ALDER BIOPHARMACEUTICALS, INC.

Clinical Trial Protocol

Clinical Trial Title	An Open Label Phase 3 Trial to Evaluate the Safety of ALD403 Administered Intravenously in Patients with Chronic Migraine
Protocol Number	ALD403-CLIN-013
Investigational Product	ALD403
Indication	Treatment for the Prevention of Chronic Migraine
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.
Protocol Date (original)	24 October 2016
Amendment 1 Date	25 January 2017
Amendment 2 Date	16 June 2017
Amendment 3 Date	20 November 2017 16 January 2018 (Administrative Changes Only)

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The confidential information in this document is provided to you as an Investigator, potential Investigator, or Consultant, for review by you, your staff, and applicable institutional review committees. This information will not be disclosed to others without written authorization from Alder BioPharmaceuticals, Inc., except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

SIGNATURE PAGE

Declaration of Sponsor

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

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]

VP, Clinical Development
Alder BioPharmaceuticals, Inc.

[redacted]

Date

DECLARATION OF THE PRINCIPAL INVESTIGATOR

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

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.

Principal Investigator

_____ _____
Signature Date

_____
Name (printed)

_____
Title

_____
Institution

1. PROTOCOL SYNOPSIS

Title	An Open Label Phase 3 Trial to Evaluate the Safety of ALD403 Administered Intravenously in Patients with Chronic Migraine
Sponsor	Alder BioPharmaceuticals, Inc. (Alder)
Investigational Product	ALD403, a humanized anti-(calcitonin gene-related peptide) (CGRP) monoclonal antibody
Safety Objective	To evaluate the long term safety of repeat doses of ALD403 administered intravenously (IV) in chronic migraine (CM) patients.
Immunogenicity and Patient Reported Outcomes	To evaluate the pharmacokinetics (PK) and immunogenicity of repeat doses of ALD403 administered IV to patients with chronic migraine. To further evaluate the impact of ALD403 on various patient reported outcomes.
Methodology	This is an open label trial in which 120 eligible subjects will receive infusions of ALD403. The trial will include two treatment phases. The primary treatment phase will include 4 ALD403 infusions 12 weeks apart. The secondary treatment phase will include 4 additional ALD403 infusions 12 weeks apart. In the primary treatment phase, visits will occur on Day 0, Weeks 2, 4, 8, 12, 24, and 36 and subjects will receive 4 IV infusions of ALD403 on Days 0, Weeks 12, 24, and 36. Subjects who receive all 4 infusions of ALD403 in the primary treatment phase may enter the secondary treatment phase. In the secondary treatment phase, subjects will receive up to 4 additional IV infusions of ALD403 for a total of 8 infusions. Visits and ALD403 IV infusions will occur on Weeks 48, 60, 72, and 84. Subjects will be followed for 20 weeks until Week 104 for a total study duration of approximately 106 weeks, including the screening period. Subjects who don't receive all 4 infusions of ALD403 in the primary treatment phase or don't consent for participation in the secondary treatment phase will be followed at Week 48 and Week 56, at which point they will have their End of Trial visit.
Number of Subjects Planned	Approximately 120 subjects will be enrolled and treated at approximately 20 centers in the US.
Subject Selection Criteria	Males and females between 18 and 65 years of age, inclusive, who were diagnosed with migraines at ≤ 50 years of age, and

	have a history of chronic migraine for ≥ 12 months before screening.
Investigational Product, Dose and Schedule	Eight intravenous infusions of 300mg ALD403 will be given 12 weeks apart. Infusions will occur on Day 0, Week 12 (Day 84 +/- 3 days); Week 24 (Day 168 +/- 3 days); Week 36 (Day 252 +/- 3 days); Week 48 (Day 336 -7/+14 days); Week 60 (Day 420 +/- 7 days); Week 72 (Day 504 +/- 7 days); and Week 84 (Day 588 +/- 7 days).
Duration of Treatment	Up to 8 IV infusions of ALD403 will be given approximately 12 weeks apart over an 84 week period.
Duration of Clinical Trial Participation	The trial participation period is approximately 106 weeks which includes: • 2-week screening period, • 48-week primary treatment administration period, • 36-week secondary treatment administration period • 20-week follow-up period.
Clinical Trial Endpoints	Safety Endpoints • Adverse events (AEs) and serious adverse events (SAEs) • Clinical laboratory assessments • Vital Signs • Electrocardiograms (ECGs) • Columbia-Suicide Severity Rating Scale (C-SSRS) Patient Reported Outcomes • Patient Global Impression of Change (PGIC) • Short-Form Health Survey (SF-36) • Health-Related Quality of Life (EQ-5D-5L) • Headache Impact Test (HIT-6) • Most Bothersome Symptom (MBS) • Migraine Disability Assessment (MIDAS) PK and Immunogenicity Endpoints • Free ALD403 plasma concentrations • Development of specific anti-ALD403 antibodies • Characterization of specific anti-ALD403 antibodies for neutralizing activity
Concomitant Medications	• Subjects on stable medication for headache prophylaxis for 3 months prior to screening will be permitted to continue use during the study, provided there are no alterations to their regimen, except as allowed per Investigator discretion. After Week 48, changes to migraine prophylactic treatment are

