogenicity Endpoints

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

7.2 Clinical Trial Design

This is a phase 3, 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 subject will be instructed to complete the eDiary daily from the screening visit through Week 48. During the screening period, an eDiary Eligibility Report will calculate headache and migraine results, and provide an eDiary compliance report. The headache and compliance data from the eDiary will be made available to and reviewed by the clinical site on a regular basis via the eDiary system portal. 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. Any subject found to be no longer eligible for the study 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 presented in Section 2.

7.3 Data Monitoring Committee

A Data Monitoring Committee (DMC), which includes appropriately qualified members who are independent of the Sponsor, will be formed to consider safety data generated during the clinical trial. These members will be appointed externally by the Sponsor, and will not be connected with management of the clinical trial.

The primary focus of the DMC will be the safety experience of the clinical trial subjects. Based on the reviews and assessments of the data, the DMC will inform the Sponsor of any safety concerns and provide recommendations about stopping, modifying, or continuing the clinical trial. The DMC may also advise the Sponsor on the validity of continuing the trial and the scientific merit of the clinical trial. The DMC is not tasked with stopping the study early for efficacy. DMC analyses will be conducted periodically through-out the study.

7.4 Methods to Minimize/Avoid Bias

To minimize bias, this clinical trial is randomized, double-blind and placebo controlled. At the point of infusion, there are no obvious differences between ALD403 and placebo, and there are

no known ALD403-specific safety or tolerability signals that could potentially unblind subjects and clinical trial staff. ALD403 is expected to have a fairly substantial impact on migraine frequency; however, the placebo effect in migraine studies is also reasonably large therefore, reduction in migraines is insufficient to deduce treatment assignment.

8 Selection and Withdrawal of Subjects

8.1 Inclusion Criteria

A subject must meet all of the following criteria within the 28 days prior to randomization to be eligible for inclusion in the trial:

1. Willing and able to read and understand the consent process and sign an Informed Consent Form (ICF) for the clinical trial approved by the Investigator's local Review Board or a central Institutional Review Board (IRB) or Ethics Committee (EC)
2. Male or female between 18 and 75 years of age inclusive (age determined at time of informed consent)
3. Diagnosis of migraine at ≤ 50 years of age (ICHD-II, 2004 Section 1 [11])
4. History of migraine ≥ 12 months with
    a. ≤ 14 headache days of which at least 4 have to be migraine days (migraine days count as headache days) in each 28 day period in the 3 months prior to screening
    b. During the 28 days following the screening visit, the subject experiences ≤ 14 headache days of which at least 4 have to be migraine days (migraine days count as headache days) as recorded in the eDiary;
5. Use of acute migraine medications ≤ 14 days per 28 day period in the 3 months prior to screening and the 28 day period prior to randomization
6. Use of triptans must be ≤ 10 days per 28 day period in the 3 months prior to screening and the 28 day period prior to randomization
7. No regular use (greater than 7 days) of prophylactic headache medication (any preventive medication or supplement with evidence of efficacy from at least 1 placebo-controlled trial, see Section 15.1) within 2 months prior to screening and during the

28 day period prior to randomization; short-term (no more than 7 days in a month) menstrual migraine prophylactics are allowed

8. No use of any botulinum toxin for migraine or for any other medical/cosmetic reasons requiring injections in the head, face, or neck 4 months prior to screening and during the 28 day period prior to randomization
9. Limited use of barbiturates (including Fiorinal®, Fioricet®, or any other combination containing butalbital) and prescription opiates by maintaining stable dose for 2 months prior to screening and dosing does not exceed 4 days per month through Week 24. (as outlined in Section 9.4), Drugs containing non-prescription codeine (16 mg or less) are permitted.
10. Not to use any approved devices, neuromodulation, neurostimulation or injectable therapy (trigger point injections, extracranial nerve blocks, facet joint injections) for headache prophylaxis are prohibited 2 months prior to screening and during the 28 day period prior to randomization
11. Women of child-bearing potential, and males with partners of child-bearing potential, must agree to use adequate contraception throughout study participation and for up to six months after last dose. Adequate contraception includes oral, transdermal or injectable [depot] estrogen, and/or progestogen, selective estrogen receptor modulator contraceptive therapy, intrauterine contraceptive device, double barrier method (e.g., condom and diaphragm or spermicidal gel) or vasectomy. Non-childbearing potential is defined as post-menopausal for at least 1 year or surgical sterilization or hysterectomy at least 3 months before screening.
12. Any hormonal therapy (e.g., contraceptives, hormone replacement therapy) use is stable and ongoing for at least 3 months prior to screening and through Week 56
13. Willing, committed, and able to comply with scheduled clinic visits and complete all trial-related procedures
14. Headache eDiary was completed on at least 25 of the 28 days prior to randomization

15. Subject agrees not to post any personal medical data related to the trial or information related to the trial on any website or social media site (e.g., Facebook, Twitter) during the trial
16. Subject is willing to complete the daily eDiary for the duration of the study and agrees to use the eDiary device for the sole purpose of the ALD403-CLIN-006 study without alteration

8.2 Exclusion Criteria

A subject who meets any of the following criteria will be excluded from the trial:

1. Confounding pain syndromes, e.g. fibromyalgia, complex regional pain syndrome or any pain syndrome that requires regular analgesia
2. Psychiatric conditions that are uncontrolled and untreated, including conditions that are not controlled for a minimum of 6 months prior to screening
3. Known or suspected Temporo-Mandibular Disorders (TMD)
4. History or diagnosis of complicated migraine (ICHD- II, 2004 Section 1 [11]), chronic tension-type headache, hypnic headache, cluster headache, hemicrania continua, new daily persistent headache, migraine with brainstem aura, sporadic and familial hemiplegic migraine
5. Unable to differentiate migraine from other headaches
6. Have present or previous malignancies, except:
    - Subjects with a history of squamous or basal skin cell carcinoma with excision for cure
    - Subjects with a history of breast or cervical cancer ≥ 10 years since diagnosis/treatment without evidence of recurrence
7. Cardiovascular disease (hypertension, ischemic heart disease), neurological disease, cerebrovascular disease, diabetes, or Raynaud's disease, life-threatening allergy (e.g, anaphylaxis); if questions arise, the Investigator should contact the Medical Monitor for guidance

8. Have a clinically significant abnormal ECG at screening or pre-dose on Day 0. An alert for a clinically significant abnormality will be set at the following interval values:
   - RR < 460 msec (or HR > 130 bpm)
   - RR > 1700 msec (or HR < 35 bpm)
   - QRS > 180 msec
   - QTcF > 500 msec (or any other QTc method if QTcF is not utilized)
9. Have any clinically significant concurrent medical condition as shown by, but not limited to:

   Hepatic
   - ALT ≥ 2 x ULN; AST ≥ 2 x ULN

   Hematology
   - Hemoglobin < 10 g/dL
   - Absolute neutrophil count < 1000cells/µL
   - Platelet count < 100,000 cells/µL (patients with 75,000-100,000 cells/ µL can be considered for enrollment if there are no comorbid conditions; contact Medical Monitor prior to enrollment)

   Renal
   - Creatinine > 2.0 mg/dL
10. Systolic blood pressure (BP) 140 mm Hg and/or diastolic BP 90 mm Hg or greater at Treatment/Day 0 (can repeat 15 minutes later to confirm)
11. Beck Depression Inventory (BDI-II) score >24 at screening
12. The subject is at imminent risk of self-harm or harm to others in the investigator's opinion, based on clinical interview and responses provided on the Columbia-Suicide Severity Rating Scale (C-SSRS). Subjects must be excluded if they report suicidal ideation of Type 4 or 5 (i.e., suicidal ideation with intent, with or without a plan) in the past 6 months or suicidal behavior in the past 2 years, as measured by the C-SSRS at Screening or Baseline.
13. Any history or evidence of substance abuse (e.g., alcohol, opiates, and barbiturates) within the past 2 years according to the International Classification of Diseases (ICD) 10: F10-19.[12]

14. Pregnant, breastfeeding, or planning to become pregnant during the trial
15. Receipt of any experimental, unregistered therapy (within or outside a clinical trial) within 30 days or 5 plasma half-lives (whichever is longer) before screening
16. Receipt of any monoclonal antibody treatment within 6 months of screening (within or outside a clinical trial)
17. Previously dosed with ALD403 or any monoclonal antibody targeting the CGRP pathway
18. Planned or current participation in any other clinical trial during the duration of this clinical trial, or within 6 months of screening
19. Recent or planned surgery, requiring general anesthesia, within 8 weeks prior to screening and during the duration of this clinical trial
20. Positive for HIV, hepatitis B surface antigen, or hepatitis C antibody at screening
21. Employees of the sponsor, CRO, or any clinical trial site involved in this trial and their immediate family members (i.e., parents, spouse, siblings, children)

8.3 Registration and Treatment Assignment

8.3.1 Registration Procedure, Subject Numbering

Each participating investigative site will be assigned a 3-digit site number (e.g., 101, 102). At the Screening Visit once the ICF is signed, a subject will be assigned a unique subject number. The first part of the subject number identifies the site and the second part identifies the subject.

