LUNDBECK SEATTLE BIOPHARMACEUTICALS, INC.

Clinical Study Protocol

Clinical Study Title	A Parallel Group, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Eptinezumab Administered Intravenously in Subjects Experiencing an Acute Attack of Migraine
Protocol Number	ALD403-CLIN-015
Study Drug	Eptinezumab
Indication	Relief from an active migraine, in patients who are candidates for preventive migraine therapy
Sponsor	Lundbeck Seattle 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] Lundbeck Seattle BioPharmaceuticals, Inc. [redacted]
Clinical Study Compliance	This clinical study 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.
IND Number	114647

Date of Protocol (original release)	27-Mar-2019
Date of Amendment I	02-Oct-2019
Date of Amendment II	06-Dec-2019
Date of Amendment III	01-Jul-2020

SIGNATURE PAGE

Declaration of Sponsor

Title: A Parallel Group, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Eptinezumab Administered Intravenously in Subjects Experiencing an Acute Attack of 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 Study Drug, with moral ethical and scientific principles governing clinical research, and in accordance with Good Clinical Practice and applicable federal and local regulations.

[redacted]

7/1/2020

Date

[redacted]

Lundbeck Seattle BioPharmaceuticals, Inc.

DECLARATION OF THE PRINCIPAL INVESTIGATOR

Title: A Parallel Group, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Eptinezumab Administered Intravenously in Subjects Experiencing an Acute Attack of Migraine

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described trial in compliance with stipulations of the protocol, regulations and ICH E6 Guideline for Good Clinical Practice (GCP).

Principal Investigator

_____ _____

Signature Date

_____

Name (printed)

_____

Title

_____

Institution

1. PROTOCOL SYNOPSIS

Title	A Parallel Group, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Eptinezumab Administered Intravenously in Subjects Experiencing an Acute Attack of Migraine
Sponsor	Lundbeck Seattle BioPharmaceuticals, Inc.
Study Phase	Phase 3B
Study Drug, Dose and Schedule	A single administration of eptinezumab, a humanized anti-calcitonin gene-related peptide (CGRP) monoclonal antibody, 100 mg or placebo provided by intravenous infusion.
Primary Objective	To evaluate the effect of eptinezumab compared to placebo with respect to time to headache pain freedom AND time to absence of most bothersome symptom during an intercurrent migraine that occurs in subjects who are candidates for preventive therapy.
Secondary Objectives	To evaluate the efficacy of eptinezumab vs. placebo on: • Headache pain freedom at timepoints up to 48 hours • Absence of most bothersome symptom at timepoints up to 48 hours • Time to headache pain relief • Sustained headache pain freedom from 2 – 48 hours • Acute rescue medication use • Effect on symptoms of the qualifying migraine • Effect on patient-reported outcomes
Methodology	This will be a parallel group, double-blind, randomized, placebo-controlled study assessing the efficacy of eptinezumab for acute migraine, as defined as an active intercurrent migraine occurring in those patients who are candidates for preventive therapy. Subjects will be randomized to receive either 100 mg eptinezumab or placebo in a 1:1 ratio. Randomization will be stratified by concomitant migraine preventive treatment and region. The total study duration will be approximately 4 to 12 weeks, including up to 8-week screening period, with clinic visits occurring on Screening, Day 0 (dosing day), and Week 4. Weekly site/subject contact attempts via a mobile application or phone call will occur between screening and Day 0. The number of weekly contacts will be based on the length of time from the Screening visit to Day 0. Randomization and dosing will be triggered by a qualifying migraine and will occur on Day 0. Study design requires that study drug administration be initiated

	within 1 to 6 hours of migraine onset, and subjects must be willing and able to travel to the site for study drug administration within this time frame. Subjects must remain at the site for 4-hours post start-of-infusion for observation. Subjects may be followed longer than 4 weeks, if necessary, for safety follow-up as described in the protocol. An eDiary will be assigned prior to dosing at the Day 0 visit and dosed subjects must complete the eDiary at the prescribed intervals through 48 hours after start of infusion (t=0). Additionally, subjects will complete eDiary data entry from Day 3 until a new migraine is reported.
Number of Subjects Planned	Approximately 450 subjects will be randomized and dosed at up to 100 sites.
Subject Selection Criteria	Male or female subjects between 18 and 75 years of age, inclusive, who were diagnosed with migraine at < 50 years of age, have a history of migraine for > 1 year before screening and a frequency of 4 – 15 migraine days per month in the 3 months prior to screening. By history, the subject's typical migraine attack, if untreated, would be associated with headache pain of moderate to severe intensity and a most bothersome symptom of nausea, photophobia, or phonophobia. Subjects must be headache free for at least 24 hours prior to onset of a qualifying migraine.
Duration of Treatment	This is a single-dose study with a 4-week follow-up period.
Duration of Clinical Study Participation	4 – 12 weeks
Clinical Study Endpoints	• Co-Primary Endpoints: o Time to headache pain freedom o Time to absence of most bothersome symptom • Key Secondary Endpoints: o Headache pain freedom at 2 hours o Absence of most bothersome symptom at 2 hours • Secondary Endpoints o Absence of headache pain at 4 hours o Absence of most bothersome symptom at 4 hours o Use of rescue medication within the first 24 hours • Exploratory Endpoints o Time to headache pain relief o Headache pain freedom at 2 hours with sustained headache pain freedom for 24 and 48 hours o Use of rescue medication within the first 48 hours