	allowed per Investigator or the subject's primary treating healthcare professional. • Barbiturates and prescription opiates are allowed for ≤ 4 days per month provided the subject has been on a stable regimen (≤ 4 days per month) for at least 2 months prior to screening and through entire study. After enrollment, the use of prescription barbiturates and opiates is allowed as medically necessary and prescribed by a licensed healthcare professional for indications other than migraine. • 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 and through entire study. • Devices, neuromodulation, neurostimulation, or injectable therapy (trigger point injections) for headache prophylaxis are prohibited 2 months prior to screening and through entire study. • Any use of monoamine oxidase inhibitors (MAOIs), ketamine, methysergide, methylergonovine, or nimesulide within 3 months prior to screening and throughout the entire trial is prohibited.
Sample Size	The planned sample size for the study is 120 treated subjects. It is assumed that over 75% of these subjects will complete the primary treatment phase resulting in at least 90 subjects with one year of safety data collection.
Statistical Analysis	Study endpoints will be summarized with descriptive statistics These summary measures will include change from baseline, where baseline is the last result prior to treatment. Testing of these change from baseline results for the SF-36, MIDAS and HIT-6 will be performed.
PK and Immunogenicity Analyses	The concentrations of ALD403 will be measured in plasma from all ALD403 treated subjects using a validated assay method. The PK analysis of plasma will include determination of the ALD403 concentrations at Day 0 (pre-dose), immediately post-dose (within 15 minutes of end of infusion), and Weeks 2, 4, 8, 12 (pre-dose), 24 (pre-dose), 36 (pre-dose), 48 (pre-dose), 72 (pre-dose), and 104 End of Trial/Early Withdrawal. Population PK analysis will be performed on the results for ALD403 concentrations obtained during this study in combination with the results from other studies of ALD403 in normal subjects and migraine patients. Blood samples will be collected for the detection of anti-ALD403 antibody, and when appropriate the samples will be analyzed also for neutralizing anti-ALD403 antibody activity at Day 0 (pre-

	dose), and on Weeks 2, 4, 8, 12 (pre-dose), 24 (pre-dose), 36 (pre-dose), 48 (pre-dose), 72 (pre-dose), and 104 End of Trial/Early Withdrawal. Subjects who test positive for specific anti-ALD403 antibodies at the time of the last study visit will be asked to provide up to two additional blood samples for immunogenicity testing at approximately 3 month intervals for up to 6 months.

2. SCHEDULE OF EVENTS

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

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

3. LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BMI	Body Mass Index
BP	Blood pressure
CGRP	Calcitonin Gene-Related Peptide
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EQ-5D-5L	Health-Related Quality of Life
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIT-6	Headache Impact Test
IB	Investigator's Brochure
ICD	International Classification of Diseases
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICHD	International Classification of Headache Disorders
IHS	International Headache Society
IgG1	Immunoglobulin G1
IP	Investigational Product
IRB	Institutional Review Board
IV	Intravenous
Kg	Kilogram
LLOQ	Lower Limit of Quantification
M	Molarity
m2	Meter squared
mAb	Monoclonal antibody

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

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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 for the prophylaxis of migraine.

5.2. Background

Migraine is a highly prevalent paroxysmal neurological disease characterized by recurrent episodes of moderate to severe headache associated with physiological disruptions of neurological, gastrointestinal, and sensory function. Episodes typically last between 4 and 72 hours and recur often without warning over decades of time. It is most prevalent through the 3rd and 4th decades of life with a significant gender bias of 3:1 for women.[1] Migraine is the most prevalent neurological disease for which medical treatment is sought, and considered the 6th leading cause of disability in the world.[2] Annually, lost work time and diminished productivity attributable to migraine costs American employers an estimated $19.6 billion.[3]

Migraine appears to have a significant genetic/epigenetic component to its etiology and it is observed in all age groups, races, and ethnicities. Generally, migraine begins as an episodic disease. Between episodes of migraine the nervous system returns to a normal (premorbid) state of function. However, approximately 2.5% of people with episodic migraine will annually transform from episodic to chronic migraine, meaning they are experiencing migraine on greater than 15 days per month for at least 3 consecutive months.[4] For those with chronic migraine, the headaches are more intense; migraine-associated symptoms, more severe; and the disease-related impact and disability are much greater than observed for episodic migraine.[5] In addition, chronic migraine is associated with more co-morbid diseases such as anxiety, depression, and non-headache pain.[6]

The pathophysiology of migraine is complex and incompletely understood. Current models of migraine are based on a genetically determined hyper-excitable nervous system characterized by a lowered threshold to sensory activation and uniqueness in its sensory processing.[7] Interactions between this migraine nervous system and specific internal and external stimuli (migraine triggers) can result in activation of the trigeminovascular system (TVS). Once activated the TVS releases various vasoactive peptides generating peripheral sensitization of trigeminal and upper

cervical nociceptors. The ensuing peripheral nociceptive stimuli synapse in the Trigeminal Nucleus Caudalis to ultimately create a state of central sensitization.[8] Clinically, this process is observed as a fully developed attack of migraine.

Central to this model of migraine is calcitonin gene-related peptide (CGRP). CGRP is one of the most abundant peptides in the human body and is produced in both peripheral and central neurons. It is abundant in trigeminal neurons and when released is involved in the vasodilation, inflammatory cascade, and pain transmission associated with migraine. In both peripheral and central pain pathways CGRP is associated with pain transmission and neuronal sensitization.[9] Intravenous (IV) infusions of CGRP can cause a migraine-like headache in susceptible individuals with migraine.[10] In addition, many pharmacological agents used as acute or prophylactic treatment of migraine are known to inhibit CGRP. Thus, CGRP is an attractive target for development of novel migraine pharmacology.

Currently the pharmacological treatment of migraine can be divided into acute treatment, that is, medications designed to reverse a migraine after it is initiated and preventive treatment that is designed to protect the nervous system from generating migraine. Acute treatments are used intermittently only as needed to stop an attack while preventative treatments are used on a sustained basis for periods of months to years. Acute treatment while generally quite effective can worsen the severity and frequency of migraine when used too frequently, a condition called medication overuse headache (MOH).[4] MOH is common in populations with frequent episodic and chronic migraine.[11]

Numerous medications are used to prevent migraine but to date none have been designed specifically for migraine. These commonly include tricyclic antidepressants, beta-blockers, and certain anticonvulsants. It is estimated that 45% of adults with frequent episodic migraine and virtually all with chronic migraine would benefit from effective preventive medications yet only an estimated 12% of this population are currently using a migraine preventive.[1] In large measure, this is due to poor tolerability, lack of efficacy, and failure to adhere to treatment. Clearly there is a medical need to develop effective, well-tolerated and safe preventive treatments for migraine.

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 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.

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 as a class effect.

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.