8.3.2 Randomization and Treatment Assignment

Randomization will occur 29 to 35 days after the screening visit after eligibility assessments are completed and eligibility verified. Sites will complete the randomization in an Interactive Web or Voice Response System (IWRS or IVRS) 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 dose groups. 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.

8.4 Subject Treatment Discontinuation and Withdrawal

Subjects may discontinue treatment or withdraw from the clinical trial at any time without penalty and for any reason without prejudice to his or her future medical care.

8.4.1 Criteria for Discontinuation from Study Treatment

Study treatment may be discontinued for the following reasons:

- Adverse Event
- Subject decision
- Investigator decision
- Subject lost to follow-up
- Termination of the study by the sponsor

If subjects discontinue from study treatment due to a medical condition, investigators must provide adequate medical treatment during the follow up visits. Prior to removing a subject from study treatment, the decision should be discussed with the Sponsor Medical Monitor or designee. The reason for discontinuation from study treatment must be recorded on the CRF. Subjects who discontinue study treatment will be encouraged to continue with study assessments until the end of the study.

8.4.2 Criteria for Withdrawal from Clinical Trial

Subjects will be withdrawn from the clinical trial for any of the following reasons:

- Withdrawal of consent for the collection of clinical trial data including further access to medical records. The reason for withdrawal of consent will be recorded.
- Termination of the trial by the Sponsor
- Investigator decision
- Lost to follow-up

The reason for withdrawal and the time of withdrawal must be recorded on the CRF.

8.4.3 Timing of Withdrawal

Subjects are considered withdrawn from the clinical trial at the time that any of the criteria listed in Section 8.4.2 are met.

8.4.4 Follow-up for Early Withdrawal

Subjects, who wish to withdraw their consent to have their medical information collected, will be asked to have an early termination visit, with associated visit assessments (see Schedule of Events in Section 2). Subjects who withdraw consent after randomization, but do not receive study treatment, may discontinue the study without any further procedures.

8.4.5 Replacement Policy

Subjects who are withdrawn from the clinical trial after randomization will not be replaced, including subjects who withdraw between randomization and treatment. However, the target sample size is based upon the number of subjects randomized and treated.

9 Clinical Trial Treatments

9.1 Investigational Product

ALD403 is an anti-(calcitonin gene-related peptide) humanized monoclonal antibody (anti-CGRP mAb) that is being developed by Alder BioPharmaceuticals, Inc., for the prophylaxis of migraine.

ALD403 Injection, 100 mg/vial, is presented in 2-mL Type I glass vials as a single-use preservative-free solution for IV administration. ALD403 is formulated at a concentration of 100 mg/mL with a pH of 5.8. Those subjects randomized to active will receive an IV infusion of ALD403 Injection in 100 mL of 0.9% saline.

9.2 Control Drug

Placebo will be supplied as a single-use preservative-free solution in a 2-mL Type I glass vial formulated with the same excipients as ALD403, without the active ingredient. Those subjects randomized to placebo will receive an IV infusion Placebo in 100 mL of 0.9% saline.

9.3 Investigational Product Dosing and Administration

The pharmacist or Investigational Product consignee responsible for dispensing and preparing the ALD403 and Placebo IV infusions will be unblinded and will not be responsible for other aspects of the clinical trial where blinding is necessary. The infusions will be prepared using aseptic techniques.

The doses of ALD403 or Placebo (total volume of 100 mL) will be administered IV over a period of 1 hour (± 15 minutes) on Day 0 and Week 12, 24 and 36, by the blinded Investigator or designee. Subjects must be monitored for 4 hours after the dosing completion. If the subject experiences a headache or migraine on dosing day, dosing may occur if it doesn't compromise the safety of the subject in the judgment of the Investigator.

Further instructions on the preparation and procedure associated with administering the IV can be found in the Pharmacy Manual.

9.3.1 Packaging and Labeling

Before the shipment to the investigative sites, Investigational Product and Placebo will be labeled with the protocol number, contents ("ALD403" or "Placebo"), directions for storage, the Sponsor, and any other information required by regulatory agencies, such as a statement that it is limited to investigational use. Investigational Product and Placebo to be administered to the subject will be labeled by the investigators in a manner (after dose preparation) that protects blinding.

9.3.2 Blinding

This clinical trial is double-blind, meaning the subjects and site personnel are blinded to treatment assignment, except for clinical trial site's unblinded pharmacist or Investigational Product consignee. The study site must have a written plan in place to ensure blinding is adequately maintained for the study. If the blind is broken, the date, time and reason must be recorded. The blind should only be broken for reasons in which knowledge of the Investigational Product is critical to the subject safety and /or trial management. The Principal Investigator will report any cases of unblinding to the sponsor within 24 hours of the incident.

Immediately prior to PK/immunogenicity sample analysis, the bioanalytical laboratory will be unblinded in order to obtain the treatment assignments. The study will remain blinded until the

last subject has completed the Week 24 visit at which time aggregate efficacy and safety data will be unblinded.

9.3.3 Storage and Handling of Investigational Product

Investigational Product/Placebo will be stored at a central depot or at the clinical site at -20°C (- 10°C to -25°C) in accordance with any accompanying instructions. Please refer to the Pharmacy Manual for additional storage and handling procedures. Diluent (0.9% saline) will be stored according to institutional standards.

Investigators shall take adequate precautions, including storage of the Investigational Product and Placebo in a securely locked, substantially constructed cabinet or other securely locked, substantially constructed enclosure, access to which is limited to maintain blind, prevent theft or diversion of the substance into illegal channels of distribution.

9.3.4 Accountability and Disposition of Investigational Product

The Investigator is responsible for maintaining accurate Investigational Product and Placebo accountability records throughout the clinical trial. The site must maintain a record of Investigational Product Accountability Log on which the unblinded responsible pharmacist, or designee, will record the receipt, lot number/retest date, quantity, dispensation and return of Investigational Product to the Pharmacy, as well as any destruction of Investigational Product/Placebo including empty Investigational Product/Placebo containers (e.g., vials) or returns to the Sponsor. Where more than one secure area is being used for storage at a site, all movement of Investigational Product through the Chain of Custody must be recorded in accountability records such that full reconciliation may be completed at the end of the trial.

Included with each Investigational Product or Placebo shipment is a form listing lot numbers and quantity shipped. The Investigator, responsible pharmacist, or designee, will sign and return to Alder BioPharmaceuticals, Inc., or designee, a statement that certifies the receipt and integrity of these supplies. A copy will be retained for the site clinical trial file.

After completion of the clinical trial, the Investigator is responsible for either returning or destroying (if authorized by Sponsor) all unused Investigational Product/Placebo. The Investigator must verify that no remaining supplies are in his/her possession. All used/partially used vials/IV bags will be destroyed onsite according to the site SOPs. Where the Sponsor has

indicated in writing that Investigational Product/Placebo is to be destroyed on site, destruction must be in accordance with local regulations for the product type and destruction documentation must be provided to the Sponsor.

If the clinical trial is terminated, suspended, discontinued, or completed, the Investigator or designee shall return the unused supplies to the Sponsor or designee, or otherwise provide for disposition of the unused supplies (as authorized by the Sponsor).

9.4 Concomitant Medications

Any concomitant therapy, used from the time the subject signs the informed consent through Week 56, must be recorded on the CRF, including medications required for treatment of any AEs or SAEs. The Medical Monitor or designee should be notified in advance of (or as soon as possible after) any instances in which restricted therapies are administered. Use of regular prescription medications for condition other than migraine must be preapproved by Medical Monitor.

The following medications are **restricted** through Week 24:

- Any prophylactic headache medication (any preventive medication or supplement with evidence of efficacy from at least 1 placebo-controlled trial, see Section 15.1) is prohibited.
- Barbiturates and prescription opiates are allowed for ≤ 4 days per month through Week 24, provided the subject does not meet the criteria for Medication Overuse Headache and has been on a stable regimen (≤ 4 days per month) for at least 2 months prior to screening. Drugs containing non-prescription codeine (16 mg or less) are permitted.
- Botulinum toxin for migraine or for any other medical/cosmetic reasons requiring injections in the head, face, or neck are prohibited 4 months prior to screening through Week 24.
- Devices, neuromodulation, neurostimulation, or injectable therapy (trigger point injections, extracranial nerve blocks, facet joint injections) for headache prophylaxis are prohibited 2 months prior to screening through Week 24.

10 Schedule of Assessment and Procedures

Assessment and procedures at each visit are summarized in Section 2 (Schedule of Events and Assessments). An electronic headache eDiary will be distributed to each subject at the time of screening visit. The subject will record information daily regarding headache characteristics, severity and length. Compliance data from the eDiary will be made available and reviewed by the trial site.