	○ Absence of photophobia at all timepoints ○ Absence of phonophobia at all timepoints ○ Absence of nausea at all timepoints ○ Change from Baseline in Headache Impact Test (HIT-6) at Week 4 ○ Change from Baseline in Migraine Treatment Optimization Questionnaire-6 (mTOQ-6) at Week 4 ○ Absence of headache pain at all timepoints other than 2 and 4 hours ○ Patient Global Impression of Change (PGIC) at Week 4 ○ Time to next migraine ○ Time to first rescue medication • Safety Endpoints ○ Adverse events (AEs) and serious adverse events (SAEs) ○ Clinical laboratory assessments ○ Vital signs ○ Electrocardiograms (ECGs) ○ Columbia-Suicide Severity Rating Scale (C-SSRS)
Concomitant Medications	Anti-CGRP treatments are prohibited for the duration of the study. Medications which are not prohibited are allowed during the study. **The following medications must be avoided for at least 24 hours prior to study drug administration and 2 hours after start of study drug administration:** • Triptans, ergotamines and ergot-derivatives • Analgesics (including but not limited to acetaminophen, tramadol, nonsteroidal anti-inflammatory drugs [NSAIDs], combination analgesics, caffeine-containing analgesics and opioids/narcotics) and other acute migraine medication(s) • Antiemetic medications (including but not limited to prochlorperazine, promethazine, droperidol, chlorpromazine, metoclopramide)

- Antihistamines (except if required to treat allergic reactions)
- Devices, neuromodulation, neurostimulation, or injectable therapy (trigger point injections, extracranial nerve blocks, facet joint injections, spinal manipulation)

Any form of magnesium or cannabis-based products intended for the acute treatment of the qualifying migraine (Day 0) is prohibited until 2 hours after study drug administration.

Botulinum toxin for migraine or for any other medical/cosmetic reasons is prohibited for the 7 days prior to study drug administration through 48 hours after study drug administration.

Systemic corticosteroids for migraine or any other reason are prohibited for the 3 months prior to study drug administration through 48 hours after study drug administration except if required to treat life threatening allergic reactions.

Rescue medication, defined as any medication to treat migraine or migraine associated symptoms, can be provided to the subject any time after 2 hours post start of infusion.

Any migraine preventive treatment use must be stable and ongoing for at least 1 month prior to screening and for the duration of the study.

Sample Size	The planned sample size for this study is 450 randomized and dosed subjects. These subjects will be allocated into 2 treatment groups, eptinezumab vs. placebo, in a 1:1 ratio. Two hundred twenty-five subjects per group provides at least 90% power to detect a 0.736 hazard ratio favoring eptinezumab at the 5% significance level for both co-primary endpoints. In addition, this sample size also provides 90% power for the key secondary endpoints, assuming that each at 5% significance level eptinezumab increases response rates for both 2-hour endpoints by at least 14.5 percentage points and that the correlation between these two endpoints is 0.8.
Statistical Analysis	For each of the co-primary time-to-event endpoints, the difference between groups with respect to time to pain freedom or time to absence of MBS will be tested using a Cox proportional hazards model at the 5% significance level. For each of the key secondary 2-hour endpoints, the treatment groups will be compared using a Cochran-Mantel-Haenszel test (CMH), adjusting for the study's stratification factor. The key secondary endpoints will be tested hierarchically at a 5% significance level (pain freedom at 2 hours, followed by absence of most bothersome symptom at 2 hours). For each of the secondary endpoints, the treatment groups will be compared the same way as for the key secondary endpoints. If both key secondary endpoints achieve statistical significance, the secondary endpoints will be tested hierarchically at 5% level of significance (pain freedom at 4 hours, followed by absence of most bothersome symptom at 4 hours, followed by use of rescue medication within 24 hours).

2. SCHEDULE OF EVENTS AND ASSESSMENTS

Table 1: Schedule of Events and Assessments

Assessment	Screening Period (Day -56 to Day -1)		Rand/ Dosing Day	End of Study/Early Term (Day 28 ± 3)
	Screening Visit	Weekly Contact [7]	Day 0 Visit	Week 4 Visit
Informed Consent	X			
Inclusion/Exclusion Criteria[1]	X		X	
Demographics	X			
Medical History (including family and social history)	X			
Height, Weight and BMI[2]	X		X	X
Physical Exam	X			X
Vital Signs[3]	X		X	X
eDiary Training[1]	X		X	
eDiary Completion[4]			X	
Migraine History	X			
Qualifying Migraine Assessment[1]			X	
HIT-6	X			X
mTOQ-6	X			X
PGIC				X
C-SSRS[5]	X	X		X
12-lead ECG	X			X
Hematology/Chemistry[1]	X		X	X
Serology (HIV/Hepatitis B and C)	X			
Urine Drug Screen[1]	X		X	
Urine Pregnancy (hCG) Test[1]	X		X	X
AE Review[1,6]	X	X	X	X
Concomitant Medication Review[1,6]	X	X	X	X
Randomization[1]			X	
Eptinezumab/placebo administration			X	

Please refer to next page for footnotes.