Definitive embryo-fetal development studies with ALD403 in rats and rabbits have been conducted. 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 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 (completed)	Phase 1 (Safety)	Healthy Volunteer	60	49	11
ALD403-CLIN-009 (completed)	Phase 1 (Safety)	Healthy Volunteer	36	24	12
ALD403-CLIN-005 (completed)	Phase 2 Safety & Efficacy	Chronic Migraine	665	531	134
ALD403-CLIN-006[2] (ongoing)	Phase 3 Safety & Efficacy	Frequent Episodic Migraine	900		
ALD403-CLIN-010[1] (completed)	Phase 1 (Safety)	Healthy Volunteer	24	16	8
ALD403-CLIN-011[2] (ongoing)	Phase 3 Safety & Efficacy	Chronic Migraine	1121		
ALD403-CLIN-012[1] (ongoing)	Phase 1 (Safety)	Type 1 Diabetic (T1DM)	21	14	7

[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

A dose of 300mg ALD403 administered by IV infusion every 12 weeks has shown efficacy in the treatment of CM and is the maximum anticipated dose and schedule. No dose limiting, treatment related adverse effects have been observed following ALD403 administration up to 1000mg. ALD403 single dose levels up to 1000mg have generally been well tolerated.

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 included 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. Safety Objective

The primary objective is:

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

6.2. Immunogenicity and Patient Reported Outcomes

The secondary objective is:

- To evaluate the pharmacokinetics (PK) and immunogenicity of repeat doses of ALD403 administered IV to patients with chronic migraine.
- To further evaluate the impact of ALD403 on various patient reported outcomes.

7. TRIAL DESIGN

7.1. Clinical Trial Endpoints

7.1.1. Safety Endpoints

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

7.1.2. Patient Reported Outcomes:

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

7.1.3. PK and Immunogenicity Endpoints:

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

7.2. Clinical Trial Design

This is an open label trial of intravenous (IV) infusions of ALD403 in patients with chronic migraine. The trial will include two treatment phases. The primary treatment phase will include 4 infusions of ALD403 12 weeks apart. The secondary treatment phase will include up to 4 additional infusions of ALD403 12 weeks apart following the primary treatment phase.

Subjects who provide informed consent will be evaluated for eligibility based upon the inclusion and exclusion criteria. In the primary treatment phase, visits will occur on Day 0, Weeks 2, 4, 8, 12, 24, and 36 and subjects will receive 4 IV infusions of ALD403 on Days 0, Weeks 12, 24, and 36.

Subjects who receive all 4 infusions of ALD403 in the primary treatment phase may enter the secondary treatment phase. In the secondary treatment phase, subjects will receive up to 4 additional infusions for a total of 8 infusions. Visits and ALD403 IV infusions will occur on Weeks 48, 60, 72, and 84. Subjects will be followed for 20 weeks until Week 104 for a total study duration of approximately 106 weeks, including the screening period.

Subjects who don't receive all 4 infusions of ALD403 in the primary treatment phase or don't consent for participation in the secondary treatment phase will be followed at Week 48 and Week 56, at which point they will have their End of Trial visit.

Approximately 120 subjects will be enrolled and treated. Study specific assessments will be conducted according to the Schedule of Events presented in Section 2.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Inclusion Criteria

A subject must meet all of the following criteria during the screening period and on Day 0 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 an Institutional Review Board (IRB) or Ethics Committee (EC).
2. Male or female 18 – 65 years of age inclusive at time of informed consent.
3. Diagnosis of migraine at ≤ 50 years of age with history of chronic migraine ≥ 1 year (ICHD-3 beta, 2013 Section 1.3).
4. Prescription or over-the-counter medication for acute and/or prophylactic treatment of migraine has been prescribed or recommended by a healthcare professional.
5. Women of child-bearing potential, and males with partners of child-bearing potential, must agree to use adequate contraception for six months after last dose of study drug. Adequate contraception includes oral, transdermal or injectable [depot] estrogen, and/or progestogen, selective estrogen receptor modulator 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.
6. Has adequate venous access for administration of the investigational product and collection of blood samples.
7. Any hormonal therapy (e.g., contraceptives, hormone replacement therapy) use is stable and ongoing for at least 3 months prior to screening and throughout the trial.
8. Willing, committed, and able to comply with scheduled clinic visits and complete all trial-related procedures.
9. Any prophylactic use of medications for headaches must be stable for at least 3 months prior to screening.

10. Limited use of barbiturates (including Fiorinal®, Fioricet®, or any other combination containing butalbital) or prescription opiates is allowed if a stable dose is maintained for 2 months prior to screening and is not expected to exceed 4 days per month.
11. 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.

8.2. Exclusion Criteria

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

1. Receipt of any monoclonal antibody treatment, including ALD403 or any monoclonal antibody targeting the CGRP pathway (within or outside a clinical trial) within 6 months before screening.
2. Confounding and clinically significant pain syndromes (e.g. fibromyalgia, chronic low back pain, complex regional back syndrome, temporomandibular disorders).
3. Psychiatric conditions that are uncontrolled and/or untreated, including conditions that are not controlled for a minimum of 6 months prior to screening. Patients with a lifetime history of psychosis, mania, or dementia are excluded.
4. History or diagnosis of complicated migraine (ICHD-III beta version, 2013), chronic tension-type headache, hypnic headache, cluster headache, hemicrania continua, new daily persistent headache, or sporadic and familial hemiplegic migraine
5. Any use of approved devices, neuromodulation, neurostimulation or injectable therapy (trigger point injections, extracranial nerve blocks, facet joint for headache prophylaxis are prohibited 2 months prior to screening and during screening.
6. Any use of botulinum toxin for migraine or for any other medical/cosmetic reasons requiring injections in the head, face, or neck within 4 months prior to screening and during screening.
7. Any use of monoamine oxidase inhibitors (MAOIs), ketamine, methysergide, methylergonovine, or nimesulide within 3 months prior to screening.
8. Have present or previous malignancies, except:

- Squamous or basal skin cell carcinoma with excision, without evidence of recurrence, or
- Malignancy ≥ 10 years since diagnosis/treatment without evidence of recurrence.