10.1 Screening Day (Day -35 to -29)

The following assessments will be performed and measurements recorded:

- Written informed consent
- Inclusion/exclusion criteria reviewed
- Demographics (gender, age, race, ethnicity)
- Medical history including Migraine History
- Height and body weight
- Physical examination
- Vital signs including blood pressure (BP) and pulse
- Beck Depression Inventory (BDI-II)
- Columbia-Suicide Severity Rating Scale (C-SSRS) Baseline/Screening Version
- 12-lead ECG
- Clinical laboratory tests, including hematology, serum chemistry, and serology (including HIV, Hepatitis B and Hepatitis C)
- Urine drugs of abuse screening
- Pregnancy test (urinary hCG) on all female subjects
- Adverse events
- Concomitant medications
- Distribute headache eDiary and instruct subject on completion and compliance of diary

10.2 Day 0 (Randomization and Treatment)

Day 0 must be 29 to 35 days after the screening visit.

The following assessments will be performed pre-dose (unless otherwise specified) and measurements recorded with review of data from eDiary:

- Review inclusion/exclusion criteria including:
    - Verification of completion of eDiary for at least 25 of 28 days following screening
    - Verification that during the 28 day period following screening, the subject experienced ≤ 14 headache days of which at least 4 have to be migraine days (migraine days count as headache days) as recorded in the eDiary.
- Body weight
- Physical examination
- Brush allodynia test
- Vital signs including BP and pulse
    - Vital signs will be obtained and recorded prior to the start of Investigational Product infusion and 4 hours post-end of infusion (± 30 minutes).
- C-SSRS Since Last Visit Version
- 12-lead ECG
    - 12-lead ECGs will be performed prior to the start of Investigational Product infusion and 4 hours post-end of infusion (± 30 minutes)
- Clinical laboratory tests, including hematology and serum chemistry
- Pregnancy test (urinary hCG) on all female subjects
    - Subjects with a positive pregnancy test will not be dosed and will be withdrawn from the trial
- Plasma Free ALD403 PK sample
    - Blood will be drawn pre-dose (within one hour prior to Investigational Product administration)
- A blood sample will be taken pre-dose for baseline determination of anti-ALD403 antibodies in serum (immunogenicity)
- SF-36 v2.0, EQ-5D-5L and ASC-12 completion by subject
- Adverse events (throughout visit)
- Concomitant medications (throughout visit)
- Randomize subject via the IWRS or IVRS system

- Dosing of ALD403 or Placebo; subject must be monitored for at least 4 hours after the dosing completion

10.3 Week 4 Visit (Day 28 ± 3 days)

The following assessments will be performed and measurements recorded:

- Headache eDiary data reviewed by trial site
    - Review compliance with completion of eDiary; if subject is not compliant with the daily eDiary, instruct regarding importance of daily completion
- Brush allodynia test
- Vital signs including BP and pulse
- C-SSRS Since Last Visit Version
- 12-lead ECG
- Clinical laboratory tests, including hematology and serum chemistry
- Plasma Free ALD403 PK sample
- A blood sample will be taken for anti-ALD403 antibodies in serum (immunogenicity)
- SF-36 v2.0, EQ-5D-5L and ASC-12 completion by subject
- Adverse events
- Concomitant medications

10.4 Week 8 Visit (Day 56 ± 3 days)

The following assessments will be performed and measurements recorded:

- Headache eDiary data reviewed by trial site
    - Review compliance with completion of eDiary; if subject is not compliant with the daily eDiary, instruct regarding importance of daily completion
- Vital signs including BP and pulse
- C-SSRS Since Last Visit Version
- 12-lead ECG
- Plasma Free ALD403 PK sample
- A blood sample will be taken for determination of anti-ALD403 antibodies in serum (immunogenicity)

- SF-36 v2.0, EQ-5D-5L and ASC-12 completion by subject
- Adverse events
- Concomitant medications

10.5 Week 12 Visit (Day 84 ± 3 days)

The following assessments will be performed pre-dose (unless otherwise specified) and measurements recorded:

- Headache eDiary data reviewed by trial site
    - Review compliance with completion of eDiary; if subject is not compliant with the daily eDiary, instruct regarding importance of daily completion
- Brush Allodynia test
- Vital signs including BP and pulse
    - Vital signs will be obtained and recorded prior to the start of Investigational Product infusion and 4 hours post-end of infusion (± 30 minutes).
- C-SSRS Since Last Visit Version
- 12-lead ECG
    - 12-lead ECGs will be performed prior to the start of Investigational Product infusion and 4 hours post-end of infusion (± 30 minutes)
- Clinical laboratory tests, including hematology and serum chemistry
- Pregnancy test (urinary hCG) on all female subjects
- Plasma Free ALD403 PK sample
    - Blood will be drawn pre-dose (within one hour prior to Investigational Product administration)
- A blood sample will be taken pre-dose for baseline determination of anti-ALD403 antibodies in serum (immunogenicity)
- SF-36 v2.0, EQ-5D-5L and ASC-12 completion by subject
- Adverse events
- Concomitant medications
- Dosing of ALD403 or Placebo; subject must be monitored for at least 4 hours after the dosing completion

10.6 Week 16 Visit (Day 112 ± 3 days)

The following assessments will be performed and measurements recorded:

- Headache eDiary data reviewed by trial site
    - Review compliance with completion of eDiary; if subject is not compliant with the daily eDiary, instruct regarding importance of daily completion
- Brush allodynia test
- Vital signs including BP and pulse
- C-SSRS Since Last Visit Version
- Plasma Free ALD403 PK sample
- A blood sample will be taken for determination of anti-ALD403 antibodies in serum (immunogenicity)
- SF-36 v2.0, EQ-5D-5L and ASC-12 completion by subject
- Adverse events
- Concomitant medication

10.7 Week 20 Visit (Day 140 ± 3 days)

The following assessments will be performed and measurements recorded:

- Headache eDiary data reviewed by trial site
    - Review compliance with completion of eDiary; if subject is not compliant with the daily eDiary, instruct regarding importance of daily completion
- Brush allodynia test
- Vital signs including BP and pulse
- C-SSRS Since Last Visit Version
- Plasma Free ALD403 PK sample
- A blood sample will be taken for determination of anti-ALD403 antibodies in serum (immunogenicity)
- SF-36 v2.0, EQ-5D-5L and ASC-12 completion by subject
- Adverse events
- Concomitant medications

10.8 Week 24 Visit (Day 168 +3 days)

Week 24 must be done on the target day or 3 days after. Three days earlier than target date is not allowed. The following assessments will be performed and measurements recorded:

- Headache eDiary data reviewed by trial site
    - Review compliance with completion of eDiary; if subject is not compliant with the daily eDiary, instruct regarding importance of daily completion
- Body weight
- Physical examination
- Brush allodynia test
- Vital signs including BP and pulse
    - Vital signs will be obtained and recorded prior to the start of Investigational Product infusion and 4 hours post-end of infusion (± 30 minutes).
- C-SSRS Since Last Visit Version
- 12-lead ECG
    - 12-lead ECGs will be performed prior to the start of Investigational Product infusion and 4 hours post-end of infusion (± 30 minutes)
- Clinical laboratory tests, including hematology and serum chemistry
- Pregnancy test (urinary hCG) on all female subjects
- Plasma Free ALD403 PK sample
    - Blood will be drawn pre-dose (within one hour prior to Investigational Product administration)
- A blood sample will be taken pre-dose for baseline determination of anti-ALD403 antibodies in serum (immunogenicity)
- SF-36 v2.0, EQ-5D-5L and ASC-12 completion by subject
- Adverse events
- Concomitant medications
- Dosing of ALD403 or Placebo; subject must be monitored for at least 4 hours after the dosing completion

10.9 Week 28 Visit (Day 196 ± 7 days)

The following assessments will be performed and measurements recorded:

- Headache eDiary data reviewed by trial site
    - Review compliance with completion of eDiary; if subject is not compliant with the daily eDiary, instruct regarding importance of daily completion
- Vital signs including BP, pulse
- 12-lead ECG
- Clinical laboratory tests, including hematology and serum chemistry
- C-SSRS Since Last Visit Version
- Adverse events
- Concomitant medications

10.10 Week 36 Visit (Day 252 ± 3 days)

The following assessments will be performed pre-dose (unless otherwise specified) and measurements recorded:

- Headache eDiary data reviewed by trial site
    - Review compliance with completion of eDiary; if subject is not compliant with the daily eDiary, instruct regarding importance of daily completion
- Physical examination
- Body weight
- Vital signs including BP, pulse will be obtained prior to the start of Investigational Product infusion and 4 hours post-end of infusion (± 30 minutes)
- 12-lead ECG
    - 12-lead ECGs will be performed prior to the start of Investigational Product infusion and 4 hours post-end of infusion (± 30 minutes)
- Clinical laboratory tests, including hematology and serum chemistry
- Pregnancy test (urinary hCG) on all female subjects
- C-SSRS Since Last Visit Version
- SF-36

- Plasma Free ALD403 PK sample
    - Blood will be drawn pre-dose (within one hour prior to Investigational Product administration)
- A blood sample will be taken pre-dose for determination of anti-ALD403 antibodies in serum (immunogenicity)
- Adverse events
- Concomitant medications
- Dosing of ALD403 or Placebo; subject must be monitored for at least 4 hours after the dosing completion

10.11 Week 48 Visit (Day 336 + 7 days)

The following assessments will be performed and measurements recorded:

- Return of Headache eDiary
- Vital signs including BP, pulse
- 12-lead ECG
- Clinical laboratory tests, including hematology and serum chemistry
- Pregnancy test (urinary hCG) on all female subjects
- Plasma Free ALD403 PK sample
- A blood sample will be taken for determination of anti-ALD403 antibodies in serum (immunogenicity)
- C-SSRS Since Last Visit Version
- Adverse events
- Concomitant medications

10.12 Week 56 Visit (Day 392 ± 7 days) End of Study or Early Termination

The following assessments will be performed and measurements recorded:

- Body weight
- Physical examination
- Vital signs including BP, pulse
- 12-lead ECG

- Clinical laboratory tests, including hematology and serum chemistry
- Pregnancy test (urinary hCG) on all female subjects
- Plasma Free ALD403 PK sample
- A blood sample will be taken for determination of anti-ALD403 antibodies in serum (immunogenicity)
    - 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 approximately 3 month intervals for up to 6 months.
- C-SSRS Since Last Visit Version
- SF-36
- Adverse events
- Concomitant medications

10.13 Early Termination

All subjects will be encouraged to complete all evaluations through Week 56. However, subjects who prematurely discontinue the study will have Early Termination assessments completed at the time of discontinuation. Subjects who are randomized but do not receive study treatment may discontinue the study without any further procedures.

11 Assessment of Safety

11.1 Adverse Events

11.1.1 Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (ICH E6)

11.1.2 Assessment of Adverse Events

The Investigator is required to monitor the occurrence of adverse events for each subject from the time of informed consent through the course of the clinical trial. Adverse events may be reported by the subject, reported by a caregiver, or reported by the investigative site through Investigator site personnel open-ended questioning, through physical examination, laboratory test, documentation in medical records, or by other means. Adverse events include:

- Any new undesirable medical experience or an unfavorable and unintended change of an existing condition that occurs during or after treatment, whether or not considered related to the Investigational Product.
- Asymptomatic abnormal findings considered by the Investigator to be clinically significant. For example, abnormal ECG or abnormal lab findings.

A new or worsening of a pre-existing or chronic condition is considered an adverse event and must be reported as such. Medical conditions, which existed prior to the time of informed consent into the clinical trial, will not be considered an adverse event unless the condition worsens. Unchanged, chronic, non-worsening or pre-existing conditions from the time of informed consent are not adverse events and should not be recorded on the AE eCRF.

Pre-existing medical conditions of clinical significance must be included in the subject's medical history and recorded on the medical history eCRF page.

Each event recorded on the AE eCRF is required to be assessed by the Investigator with regard to the following; seriousness, severity, and relationship to Investigational Product, as outlined below.

Seriousness

An adverse event or suspected adverse event is considered serious if in the view of either the Investigator or Sponsor, it results in;

- Death
- Is life-threatening (this means that the subject is at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe)

- Inpatient hospitalization or prolonged existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/ birth defect
- Important medical events that may not result in death, be life-threatening or require hospitalization may be considered serious when, based upon appropriate medical judgement, they may jeopardize the patient or subject and/or may require medical or surgical intervention to prevent one of the outcomes listed in the definition. (21 CFR 312.32(a) and ICH E2A)

Severity

The severity of an AE will be graded as follows:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL).
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

Relationship to Investigational Product

The Investigator is required to assess the causality/relationship between each AE and the Investigational Product as not related or related and record the assessment on the source documents and in the eCRF AE page. Medical judgment should be used to determine the likely relationship of the AE to the Investigational Product considering all relevant factors including (but not limited to) relevant history, concomitant medical condition and concomitant medications. Determination should be based on assessment of temporal relationships, biologic

plausibility, association (or lack of association) with underlying disease, and presence (or absence) of a more likely cause.

Not Related: It is plausible that the AE has an etiology other than the Investigational Product (e.g., pre-existing condition, underlying disease, concomitant medical condition, or concomitant medication).

Related: The AE cannot reasonably be explained by the subject's clinical state, concomitant\medical condition or concomitant therapies, and a temporal relationship exists between the event onset and administration of the Investigational Product.

11.1.3 Recording Adverse Events

Event reporting will extend from time of informed consent until completion of the final visit. Serious adverse events occurring after the end of the clinical trial must be reported if the Investigator considers there to be a causal relationship with the Investigational Product.

SAE Notification Form should be used to report any related SAEs which occur after the end of the clinical trial.

Adverse events (AEs) should be recorded on the AE eCRF, whether believed by the Investigator to be related or not related to the Investigational Product.

AE reporting should contain;

- a brief description of the event,
- date of onset,
- date of resolution,
- severity,
- actions taken or treatment required,
- relationship to Investigational Product,
- outcome, and
- whether the event is considered serious.

Whenever possible, the Investigator should group signs or symptoms that constitute a single diagnosis into a single event term. For example, "cough, rhinitis, and sneezing" might be grouped together as "upper respiratory tract infection".

Asymptomatic abnormal findings considered by the Investigator to be clinically significant should be recorded as an AE, unless it is associated with a clinical syndrome that has already been reported as an AE.

11.1.4 Reporting Serious Adverse Events

All SAEs that occur during the period of observation, whether considered to be related to the Investigational Product or not, must be reported within 24 hours of awareness or knowledge of the event. The date the site personnel became aware of the serious adverse event must be recorded in the source document. To report the SAE, complete the eCRF AE page and indicate the reason for seriousness. The minimum information required for an initial report is:

- Sender of report (name, address of Investigator)
- Subject identification (screening/randomization number, initials, NOT subject name)
- Protocol number
- Description of SAE (e.g., event term)
- Seriousness criteria
- Relationship assessment

After receipt of the initial report, the Medical Monitor or designee will review the information and, if necessary, contact the Investigator to obtain further information for assessment of the event. The Sponsor or designee will be responsible for information processing and reporting in accordance with applicable local and regulatory requirements.

The Sponsor or designee will determine if an SAE requires expedited reporting to regulatory agencies. The clinical trial site personnel are responsible for reporting these events to their EC/IRB according to the institution's EC/IRB reporting requirements and in accordance with applicable local and regulatory requirements.

Should the EDC System not be available, serious adverse events must be reported on the paper SAE Notification Form. Additional details can be found in the Site Manual. This does not replace the EDC reporting system; information must be entered in the EDC system once the system returns to normal function.

11.1.5 Unexpected and Related Serious Adverse Events

Unexpected SAEs are those which:

- Are not previously reported as associated with ALD403, as referenced in the Investigator's Brochure.
- May be symptomatically and pathophysiologically related to an AE listed in the Investigator's Brochure, but differ from the event due to greater severity, frequency or specificity.

The Sponsor or designee will report, to the appropriate regulatory authorities according to local and regulatory requirements, unexpected SAEs which are considered related to ALD403 (suspected unexpected serious adverse reactions [SUSARs]). The clinical trial site personnel are responsible for reporting these events to their EC/IRB in accordance with applicable local and regulatory requirements.

11.1.6 Follow-up of Adverse Events

Irrespective of the suspected causality, AEs will be monitored until resolution, stabilization in the judgment of the Investigator, or the subject is lost to follow up or withdraws from the trial.

11.1.7 Clinical Laboratory Tests

Serum chemistry tests include albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea nitrogen, calcium, bicarbonate, creatinine, globulin, glucose, phosphorus, potassium, sodium, total bilirubin, total cholesterol, total protein, triglycerides, magnesium and uric acid.

Hematology tests include hematocrit, hemoglobin, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet count, red blood cell (RBC) count, RBC morphology, and white blood cell (WBC) count with differentials (neutrophils, lymphocytes, monocytes, eosinophils, and basophils).

11.1.8 Pregnancy

In the event that a female subject becomes pregnant following administration of Investigational Product(s) or may have been pregnant at the time of Investigational Product(s) exposure, or the partner of a male subject becomes pregnant following administration of Investigational

Product(s), the pregnancy must be reported to the Sponsor within five business days of the Investigator becoming aware of the pregnancy. Pregnancy information will be reported to the Sponsor using the Exposure In-Utero Forms.

Although pregnancy *per se* is not considered an AE, the outcome of a pregnancy that results in a birth defect or congenital anomaly or hospitalization for any reason is considered to be an SAE. Every attempt should be made to follow a pregnancy to conclusion.

Follow-up information is to be collected by the Investigator and provided to the Sponsor regarding;

- the course of the pregnancy including; perinatal and neonatal outcome, or premature termination of the pregnancy, or miscarriage
- offspring information including; birth weight, and birth defects (if any)

11.1.9 Suicidal Ideation and Behavior

Recent meta-analyses, spontaneous reports, and published case reports regarding suicidal ideation and behavior arising from drugs tested in clinical trials have been noted as an area of general concern. Based on this information, the United States Food and Drug Administration (FDA) has provided guidance to prospectively assess suicidal ideation and behavior in clinical trials to ensure that subjects in clinical trials who are experiencing suicidal ideation and behavior are properly recognized and adequately treated and to ensure the collection of more timely and more complete data on suicidal ideation and behavior than have been collected in the past [13]. The C-SSRS (Columbia-Suicide Severity Rating Scale) will be used for this purpose. Any subject who answers 'yes' to questions 4 or 5 of the C-SSRS during the screening visit will be referred to a mental health specialist by the investigator. During the course of the trial after dosing, any subject who answers 'yes' to questions 4 or 5 of the C-SSRS will be discontinued from the study treatment and referred by investigators to a mental health specialist.