9. Subject has known history or evidence of cardiovascular disease, arteriosclerosis, cardiomyopathy, coronary artery disease, serious heart rhythm abnormalities, neurological disease, cerebrovascular disease, diabetes, Raynaud's disease, or life-threatening allergy (e.g, anaphylaxis). If questions arise, the Investigator should contact the Medical Monitor for guidance.
10. Primary hypertension that is uncontrolled or newly diagnosed (systolic BP of >139 mm Hg or diastolic BP of >89 mm Hg) at screening or secondary hypertension. Mild primary hypertension that is well-controlled for ≥6 months prior to screening is allowed.
11. Clinically significant abnormal ECG at screening or on Day 0.
12. Any clinically significant concurrent medical condition or clinically significant laboratory abnormality at screening or on Day 0.
13. Body Mass Index (BMI) ≥ 39 kg/m2 at screening.
14. The subject is at 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 have a lifetime history of a serious suicide attempt or multiple suicide attempts (i.e., actual, interrupted, or aborted attempts), had any suicidal behavior in the past 5 years (i.e., preparatory acts or behavior), or had suicidal ideation of Type 3, 4 or 5 (i.e., suicidal ideation with any method without intent to act or suicidal ideation with intent to act, with or without a plan), in the past 6 months, as measured by the C-SSRS at screening or on Day 0.
15. Any history or evidence of substance abuse or dependence (e.g., alcohol, opiates, amphetamines, and barbiturates) within the past 2 years according to the International Classification of Diseases (ICD) 10: F10-19.
16. Pregnant, breastfeeding, or planning to become pregnant during the trial.
17. 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.

18. Planned or current participation in any other clinical trial for the duration of this clinical trial, or within 6 months prior to screening. NOTE: Subjects who participated in prior clinical trials of CGRP antagonists, including ALD403-CLIN-005, may be eligible to participate if they
    - had their last dose of study drug more than 6 months prior to screening, AND
    - had no clinically significant adverse events related to study drug during their participation in the prior trial as assessed by the Investigator prior to enrollment.
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. Any condition that, in the opinion of the investigator, would make the subject unsuitable for the clinical trial.
22. Employees of Alder, the CRO(s), 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 subject signs the ICF they are registered in the Interactive Web Response System (IWRS), which will assign a unique subject number. The first three digits of the subject number identify the site, and the remaining digits identify the subject.

Subjects who fail screening may be rescreened if approved in advance by the Medical Monitor.

8.4. Subject Treatment Discontinuation and Early Withdrawal

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

8.4.1. Criteria for Discontinuation from Study Treatment

Study treatment must be discontinued for the following reasons:

- Pregnancy
- Suicidal ideation with intent, with or without a plan (i.e., 'Yes' to suicidal ideation questions 4 or 5) or any suicidal behavior as determined by the C-SSRS.

Subjects discontinued due to suicidal ideation and/or suicidal behavior must be referred to a mental health specialist as specified in Section 11.1.9.

Study treatment may also be discontinued for the following reasons:

- Adverse Event
- Subject decision
- Investigator decision
- Termination of the study by Alder

If a subject discontinues study treatment due to a medical condition, Investigators must provide adequate medical treatment during study visits. Prior to removing a subject from study treatment, the decision should be discussed with the 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 the 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 Alder
- Investigator decision
- Lost to follow-up

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

8.4.2.1. 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 and the last study assessment is performed.

8.4.2.2. Follow-up for Early Withdrawal

Subjects who withdraw early from study participation due to any reasons 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 screening but do not receive study treatment may discontinue the study without any further procedures.

8.4.3. Replacement Policy

Subjects who are withdrawn from the clinical trial after dosing will not be replaced.

8.4.4. Lost to Follow-Up

If the subject fails to attend scheduled study visits or to respond to requests for follow-up, the clinical trial site will send a registered letter, at a minimum, to the subject requesting contact with the clinic. All attempts to resume contact (including copies of written correspondence and documentation of telephone and email contact attempts) will be included in the source documentation. Subjects who do not respond to requests for follow-up after all reasonable attempts to establish contact will be considered lost to follow-up.

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 for the prevention 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. Subjects will receive an IV infusion of ALD403 300 mg Injection in 100 mL of 0.9% saline.

9.2. Investigational Product Administration

ALD403 (approximate volume of 100 mL) is administered IV over a period of 30 (+15) minutes at the visits specified in Schedule of Events in Section 2, by the Investigator or designee. Infusions may be administered for a total duration of up to 1 hour, if needed in the judgement of the Investigator.

If the subject experiences a headache or migraine on dosing day, dosing may occur if, in the investigator's opinion, it will not compromise the safety of the subject. The Medical Monitor may be consulted as needed. Subjects must remain in the care facility and be monitored by site staff for at least 2 hours after the infusion ends. The Investigator or sub-investigator must be immediately available during the infusion and for at least 2 hours after the end of infusion to assess each subject for the occurrence of adverse events. Subjects will be requested to stay longer than 2 hours after the end of infusion should the investigator determine it is clinically warranted (i.e., subjects should be observed until all AEs are resolved or clinically stable). The timeframe for the post-dose observation period must be documented in the source record.

Further instructions on ALD403 preparation and administration can be found in the Pharmacy Manual.

9.2.1. Packaging and Labeling

Before the shipment to the investigative sites, ALD403 will be labeled with information required by regulatory agencies, such as a statement that it is limited to investigational use. At the investigative site, each ALD403 preparation will be labeled by the site.

9.2.2. Storage and Handling of Investigational Product

ALD403 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 manufacturer instructions.

Investigators shall take adequate precautions, including storage of ALD403 in a securely locked, substantially constructed cabinet or other securely locked, substantially constructed enclosure, access to which is limited to prevent theft or diversion of the substance into illegal channels of distribution.