11.2 Management of Reactions to ALD403

There are no specific antidotes to ALD403.

Each medical emergency should be treated appropriately by the Investigator using proper standard of care, according to their typical clinical practice and local guidelines for that

emergency condition. Emergency equipment and medication for the treatment of these potential adverse events must be available for immediate use.

Should a medical condition arise that the Investigator believes is related to the Investigational Product, clinical judgment should be used to provide the appropriate response including the consideration of discontinuation of Investigational Product.

If a subject experiences a potential systemic allergic reaction as assessed by the PI, the site will collect additional blood specimen(s) using the anaphylactic kit (unscheduled kit Type E) at the time of the event as per the PPD laboratory manual. This assessment includes serum histamine, serum tryptase, immunoglobulin E, and complement components.

As a guideline, if a site does not have a formal "crash cart", the following should be considered as a requirement at the site:

- Clinical personnel should be CPR certified
- Clinic should have an automated external defibrillator

The site should have the following emergency medications available: antihistamines, bronchodilators, IV saline, corticosteroids, acetaminophen, and epinephrine.

12 Assessment of Efficacy, Pharmacokinetics and Immunogenicity

12.1 Efficacy

12.1.1 eDiary

Subjects will complete a daily headache eDiary from the time of screening to Week 48. The diary should 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 compliance data from the eDiary will be made available to the trial site for review. Sites are to review the diary results with the subject and if the subject has not completed the diary daily, counsel the subject on the importance of daily completion of the diary.

The eDiary data from the 28 days following screening visit will be used to determine eligibility criteria, and the baseline migraine and headache results.

12.1.2 Endpoints

Headache episodes will be self-reported by the subject. An episode is a single headache event that the subject reported as having a start and an end and which lasts at least 30 minutes. The term headache will encompass both headaches and migraine headaches. The migraine and headache endpoints will be summarized in four week, twelve week and the twenty-four week interval. 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.

Migraine Day

A migraine day is defined as any day with a headache that meets the migraine or probably migraine characteristics as outlined in Section 7. Specifically, a migraine is defined as a self-reported headache which:

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.

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 these four week intervals will be combined to produce 12 and 24 week responder endpoints. A responder will be a subject who achieves the specified percent reduction in migraine headache days within these intervals based upon the average change from baseline measures.

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. 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 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 post baseline interval and baseline.

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.

Time to First Migraine

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

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, see Appendix 15.3. 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.

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.

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," see Appendix 15.5. 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 study, 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

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. [14] 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.[15]

12.2 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 analysed for the potential presence of Free ALD403 using validated assay methods.

Additional sample handling, processing, storage, labelling and shipping instructions will be provided to the site in a laboratory manual.

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.

12.3 Immunogenicity

Serum blood samples will be taken pre-dose on Day 0, and Weeks 4, 8, 12, 16, 20, 24, 36, 48 and 56 to test for antibodies to ALD403. The immunogenicity will be assessed in serum from all ALD403-treated subjects using validated assay methods. Immunogenicity will not be assessed in placebo subjects.

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

Additional sample handling, processing, storage, labelling and shipping instructions will be provided to the site in a laboratory manual.

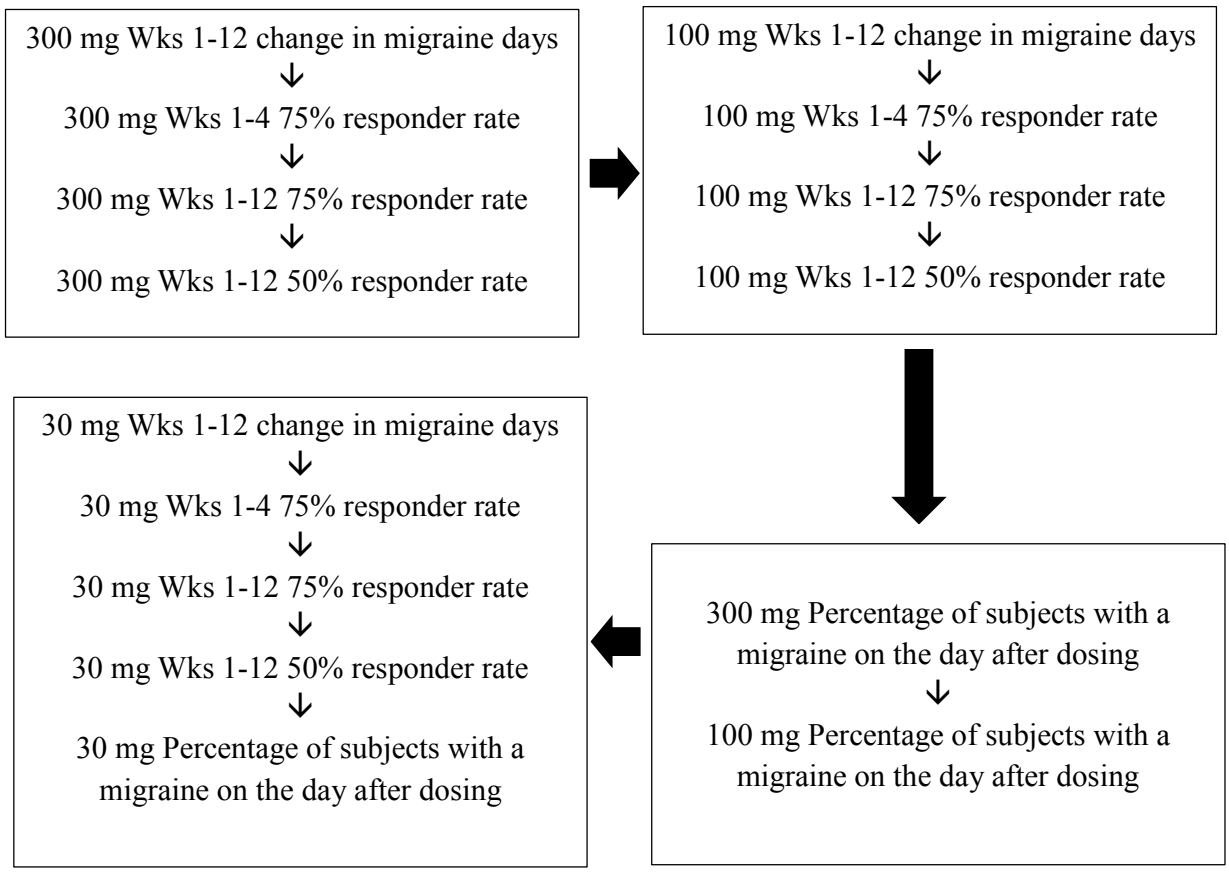
13 Statistical Considerations

13.1 Decision Rule

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. This testing algorithm is presented below.

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



13.2 Sample Size

The planned sample size for this study 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. [16]

13.3 General Considerations

13.3.1 Definition of Baseline

Baseline 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.

13.3.2 Handling of 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.

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. If the diary has been completed at least 21 days in a 28 day interval, then normalization will be used. The results will be normalized to 28 days by multiplying the observed results by the inverse of the completion rate (i.e. if a subject does not complete the diary 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). If the diary 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 to the results from the current interval as the diary completion rate increases. Specifically, the results will be derived as

$$28\big(WX_c + (1-W)X_p\big),$$

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

13.3.3 Populations to be Analyzed

The populations to be analyzed are as follows:

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. This population will be used for the safety analyses.

13.4 Statistical Methods

Continuous variables will be summarized with mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized with frequency and percentage.

13.4.1 Subject Disposition, Demographics and Baseline Characteristics

An accounting of all randomized trial subjects by disposition will be presented. This summarization will include a summary of all subjects who have received trial drug. Demographic, baseline characteristics, migraine history and concomitant medications (coded by the World Health Organization Drug Dictionary) will be summarized descriptively by treatment group.

13.4.2 Efficacy Analyses

Efficacy endpoints will be summarized with descriptive statistics. The migraine and headache endpoints will be summarized by four, twelve and twenty-four week intervals with the remaining endpoints being summarized by study week.

Primary Efficacy Analyses

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 12.1.2 and will utilize the missing data rules provided in Section 13.3.2. The hypotheses tested are

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

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 predictor) will be the independent variables.

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.

The missing data rules provided in Section 13.3.2 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 diary on the day following dosing will be included in 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.

13.4.3 Pharmacokinetic Analyses

Analysis of Drug Concentrations

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

Plots of the individual concentrations of Free ALD403 will be presented over time (linear and log scales). Plots of the mean or median concentration will be presented over time (linear and log scales). When the scale is linear, concentrations below the lower limit of quantification will be set to zero. In the log-scaled figures, concentrations below the LLOQ will be imputed as LLOQ/2. Population pharmacokinetic analysis will be performed on the results for Free ALD403 concentrations obtained during this study in combination with the results from previous studies of ALD403 in normal subjects and migraine patients.