9.2.3. Accountability and Disposition of ALD403

The Investigator is responsible for maintaining accurate ALD403 accountability records throughout the clinical trial. The site must maintain an Investigational Product Accountability Logas per the study Pharmacy Manual. Where more than one secure area is being used for storage at a site, all movement of ALD403 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 ALD403 shipment is a form listing lot numbers and quantity shipped. The Investigator, responsible pharmacist, or designee, will sign and return to Alder, 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 all unused ALD403. 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 or returned according to Alder directive. Destruction must be in accordance with local regulations for the product type and destruction documentation must be provided to Alder.

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

9.3. Concomitant Medications

Any concomitant therapy used from the time the subject signs the informed consent through Week 104 must be recorded on the CRF, including medications required for treatment of any AEs or SAEs. The medication name, dosage, date, and indication for use must be recorded. 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.

Subjects on stable medication for headache prophylaxis for 3 months prior to screening will be permitted to continue use during the study, provided there are no alterations to their regimen, except as allowed per Investigator discretion. After Week 48, changes to migraine prophylactic treatment are allowed per Investigator or the subject's primary treating healthcare professional. A list of the migraine preventive therapies with established or probable efficacy is in Section 15.1 for reference. Sites are required to indicate if a medication is used for prophylaxis purposes or if it is used for the acute treatment of migraines.

The following medications are **restricted:**

- Prescription barbiturates and opiates are allowed for ≤ 4 days per month provided the subject has been on a stable regimen (≤ 4 days per month) for at least 2 months prior to screening and throughout the entire trial. After enrollment, the use of prescription barbiturates and opiates is allowed as medically necessary and prescribed by a licensed healthcare professional for indications other than migraine.
- 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 and throughout the entire trial.
- Devices, neuromodulation, neurostimulation, or injectable therapy (trigger point injections) for headache prophylaxis are prohibited 2 months prior to screening and throughout the entire trial.

- Any use of monoamine oxidase inhibitors (MAOIs), ketamine, methysergide, methylergonovine, or nimesulide within 3 months prior to screening and throughout the entire trial.

10. STUDY ASSESSMENTS AND PROCEDURES

10.1. Schedule of Events

Assessments and procedures at each visit are summarized in Section 2 - Schedule of Events.

10.2. Assessments and Procedures

10.2.1. Demographics

The year of birth, age, sex, ethnicity, race, and how the subject was recruited to the trial will be collected in source records and in the CRF.

10.2.2. Medical History

Significant historic and current medical conditions or illnesses, allergies to medications, and prior surgical interventions will be recorded in the source records and in the CRF. Symptoms that are ongoing at the time of informed consent will be considered medical history.

Migraine history will also be collected in the source records and the CRF, including age at diagnosis of chronic migraine as well as other details of the subjects' history with migraine. If the subject is not a current or past user of a prescribed medication for migraine, the Medical Monitor should be consulted.

Investigators should demonstrate due diligence in trying to obtain medical records. All attempts to obtain medical records should be documented. If medical records cannot be obtained, history may be confirmed via patient interview in order to obtain sufficient information to confirm all eligibility criteria are met.

10.2.3. Physical Examinations

Physical examinations will be performed at the times noted in the Schedule of Events in Section 2 and must be performed by an Investigator who has been trained and delegated the task on the Delegation of Authority Log.

The screening physical examination will include a review of all body systems. For all other visits that call for a physical examination, the body systems reviewed will be at the discretion of the Investigator.

Physical examination may include weight measurement as specified in Schedule of Events in Section 2. Height will be measured at screening only.

Abnormal physical examination findings at the screening visit will be recorded as medical history. Any new or worsening physical examination finding identified after informed consent will be considered an AE.

10.2.4. Vital Signs

Vital signs, including blood pressure (BP) and pulse will be measured at the time points specified in the Schedule of Events in Section 2.

When measuring vital signs, the subject should be seated comfortably, with back supported and rested for 5 minutes before the measurements begin.

For BP measurements, the subject should have their upper arm positioned so that it is level with their heart and feet flat on the floor. Excess clothing that might interfere with the BP cuff or constrict blood flow in the arm should be removed. A blood pressure cuff of appropriate size should be wrapped around the bare upper arm such that the bladder portion of the cuff extends at least 80% around the arm. The center of the bladder should be in line with the brachial artery so as to allow the stethoscope diaphragm clear access to the brachial artery. Site staff and subject should refrain from talking during the reading. Blood pressure may be repeated to confirm measurement.

10.2.5. Questionnaires

Questionnaires should be administered to subjects in the order listed below at the time points specified in the Schedule of Events in Section 2:

1. Columbia-Suicide Severity Rating Scale (C-SSRS)
2. Most Bothersome Symptom (MBS)
3. Patient Global Impression of Change (PGIC)
4. Short-Form Health Survey (SF-36)
5. Health-Related Quality of Life (EQ-5D-5L)
6. Headache Impact Test (HIT-6)
7. The Migraine Disability Assessment (MIDAS)

All questionnaires should be administered prior to dosing at dosing visits. Protocol number, subject number and date and time of administration must be captured on all questionnaires. All questionnaires completed by subjects must be reviewed for completeness and clarity by site staff prior to the subject leaving the clinic. The subject should be asked to complete any unanswered questions.

10.2.5.1. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS will be administered by trained (i.e., C-SSRS certified) site staff at the time points specified in the Schedule of Events in Section 2. The C-SSRS must be administered prior to dosing at dosing visits. The C-SSRS "Baseline/Screening" version will be used for the screening visit, and the C-SSRS "Since Last Visit" version will be used for all subsequent visits.

10.2.5.2. Most Bothersome Symptom (MBS)

The Investigator will verbally obtain the most bothersome symptom associated with the subject's migraines during the screening visit. The most bothersome symptom will be captured in the eCRF and may include nausea, vomiting, sensitivity to light, sensitivity to sound, mental cloudiness, fatigue, pain with activity, mood changes, or other migraine related symptom.

At each subsequent visit, the site staff will provide the questionnaire along with the other subject-completed questionnaires listed in Section 10.2.5.

10.2.5.3. Other Questionnaires

The following questionnaires will be administered at days and times provided in the Schedule of Events in Section 2. Subjects will be given the questionnaires in the order specified below and asked to review the brief instructions on each questionnaire and complete.