13.4.4 Safety Analyses

13.4.4.1 Adverse Events

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 Medical Dictionary for Regulatory Activities (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.

An overview of AEs, which includes subject incidence of AEs, treatment-related AEs, SAEs, deaths, and AEs leading to discontinuation, will be presented. For AEs presented by severity, the worst severity during the clinical trial will be presented for each subject.

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

13.4.4.2 Serious Adverse Events

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

13.4.4.3 Clinical Laboratory Results

Clinical laboratory values will be measured by a central laboratory.

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.

13.4.4.4 Electrocardiogram (ECG) Results

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

13.4.4.5 Vital Signs

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

13.4.4.6 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.

14 Ethical, Legal and Administrative Aspects

14.1 Data Quality Assurance

The Sponsor or designee will assess the site to verify the qualifications of each Investigator, according to Sponsor's or applicable SOPs. There will be an inspection of site facilities, and Investigator will be further informed of responsibilities and the procedures for ensuring adequate and correct documentation.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the clinical trial for each clinical trial subject. All information recorded on the CRFs for this clinical trial must be consistent with the subjects' source documentation (i.e., medical records).

14.2 Case Report Forms and Source Documents

As part of the responsibilities assumed by participating in the study, the principal investigator or sub-investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The principal investigator or sub-investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents include laboratory reports and original ECGs.

14.3 Study Documentation

Source document is defined as any hand written or computer generated document that contains medical information or test results that have been collected for or are in support of the protocol specifications, eg, clinical laboratory reports, clinic notes, drug disbursement log, subject sign in sheets, subject completed questionnaires if applicable, telephone logs, ECGs, etc. All draft, preliminary and pre-final iterations of a final report are also considered to be source documents, eg, faxed laboratory reports and hard copy laboratory reports, faxed initial results and hard copy, final report.

14.4 Data Collection and Electronic Data Capture (EDC)

The data collected during the study (except clinical laboratory test results, ECG results, PK analyses, Immunogenicity) will be recorded in the subject's electronic CRF. The Short-Form Health Survey (SF-36), Health related Quality of Life (EQ-5D-5L), Allodynia Symptom Checklist-12 (ASC-12) and C-SSRS will be completed on paper forms and then entered into the EDC system. The study site(s) will use an EDC system that is compliant with relevant Food and Drug Administration (FDA) regulatory requirements per 21 CFR Part 11. Data queries and data corrections will be handled through the same system. All transactions within the EDC system are fully documented within an electronic audit trail. Each set of completed CRFs must be reviewed after being source verified by monitor and electronically signed and dated by the Investigator.

14.5 Archiving Clinical Trial Records

According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the Investigational Product. However, these documents should be retained for a longer period if required by applicable legal requirements.

It is the responsibility of the Investigator and clinical trial staff to maintain a comprehensive and centralized filing system of all clinical trial-related documentation. This centralized file should be available for inspection at any time by the Monitor or Quality Assurance staff for monitoring or auditing by Alder BioPharmaceuticals, Inc. and regulatory authorities. Elements of clinical trial documentation should include:

- Subject files containing the completed CRF supporting source documentation and the signed ICF
- Clinical trial files, containing the protocol with all amendments, the Investigator Brochure, copies of all clinical trial documentation, and all correspondence to and from the ethics committee and Alder BioPharmaceuticals, Inc.

- Pharmacy files, containing the Investigational Product Accountability Records or dispensation logs and all clinical trial agent-related correspondence

14.6 Good Clinical Practice

The procedures set out in this clinical trial protocol are designed to ensure that the Sponsor and Investigator abide by the principles of the GCP guidelines of the ICH and applicable federal and local regulations. The clinical trial also will be conducted in keeping with local legal requirements.

14.7 Informed Consent

Before each subject is admitted to the clinical trial, informed consent will be obtained from the subject (or his/her legally authorized representative) according to the regulatory and legal requirements of the participating country. The consent forms must be dated and retained by the Investigator as part of the clinical trial records. The Investigator will not undertake any investigation specifically required for the clinical trial until valid consent has been obtained. The terms of the consent and when it was obtained must also be documented in the CRF. Each subject will receive a fully-signed copy of each consent form that he/she signs for the clinical trial.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate ethics committee, and signed by all subjects subsequently enrolled in the clinical trial as well as those currently enrolled in the clinical trial. If subject or subject's partner, becomes pregnant during their participation in the trial, a separate pregnancy informed consent form will be obtained, to follow the pregnancy, any complications, and the health of the baby. The pregnancy consent should be obtained at the time the investigator becomes aware of the pregnancy.

14.8 Protocol Approval and Amendment

Before the start of the clinical trial, the clinical trial protocol and/or other relevant documents will be approved by the ethics committee, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the clinical trial.

The procedures outlined in the protocol and CRFs will be carefully reviewed by the Investigator and staff prior to clinical trial initiation to ensure appropriate interpretation and implementation. No deviations from the protocol should be made except in emergency situations where alternative treatment is necessary for the protection, proper care and well-being of subjects.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, and approvals must be received from the appropriate personnel and from the ethics committee before implementation (if appropriate). Amendments will originate from Alder BioPharmaceuticals, Inc. and will be provided to the Investigator for submission to his/her ethics committee for their review and approval prior to implementation (if appropriate). It should be noted that when an amendment to a protocol substantially alters the clinical trial design or increases potential risk to the clinical trial subject, the ICF should be revised and, if applicable, subject's consent to continue participation should be obtained.

Administrative changes may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

14.8.1 Premature Termination of the Clinical Trial

Alder BioPharmaceuticals, Inc. reserves the right to terminate this clinical trial at any time. The FDA or other governing national authority may also terminate the clinical trial.

The Principal Investigator may discontinue participation in the trial. If the clinical trial is terminated prior to scheduled completion, the Investigator will be notified and given any necessary instructions concerning final examinations that are required. If the Investigator, the Sponsor, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to subjects if the clinical trial continues, the clinical trial may be terminated after appropriate consultation between the relevant parties.

14.9 Confidentiality

All clinical trial findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participating subjects must be maintained. Subjects will be identified on CRFs and other documents by their subject number, initials and/or birth date, not by name and subject in accordance with local requirements. Documents not to be submitted that identify the subject (e.g., the signed informed consent) must be maintained in confidence by the Investigator.

14.10 Publication Policy

By signing the clinical trial protocol, the Investigator agrees with the use of results of the clinical trial for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

An Investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with the Sponsor in advance. The information provided in support of or generated as a result of this clinical trial is confidential. Any use or reproduction thereof, including but not limited to publications or presentations by the Investigator or his/her associates, must be submitted to Alder BioPharmaceuticals, Inc. for review and approval in accordance with the provisions contained in the clinical trial agreement. All publications must acknowledge the Sponsorship of Alder BioPharmaceuticals, Inc.

All information not previously published concerning ALD403 and Alder BioPharmaceuticals, Inc. operations, including but not limited to patent applications, formulas, manufacturing processes, basic scientific data, and formulation information, supplied by Alder BioPharmaceuticals, Inc. to the Investigator is considered confidential and shall remain the sole property of Alder BioPharmaceuticals, Inc. The Investigator agrees to use and maintain the confidentiality of this information in accordance with the provisions contained in the clinical trial agreement.

15 Appendices

15.1 Preventative Medications or Supplements with Evidence of Efficacy

The list below includes, but is not limited to following medications or supplements which have evidence of efficacy with at least 1 randomized, placebo-controlled trial: [18, 19]

- Antiepileptic drugs
  - divalproex sodium
  - sodium valproate
  - topiramate
- B-Blockers
  - metoprolol
  - propranolol
  - timolol
  - atenolol
  - nadolol
- Triptans
  - frovatriptan
  - naratriptan
  - zolmitriptan
- Antidepressants
  - amitriptyline
  - venlafaxine
- Herbal preparations, vitamins, minerals
  - petasites
  - magnesium
  - MIG-99 (feverfew)
  - riboflavin
- NSAIDS
  - fenoprofen
  - ibuprofen
  - ketoprofen
  - naproxen
  - naproxen sodium
- Histamines
  - histamine SC

15.2 Columbia-Suicide Severity Rating Scale (C-SSRS) Risk Assessment

15.2.1 Baseline/Screening Version

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past 6 Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*) Past 6 Months - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past _2_ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

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15.2.2 Since Last Visit Version

COLUMBIA-SUICIDE SEVERITY

RATING SCALE

(C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** **No** ☐ ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** **No** ☐ ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** **No** ☐ ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** **No** ☐ ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?***	**Yes** **No** ☐ ☐

If yes, describe:	
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on	____

and to end/stop the pain	living with the pain or how you were feeling) (0) Does not apply	

SUICIDAL BEHAVIOR	Since
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** **No** ☐ ☐ Total # of Attempts _____ **Yes** **No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.	**Yes** **No** ☐ ☐
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.	**Yes** **No** ☐ ☐

Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).	**Yes** **No** ☐ ☐
Suicidal Behavior:	**Yes** **No**
Suicide:	**Yes** **No**
Answer for Actual Attempts Only	Most Lethal Attempt
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).	*Enter Code*

15.3 Short-Form Health Survey (SF-36 v2.0)

Sample Short-Form Health Survey (SF-36 v2.0)

This survey asks for your views about your health. This information will help you keep track of how you feel and how well you are able to do your usual activities.

Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully, and click on the circle that best describes your answer. *Thank you for completing this survey!*

1) In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
●	●	●	●	●

2) Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
●	●	●	●	●

3) The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous Activities, such as running, lifting heavy objects, participating in strenuous sports	●	●	●
b. Moderate Activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	●	●	●
c. Lifting or carrying groceries	●	●	●
d. Climbing several flights of stairs	●	●	●
e. Climbing one flight of stairs	●	●	●
f. Bending, kneeling, or stooping	●	●	●
g. Walking more than a mile	●	●	●
h. Walking several hundred yards	●	●	●
i. Walking one hundred yards	●	●	●

j. Bathing or dressing yourself	●	●	●

4) During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	●	●	●	●	●
b. Accomplished less than you would like	●	●	●	●	●
c. Were limited in the kind of work or other activities	●	●	●	●	●
d. Had difficulty performing the work or other activities (for example, it took extra effort)	●	●	●	●	●

5) During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	●	●	●	●	●
b. Accomplished less than you would like	●	●	●	●	●
c. Did work or activities less carefully than usual	●	●	●	●	●

6) During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
●	●	●	●	●

7) How much bodily pain have you had during the past 4 weeks?

None	Very Mild	Mild	Moderate	Severe	Very Severe
●	●	●	●	●	●

8) During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
●	●	●	●	●

9) These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	●	●	●	●	●
b. Have you been very nervous?	●	●	●	●	●
c. Have you felt so down in the dumps that nothing could cheer you up?	●	●	●	●	●
d. Have you felt calm and peaceful?	●	●	●	●	●
e. Did you have a lot of energy?	●	●	●	●	●
f. Have you felt downhearted and depressed?	●	●	●	●	●
g. Did you feel worn out?	●	●	●	●	●
h. Have you been happy?	●	●	●	●	●
i. Did you feel tired?	●	●	●	●	●

10) During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
●	●	●	●	●

11) How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	●	●	●	●	●
b. I am as healthy as anybody I know	●	●	●	●	●
c. I expect my health to get worse	●	●	●	●	●
d. My health is excellent	●	●	●	●	●

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

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

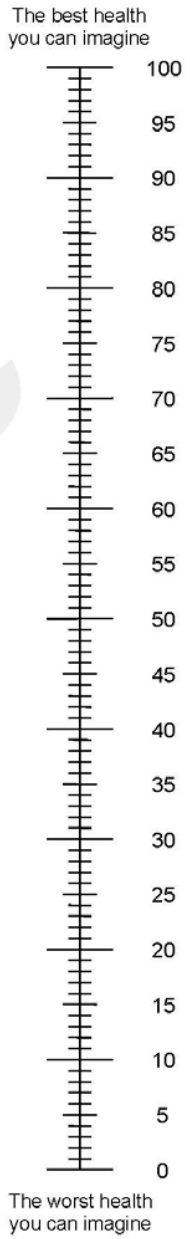
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



3

15.5 Allodynia Symptom Checklist (ASC-12)

Allodynia Symptom Checklist (ASC-12)

Question: How often do you experience increased pain or an unpleasant sensation on your skin during your most severe type of headache when you engage each of the following?	Does not apply to me	Never	Rarely	Less than half the time	Half the time or more
	Score: 0	Score: 0	Score: 1	Score: 2	Score: 2
Combing your hair					
Pulling your hair back (e.g., ponytail)					
Shaving your face					
Wearing eyeglasses					
Wearing contact lenses					
Wearing earrings					
Wearing a necklace					
Wearing tight clothing					
Taking a shower (when shower water hits your face)					
Resting your face or head on a pillow					
Exposure to heat (e.g., cooking, washing your face with hot water)					
Exposure to cold (e.g., using an ice pack, washing your face with cold water)					
Total score					
Sum of total scores					

Allodynia	ASC range
None	(0-2)
Mild	(3-5)
Moderate	(6-8)
Severe	(9 or more)

15.6 Change Table for Amendment 4

Section	Pg	Change From	Change To	Justification
Cover page	1	[redacted]	[redacted]	Change in Sponsor's Medical Monitor
Signature Page	2	[redacted]	[redacted]	Change in Sponsor's Medical Monitor
1 Protocol Synopsis - Clinical Trial Endpoints	5	Key Secondary Endpoints • 75% migraine responder rate (Weeks 1-4) • 75% migraine responder rate (Weeks1-12)	Key Secondary 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	Inclusion of additional endpoints that are believed to be clinically meaningful and would provide additional support and understanding of ALD403's effectiveness in migraine prophylaxis.
	6	Other Secondary Endpoints • Headache/migraines with acute medication usage • 50% and 100% migraine responder rates (Weeks 1-12) • Short-Form Health Survey (SF-36) • 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.	Other Secondary Endpoints • Change in acute migraine medication days (Weeks 1-12) • Headache/migraines with acute medication usage • 100% migraine responder rates (Weeks 1-12) • Short-Form Health Survey (SF-36) • Health-Related Quality of Life (EQ-5D-5L) • Allodynia Symptom Checklist-12 (ASC-12)	The change in acute migraine medication days endpoint has been added as requested by the FDA.

Section	Pg	Change From	Change To	Justification
		• 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	• 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	
1 Protocol Synopsis - Statistical Analysis	9	The key secondary endpoints will be tested with a Cochran Mantel Haenszel (CMH) test controlling for the randomization stratification factor.	The key secondary responder rate and percentage of subjects with a migraine on the day after dosing endpoints will be tested with a Cochran Mantel Haenszel (CMH) test controlling for the randomization stratification factor.	Based upon changes to the key secondary endpoints.
2 Schedule of Events	11	[13]Subjects who test positive for anti-ALD403 antibodies at the last study visit will be asked to provide up to 2 additional blood samples for immunogenicity testing at 3 month intervals for up to 6 months.	[13]Subjects 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 approximately 3 month intervals for up to 6 months.	Clarification in immunogenicity testing visit window.

Section	Pg	Change From	Change To	Justification
5.3.2 Summary of Clinical Trials	23-26	A double-blind, randomized, placebo-controlled, ascending dose phase 1 study (Protocol ALD403-CLIN-001) to determine the safety and tolerability of ALD403 was conducted in two parts. In Part A (dose escalation), 1 of 7 ALD403 dose levels (range 1 mg to 1000 mg) or placebo was administered intravenously to healthy male subjects, and ALD403 300 mg or placebo was administered intravenously to healthy female subjects. Additionally, ALD403 100 mg or placebo was subcutaneously (SC) administered to a cohort of healthy male subjects. In Part B, sumatriptan 6 mg was administered SC 4 hours after either ALD403 300 mg IV or placebo IV to healthy subjects. In this trial, a total of 55 subjects received a single intravenous dose of ALD403 (range 1 mg to 1000 mg) and 31 subjects received a single dose of placebo, 12 subjects received a single subcutaneous dose of ALD403 (100 mg) and 6 subjects received a single subcutaneous dose of placebo. A total of 179 treatment emergent adverse events (TEAEs) were reported during the trial period in 73 subjects (70.2%). Only one serious adverse event (SAE) was reported. This event was considered unrelated to ALD403. There were no TEAEs that resulted in study	Detailed descriptions of the relevant clinical findings for ALD403 are provided in the Investigator's Brochure (IB). A summary of completed and ongoing ALD403 clinical trials is shown in Table 5.3 *Added Table 5.3 ALD403 Clinical Trials*	Summary of Clinical Trials section updated with most current information.

Section	Pg	Change From	Change To	Justification
		drug administration interruption, death, or study discontinuation; no TEAEs were considered to be severe, life-threatening/disabling, or fatal. ALD403 inhibited capsaicin induced increases in skin blood flow (mediated by CGRP) in a dose dependent manner. The terminal elimination half-life of ALD403 was approximately 28 days. In a second study of frequent episodic migraine (Protocol ALD403-CLIN-002), subjects with 5 to 14 migraine days per month were randomized to receive a single intravenous dose of ALD403 1000 mg or placebo in a double-blind fashion. The primary endpoint was the mean change in frequency of migraine headache days from baseline to Weeks 5-8. Subjects were followed for 24 weeks for additional safety and efficacy analyses. Of 174 subjects randomized, 163 subjects received either ALD403 (81) or placebo (82). There were no significant differences in baseline demographics or characteristics between the two treatment groups. The mean change in migraine days between Weeks 5-8 and baseline was -5.6 (66% decrease) vs. -4.6 (52% decrease) for ALD403 and placebo, respectively (one-sided $p = 0.034$). The proportion of subjects with a 100% reduction in migraine days for 12 weeks		

Section	Pg	Change From	Change To	Justification
		for ALD403 and placebo was 16% vs 0%, respectively ($p <$ 0.001). There were no differences in the type or frequency of adverse events, vital signs, or laboratory safety data between the two treatment groups. A single intravenous dose of ALD403 1000 mg demonstrated efficacy for the preventive treatment of migraine in subjects with frequent episodic migraine. Overall, 89 subjects experienced a total of 199 AEs. Most AEs were transient and mild to moderate in severity. In the ALD403 treatment group, 46 (56.8%) subjects had at least 1 TEAE, and in the placebo group, 43 (52.4%) subjects had at least 1 TEAE. Three subjects (2 in the ALD403 group; 1 in the placebo group) had a total of 6 SAEs, all of which were considered unrelated. There were no TEAEs that resulted in study drug infusion interruption, death, or study discontinuation; no TEAEs were considered to be life-threatening/disabling, or fatal. A second clinical trial (ALD403-CLIN-003) in healthy volunteers has been completed. The trial was a multiple dose, placebo-controlled trial to determine the safety, tolerability, pharmacodynamics, and pharmacokinetics of ALD403 administered subcutaneously in healthy volunteers.		

Section	Pg	Change From	Change To	Justification
		In ALD403-CLIN-003 study 60 subjects were dosed; 36 subjects with ALD403 and 24 subjects with placebo. A total of 58 out of 60 subjects received three doses of assigned study treatment with an interval of one month between each dose. Two out of 60 subjects only received one dose of assigned study treatment. One subject who received one dose withdrew from the trial due to a job change and one subject experienced an unrelated serious adverse event and withdrew from treatment. There were no changes in laboratory parameters, vital signs, or ECGs in subjects dosed with ALD403 or placebo. Treatment-emergent adverse events were reported in 52 (86.7%) of 60 subjects. No significant differences were observed between subjects who received ALD403 and subjects who received placebo in terms of incidence, type, severity, relationship or frequency of TEAEs with the exception of injection site reactions. Only subjects who received ALD403 experienced injection site reactions. These reactions were mild to moderate and included erythema, pruritus and induration. One serious adverse event was reported: musculoskeletal soft tissue injury secondary to a car accident. The event was considered not related to study treatment by the Investigator.		

Section	Pg	Change From	Change To	Justification
		There were no deaths during the trial. A clinical trial (ALD403-CLIN-007) in healthy volunteers was conducted in Australia. This was a multi- dose, placebo-controlled trial to determine the safety, tolerability, pharmacodynamics, and pharmacokinetics of ALD403, a humanized anti-(calcitonin gene-related peptide) monoclonal antibody administered by intramuscular injection. All study visits have been completed as of Dec 10th, 2015 and final data analysis is ongoing. Another clinical trial (ALD403-CLIN-005) in patients with chronic migraine is ongoing in the United States, Australia, New Zealand and Georgia. This trial is a randomized, placebo- controlled, dose-ranging phase 2 trial to evaluate the efficacy, safety, and pharmacokinetics of 10, 30, 100, and 300 mg of ALD403 administered as a single dose intravenously in patients with chronic migraine. Recruitment for this study is complete and follow-up visits are ongoing. Eighteen serious adverse events in twelve subjects have been reported in the ongoing ALD403-CLIN-005 clinical trials as of Feb 5th, 2016. There have been no TEAEs that resulted in death; no TEAEs have been considered to be,		

Section	Pg	Change From	Change To	Justification
		life-threatening/disabling, or fatal.		
5.4 Risks and Benefits	27-28	Migraine patients may gain benefit from the prevention of their migraine with ALD403. No specific toxicities or adverse effects related to the blockade of CGRP by ALD403 have been identified in either the nonclinical toxicology program or the three clinical trials with ALD403 that have been completed to date. Given the limited number (N=184) of subjects who have received ALD403 as of this protocol, there may be uncommon treatment related adverse effects that have not yet been identified. As with all protein therapeutics, there is a risk of a serious allergic reaction. However, no serious allergic reactions have been observed with the administration of ALD403 in humans, to date.	ALD403 may prevent migraine from occurring in patients treated in this trial. No specific toxicities or adverse effects related to the blockade of CGRP by ALD403 have been identified in either the nonclinical toxicology program or the clinical trials with ALD403 that have been completed to date. There may be unknown adverse effects and unforeseeable risks associated with study drug administration or unexpected interactions with another drug that have not yet been identified. As with all protein therapeutics, there is a risk of a serious allergic reaction. In completed ALD403 trials conducted to date, no serious allergic reactions have been observed with the administration of ALD403 in humans. In the completed ALD403 clinical trials with headache patients, the most common observed adverse events (>5%) with receiving ALD403 or placebo included upper respiratory tract infection, back pain, dizziness, arthralgia, urinary tract infection, and headache. The majority of these adverse events were categorized as mild to moderate.	Risk section updated with most current information.

Section	Pg	Change From	Change To	Justification
			Long term data with ALD403 is limited. • Healthy volunteer trials have included limited dosing, short duration of follow up and have not include long term follow-up. • Trials in migraine patients have also included limiting dosing. These trials are currently ongoing and no new significant findings have been noted during the follow-up period to date. The safety findings to date indicate that ALD403 Injection is well tolerated, with ALD403 demonstrating a favorable benefit-risk profile based on review of nonclinical, clinical, and scientific literature data. The sponsor will continue to monitor for significant new information and suspected adverse reactions associated with the use of ALD403.	
7.1.2 Key Secondary Endpoints	29	• 75% migraine responder rate (Weeks 1-4) • 75% migraine responder rate (Weeks 1-12)	• 75% migraine responder rate (Weeks 1-4) • 75% migraine responder rate (Weeks 1-12) • 50% migraine responder rate (Weeks 1-12) • Percentage of subjects with a migraine on the day after dosing	Inclusion of additional endpoints that are believed to be clinically meaningful and would provide additional support and understanding of ALD403's effectiveness in

Section	Pg	Change From	Change To	Justification
				migraine prophylaxis.
7.1.3 Other Secondary Endpoints	29-30	• Headache/migraines with acute medication usage • 50% and 100% migraine responder rates (Weeks 1-12) • Short-Form Health Survey (SF-36) • 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	• Change in acute migraine medication days (Weeks 1-12) • Headache/migraines with acute medication usage • 100% migraine responder rates (Weeks 1-12) • Short-Form Health Survey (SF-36) • 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	The change in acute migraine medication days endpoint has been added as requested by the FDA.

Section	Pg	Change From	Change To	Justification
			• Headache/migraines with severe intensity	
10.12 Week 56 Visit (Day 392± 7 days) End of Study or Early Termination	50	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.	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 approximately 3 month intervals for up to 6 months.	Clarification in immunogenicity testing visit window.
12.1.1 eDiary	57	Subjects will complete a daily headache eDiary from the time of screening to Week 48. The diary should be completed each trial day whether or not the subject had a headache. The compliance data from the eDiary will be made available to the trial site for review. Sites are to review the diary results with the subject and if the subject has not completed the diary daily, counsel the subject on the importance of daily completion of the diary.	Subjects will complete a daily headache eDiary from the time of screening to Week 48. The diary should be completed each trial day whether or not the subject had a headache. These daily entries should also record if the subject took acute migraine medication on that day. The compliance data from the eDiary will be made available to the trial site for review. Sites are to review the diary results with the subject and if the subject has not completed the diary daily, counsel the subject on the importance of daily completion of the diary.	Provide additional information related to the new acute migraine medication endpoint.
12.1.2 Endpoints	60		*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	Provide additional information related to new endpoints.

Section	Pg	Change From	Change To	Justification
			that make up those wider intervals (e.g. the secondary endpoint of Weeks 1-12 will be the average of the Weeks 1-4, 5-8 and 9-12 results). The change from baseline for these measures will be the difference between the post baseline interval and baseline. *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.	
12.3 Immunogenicity	62	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.	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.	Clarification in immunogenicity testing visit window.
13.1 Decision Rule	62-63	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 the key secondary endpoints for 300 mg (first the Weeks 1-4, 75% responder endpoint and then the Weeks 1-12 75% responder endpoint). The procedure will then move on to the 100 mg group the primary endpoint and subsequently the secondary endpoints and then	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	Change in the multiplicity rules to reflect the new key secondary endpoints.

Section	Pg	Change From	Change To	Justification
		similarly to the 30 mg group. Statistical testing will be conducted at the 5% alpha level.	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. This testing algorithm is presented below. Statistical testing will be conducted at the 5% alpha level. *Added statistical chart*	
13.2 Sample Size	63-64	The planned sample size for this study 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. These sample size	The planned sample size for this study 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%	Provide additional information related to the new key secondary endpoints.

Section	Pg	Change From	Change To	Justification
		calculations have been performed using Pass 2008 and are based upon a t-test and Chi-squared tests that should approximate the ANCOVA and CMH tests. [16]	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. [16]	
13.4.2 Efficacy Analyses	66-67	*Secondary Efficacy Analyses* Summary statistics including confidence interval for the treatment differences will be used to summary the results for the secondary endpoints. Testing will be performed for the key secondary responder rate endpoints. This testing will utilize a CMH test. The tests will be stratified by the randomization stratification factor. The time to first migraine analysis will be based upon Kaplan-Meier methods.	*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	Provide additional information related to the new endpoints.

Section	Pg	Change From	Change To	Justification
			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. The missing data rules provided in Section 13.3.2 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 diary on the day following dosing will be included in 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.	

16 References

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