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

10.2.6. 12-Lead ECG

ECGs will be performed using a 12-lead ECG device provided for the study at the time points specified in the Schedule of Events in Section 2. On dosing visits ECGs must be performed prior to dosing and up to 2 hours (+ 30 min) after dosing.

ECG data will be transmitted and read centrally by a cardiologist, however, the Investigator must review the ECG to ensure there are no clinically significant abnormalities prior to dosing. In addition, all centrally read ECG reports must be reviewed by the Investigator and evaluated for clinical significance.

All ECGs are expected to be performed on the ECG device provided to the site by Alder. A local ECG device may be used only in the event that there are technical issues with the central ECG device that cannot be resolved while the subject is onsite. All technical issues must be reported immediately to the ECG vendor help desk.

10.2.7. Laboratory Samples and Testing

10.2.7.1. Urine Drug Screening

Drugs of abuse testing will be performed on urine samples during the screening visit. Urine drug screen kits will be provided by the central lab and the test performed on site.

10.2.7.2. Pregnancy Testing

Urine pregnancy tests will be performed for all female subjects, regardless of childbearing potential, at the specified time points in the Schedule of Events, Section 2. On dosing visits urine pregnancy tests must be performed prior to dosing.

Urine pregnancy test kits will be provided by the central lab, and the test performed on site.

The contraceptive method used by females of child-bearing potential and males with partners of child-bearing potential must be confirmed with the subject and recorded in the source record at screening, and reconfirmed with the subject and recorded in the source record at each subsequent study visit.

10.2.7.3. Clinical Laboratory Testing

Blood samples for clinical laboratory tests, including hematology, serum chemistry and serology (including HIV, Hepatitis B, and Hepatitis C), will be collected at the time points specified in the Schedule of Events in Section 2. Clinical laboratory tests performed are listed in Section 11.1.7.

All clinical laboratory samples will be initially processed by site staff and shipped to a central laboratory for analysis as specified in the Laboratory Manual. An Investigator listed on the Form FDA 1572 will review all lab reports and document clinical significance for any out-of-range lab value(s) listed in the report.

10.2.7.4. Pharmacokinetic and Immunogenicity Sampling

Blood samples will be collected for ALD403 plasma PK and for determination of anti-ALD403 antibodies in serum (immunogenicity) at specified time points in the Schedule of Events in Section 2. All samples will be initially processed, stored, and shipped as specified in the Laboratory Manual.

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.
- Any abnormal assessment or laboratory findings considered by the Investigator to be clinically significant. Clinically significant findings include but are not limited to those that lead to discontinuation or interruption of study treatment, require therapeutic intervention, or require a change in subject management.

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 ALD403, as outlined below.

Seriousness

An adverse event or suspected adverse event is considered serious if in the view of either the Investigator or Alder, 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).

Of note:

  - A social hospitalization (i.e., hospitalizations for pre-admissions not due to an acute medical issue) is not considered an SAE.
  - Hospitalization is considered a greater than 24 hour hospital admission.

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 ALD403

The Investigator is required to assess the causality/relationship between each AE and the ALD403 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 ALD403 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 ALD403 (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 ALD403.

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 ALD403.

An 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 ALD403.

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
- 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 ALD403 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/enrollment number, 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. Alder, or Alder's designee will be responsible for information processing and reporting in accordance with applicable local and regulatory requirements.

Alder 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.

Alder, or Alder's 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, platelet count, red blood cell (RBC) count, 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 ALD403 or may have been pregnant at the time of ALD403 exposure, or the partner of a male subject becomes pregnant following ALD403 administration to the male subject, the pregnancy must be reported to Alder within five business days of the Investigator becoming aware of the pregnancy. Pregnancy information will be reported to Alder using the Exposure In-Utero Forms in EDC. An Exposure In-Utero Notification Form should be used to report a pregnancy that occurs within 30 days after completion of the trial.

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 Alder regarding:

- The course of the pregnancy including perinatal and neonatal outcome, 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.[12] 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 in the Suicidal Ideation section or answers "yes" to any question in the Suicidal Behavior section of the C-SSRS will be discontinued from the study treatment as specified in Section 8.4.1, and referred by Investigators to a mental health specialist. Affirmative answers to questions 4 or 5 for suicidal ideation or to any question for suicidal behavior will be reported in EDC as an AE.

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 ALD403, clinical judgment should be used to provide the appropriate response including the consideration of discontinuation of ALD403. Subjects who have experienced a potential significant allergic reaction after administration of ALD403 should not receive subsequent doses until discussed with the Medical Monitor and an appropriate disposition has been agreed upon.

If a subject experiences a potential systemic allergic reaction, as assessed by the Investigator, the site will collect additional blood specimens using the immune response lab kit at the time of the event as per laboratory manual. The Medical Monitor may request a 2nd immune response lab kit be collected in approximately 4-6 weeks after the 1st collection. This immune response assessment includes serum histamine, serum tryptase, immunoglobulin E, and complement components.

Whether maintained in a "formal crash cart" or separately, the following is a requirement at the site:

- CPR certification by site staff performing study assessments
- Automated external defibrillator (AED)
- Emergency medications including antihistamines, bronchodilators, IV saline, corticosteroids, acetaminophen, and epinephrine

The AED and emergency medication should be immediately available on an Investigational product infusion day.

12. ASSESSMENT OF QUESTIONNAIRES, PK, AND IMMUNOGENICITY

12.1. Questionnaires

Patient Global Impression of Change (PGIC)

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

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

The SF-36 v2.0 is a health survey containing 36 questions consisting of eight scaled scores to measure quality of life over the past 4 weeks. See Appendix 15.4. 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.

Headache Impact Test (HIT-6 v1.0)

The Headache Impact Test (HIT) is a tool used to measure the impact and effect on the ability to function normally in daily life when a headache occurs. The HIT is a 6 question, Likert-type, self-reporting questionnaire with responses ranging from "Never" to "Always" with the following response scores: Never=6, Rarely=8, Sometimes=10, Very Often=11, Always=13. See Appendix 15.3. The total score for the HIT is the sum of each response score and will be treated

as missing if the response is missing for one or more questions. The HIT total score ranges from 36 to 78, with score ranges having the following life impact:

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

Most Bothersome Symptom (MBS)

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

The Migraine Disability Assessment (MIDAS)

The MIDAS questionnaire measures the effect headaches have on the subject's daily functioning. Midas is composed of five questions that ask about the subject's performance over the past 3 months. The response to each question is provided in number of days which are totaled to determine the level of disability: 0-5, MIDAS Grade I, Little or no disability; 6-10, MIDAS Grade II, Mild disability; 11-20, MIDAS Grade III, Moderate disability; 21+, MIDAS Grade IV, Severe disability.

12.2. Pharmacokinetics

The concentrations of ALD403 will be measured in plasma from all treated subjects using a validated assay. The PK analysis will include evaluations of concentration-time profiles for free ALD403 on Day 0 (pre-dose and immediately post-dose (within 15 minutes of end of infusion), and Weeks 2, 4, 8, 12 (pre-dose), 24 (pre-dose), 36 (pre-dose), 48 (pre-dose), 72 (pre-dose), and 104 or ET.

All plasma PK samples will be stored at -20°C or below prior to shipping to the central laboratory.

Additional sample handling, processing, storage, labeling, 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 on Day 0 (pre-dose), and Weeks 2, 4, 8, 12 (pre-dose), 24 (pre-dose), 36 (pre-dose), 48 (pre-dose), 72 (pre-dose) and 104 or ET to test for the development of antibodies to ALD403. The immunogenicity will be assessed in serum from all ALD403-treated subjects using a validated assay.

If a subject terminates early from the clinical trial, all efforts will be made to collect blood samples to analyze for 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 anti-ALD403 antibody for the potential to neutralize (NAb) ALD403 activity. Subjects who test positive for specific anti-ALD403 antibodies at the time of the last study visit will be asked to provide up to 2 additional blood samples for immunogenicity testing at approximately 3 month intervals for up to 6 months.

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

13. STATISTICAL CONSIDERATIONS

13.1. Sample Size

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

13.2. General Considerations

13.2.1. Definition of Baseline

The baseline assessment will be the latest available valid measurement taken prior to the administration of Investigational Product. This will generally be Day 0.

13.2.2. Handling of Missing Data

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

13.2.3. Populations to be Analyzed

The Safety Population, the analysis population for this study, includes all subjects who received at least one dose of treatment.

13.3. Interim Analyses

This study will include a formal interim analysis after all subjects have completed the primary treatment phase.

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. Change from baseline will be summarized as well as the results at the time point.

13.4.1. Subject Disposition, Demographics, and Baseline Characteristics

An accounting of subjects by disposition will be presented. This summarization will include a summary of all subjects who have received trial drug ALD403. Demographic, baseline characteristics, migraine history and concomitant medications (coded by the World Health Organization Drug Dictionary) will be summarized descriptively.

13.4.2. Efficacy Analyses

The Secondary endpoints will be summarized with descriptive statistics by time point. These summary measures will be based upon the observed results and where appropriate the change from baseline results. Testing of these change from baseline results for the SF-36, MIDAS and HIT-6 will be performed at Weeks 12, 24, 36, 48, 60, 72, 84 and 104. For SF-36 tests will be performed for the change in the Mental Component and Physical Component scores and for the HIT-6 and MIDAS tests will be performed based upon the change in total score. The tests will be a t-test.

13.4.3. Pharmacokinetic Analyses

Analysis of Drug Concentrations

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

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

13.4.4. Safety Analyses

13.4.4.1. Adverse Events

The incidence of all AEs will be tabulated. 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 treatment administration will be listed.

An overview of AEs, which includes subject incidence of 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 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

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 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

Alder, or Alder's designee will assess each site to verify the qualifications of the Investigator, according to Alder's, or designee's SOPs. Site facilities will be inspected, and the Investigator will be 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, but are not limited to, laboratory reports and original ECGs.

14.2.1. 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, e.g., 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, e.g., faxed laboratory reports and hard copy laboratory reports, faxed initial results and hard copy, final report.

14.2.2. Case Report Form

The data collected during the study (except clinical laboratory test results, ECG results, PK analyses, Immunogenicity) will be recorded in the subject's eCRF. The Short-Form Health

Survey (SF-36), Health related Quality of Life (EQ-5D-5L), Headache Impact Test (HIT-6), Patient Global Impression of Change (PGIC), Most Bothersome Symptom (MBS) and C-SSRS will be completed on paper forms and then entered into the EDC system. The study site(s) will use an electronic data capture (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 eCRFs must be reviewed after being source verified by the Monitor and electronically signed and dated by the Investigator.

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

14.4. Good Clinical Practice

The procedures set out in this clinical trial protocol are designed to ensure that Alder and the 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.

14.5. 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 screened for the clinical trial as well as those currently enrolled in the clinical trial. If a male subject's partner becomes pregnant during the subject's participation in the trial, the partner will be asked to sign a separate pregnancy informed consent form to follow the pregnancy outcome, any complications, and the health of the baby. The pregnancy consent should be obtained at the time the Investigator becomes aware of the pregnancy.

14.6. 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. Alder must ensure that all ethical and legal requirements have been met before the first subject is screened in the clinical trial.

The procedures outlined in the protocol and eCRFs 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 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.

14.6.1. Premature Termination of the Clinical Trial

Alder 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 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, Alder, 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.

14.7. 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 Alder.

The anonymity of participating subjects must be maintained. Subjects will be identified on CRFs and other documents by their subject number and year of birth date, not by name and in

accordance with local requirements. Documents that identify the subject (e.g., the signed informed consent) must be maintained in confidence by the Investigator.

14.8. 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 Alder 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 for review and approval in accordance with the provisions contained in the clinical trial agreement. All publications must acknowledge the sponsorship of Alder.

All information not previously published concerning ALD403 and Alder operations, including but not limited to patent applications, formulas, manufacturing processes, basic scientific data, and formulation information, supplied by Alder to the Investigator is considered confidential and shall remain the sole property of Alder. 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. Migraine preventive therapies with established or probable efficacy [13, 14, 15]

- Divalproex sodium
- Valproic Acid
- Topiramate
- Amitriptyline
- Venlafaxine
- Flunarizine
- Cinnarizine
- Fluoxetine
- Gabapentin
- Verapamil
- Lamotrigine
- Metoprolol
- Propranolol
- Timolol
- Atenolol
- Nadolol
- Bisoprolol
- Butterbur
- Feverfew
- Pizotifen
- Frovatriptan*
- Naratriptan*
- Zolmitriptan*

**only considered as prophylaxis when specifically, used for menstrually-related migraine (MRM)*

Other drugs for prophylaxis will be considered on a case by case basis.

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

 C-SSRS—Baseline/Screening (Version 1/14/09)

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 5 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* _____

C-SSRS—Baseline/Screening (Version 1/14/09)
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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

C-SSRS Since Last Visit - United States/English - Mapi
C-SSRS-SinceLastVisit_AUS.1_eng-USorl.doc

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?*** If yes, describe:	**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). ***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 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)*	**Since Last Visit**
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. ***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 _____
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 _____
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 ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal 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* _____
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* _____

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

HIT-6™ HEADACHE IMPACT TEST

This questionnaire was designed to help you describe and communicate the way you feel and what you cannot do because of headaches.

To complete, please check one box for each question.

1. When you have headaches, how often is the pain severe?

☐ Never ☐ Rarely ☐ Sometimes ☐ Very Often ☐ Always

2. How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?

☐ Never ☐ Rarely ☐ Sometimes ☐ Very Often ☐ Always

3. When you have a headache, how often do you wish you could lie down?

☐ Never ☐ Rarely ☐ Sometimes ☐ Very Often ☐ Always

4. In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?

☐ Never ☐ Rarely ☐ Sometimes ☐ Very Often ☐ Always

5. In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?

☐ Never ☐ Rarely ☐ Sometimes ☐ Very Often ☐ Always

6. In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?

☐ Never ☐ Rarely ☐ Sometimes ☐ Very Often ☐ Always

15.4. 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	●	●	●	●	●

15.5. 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

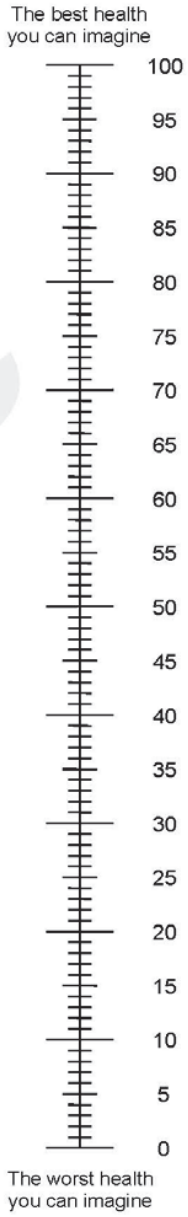
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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 = ☐



15.6. Patient Global Impression of Change (PGIC)

Patient Global Impression of Change (PGIC)

This section to be completed by site staff

Protocol: ALD403-CLIN-013 Subject #: _____ Visit Date: _____

Visit (please check one):

☐ Week 4 ☐ Week 8 ☐ Week 12 ☐ Week 24 ☐ Week 36

☐ Week 48 ☐ Week 56 or ET ☐ Week 60 ☐ Week 72 ☐ Week 84

☐ Week 104 or ET

Since first receiving study drug in this study, how would you describe the change (if any) in ACTIVITY LIMITATIONS, SYMPTOMS, EMOTIONS and OVERALL QUALITY OF LIFE, as related to your migraine? Choose ONE.

___ Very Much Improved

___ Much Improved

___ Minimally Improved

___ No Change

___ Minimally Worse

___ Much Worse

___ Very Much Worse

Version Date: 17 Nov 2017

15.7. Most Bothersome Symptom (MBS)

Most Bothersome Symptom (MBS)

This section to be completed by site staff at each visit, Screening through Week 56, or ET

Protocol: ALD403-CLIN-013 Subject #: _____ Visit Date: _____

Visit (please check one):

☐ Screen ☐ Day 0 ☐ Week 4 ☐ Week 8 ☐ Week 12

☐ Week 24 ☐ Week 36 ☐ Week 48 ☐ Week 56 or ET

Most Bothersome Symptom (as noted by subject at screening visit): _____

This section to be completed by subject at each visit, Day 0 through Week 56, or ET

Since beginning this study, how would you describe the change (if any) in your most bothersome symptom? Choose ONE.

___ Very Much Improved

___ Much Improved

___ Minimally Improved

___ No Change

___ Minimally Worse

___ Much Worse

___ Very Much Worse

Version Date: 16 SEP 2016

15.8. The Migraine Disability Assessment (MIDAS)

MIDAS QUESTIONNAIRE

INSTRUCTIONS: Please answer the following questions about ALL the headaches you have had over the last 3 months. Write your answer in the box next to each question. Write zero if you did not do the activity in the last 3 months. (Please refer to the calendar below, if necessary.)

1. On how many days in the last 3 months did you miss work or school because of your headaches? ..... |___|___| days

2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? *(Do not include days you counted in question 1 where you missed work or school)* ..... |___|___| days

3. On how many days in the last 3 months did you **not** do household work because of your headaches? ..... |___|___| days

4. How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches? *(Do not include days you counted in question 3 where you did not do household work)* ..... |___|___| days

5. On how many days in the last 3 months did you miss family, social, or leisure activities because of your headaches? ..... |___|___| days

A. On how many days in the last 3 months did you have any headache? (If a headache lasted more than one day, count each day) ..... |___|___| days

B. On a scale of 0 - 10, on average how painful were these headaches? (*where 0 = no pain at all, and 10 = pain which is as bad as it can be*) ..... |___|___|

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