[1] Prior to dosing on Dosing Day
[2]Height and BMI only collected at Screening visit. Weight collected at Screening, Day 0 and Week 4 visits.
[3] On Day 0, vital signs should be collected pre-dose and any time prior to the subject leaving the site post-dose.
[4] An electronic diary (eDiary) will be assigned before dosing on the Day 0 visit to collect migraine data pre-dose through 48 hours. Additionally, subjects will complete eDiary data entry from Day 3 until a new migraine is reported.
[5] C-SSRS "Baseline/Screening Version" should be used at the screening visit and C-SSRS "Since Last Visit Version" should be used at all subsequent timepoints. Complete C-SSRS at Screening, Week 4 and, if applicable, the weekly contact after the subject has been in screening for 4 weeks. If the screening period exceeds 28 days, the C-SSRS "Since Last Visit Version" should be completed via a phone call to the subject on Screening Day 29 (+7 days).
[6] If the screening period exceeds 28 days, AEs and concomitant medications should be reviewed via a phone call to the subject on Screening Day 29 (+7 days).
[7] Weekly contact attempts will occur in which updates are obtained from the subject via a mobile application or a phone call from the site staff to check in with the subject during the screening period.

Table 2: Schedule of Events and Assessments for Day 0 through 48 Hours

Assessment	Pre-dose	Dose		Post Start of Infusion												
			Start of Infusion	0.5 hr (+20 min)	1 hr (+20 min)	1.5 hr (+20 min)	2 hr (+20 mins	2.5 hr (+20 min)	3 hr (+20 min)	3.5 hr (+20 mins)	4 hr (+2 hr)	6 hr (+3 hr)	9 hr (+3 hr)	12 hr (+12 hr)	24 hr (+12 hr)	48 hr (+12 hr)
Inclusion/Exclusion Criteria	X															
eDiary Training	X															
eDiary Completion[1]	X		X[3]	X	X	X	X	X	X	X	X	X	X	X	X	X
Qualifying Migraine Assessment	X															
Vital Signs[2]	X										X					
Hematology/Chemistry	X															
Urine Drug Screen	X															
Urine Pregnancy (hCG) Test	X															
Adverse Event Review	X															
Concomitant Medication Review	X															
Randomization	X															
Eptinezumab/placebo administration		X														

[1] An electronic diary (eDiary) will be assigned before dosing on the Day 0 visit to collect migraine data. eDiary will be completed by the subject. While the subject is in the clinic the study staff will provide close oversight to ensure subject completes eDiary at all timepoints, as close to the beginning of the window as possible.
[2] On Day 0, vital signs should be collected pre-dose and any time prior to the subject leaving the site post-dose.
[3] Immediately when the infusion is started, the subject will be required to press a button on the eDiary device to indicate that the infusion has started.
Note: Timepoint windows only pertain to subject completion of eDiary.

3. LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
AE	Adverse event
AED	Automated external defibrillator
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
BMI	Body Mass Index
BP	Blood pressure
CGRP	Calcitonin Gene-Related Peptide
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
eDiary	Electronic Diary
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
IRB	Institutional Review Board
IV	Intravenous
IRT	Interactive Response Technology
mAb	Monoclonal antibody
MBS	Most Bothersome Symptom
MedDRA	Medical Dictionary for Regulatory Activities
MOH	Medication Overuse Headache
MTOQ-6	Migraine Treatment Optimization Questionnaire-6
NSAID	Non-steroidal anti-inflammatory drug

PGIC	Patient Global Impression of Change
RBC	Red blood cell
SAE	Serious adverse event
TMD	Temporomandibular Disorder
TVS	Trigeminovascular System
WBC	White blood cell

4. TABLE OF CONTENTS

LIST OF TABLES

5. INTRODUCTION

5.1. 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. Attacks of migraine typically last between 4 and 72 hours, produce significant disability, and recur often without warning, over decades of time. Migraine is more common in women and most prevalent through the 3rd and 4th decades of life, amplifying its impact on family and career development (Lipton, 2007). Migraine is one of the most prevalent neurological disease for which medical treatment is sought, and worldwide, is considered the leading cause of disability for people under the age of 50 and 2nd leading cause of disability worldwide (Leonardi, 2005). Annually, lost work time and diminished productivity attributable to migraine costs American employers an estimated $19.6 billion (Stewart, 2003).

Generally, migraine begins as an episodic disease. Between attacks 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 (Headache Classification Committee, 2018). For those with chronic migraine, the headaches are more intense; associated with more migraine-associated symptoms, and there is greater disease-related impact and disability and in general there is a failure to return to normal (pre-morbid) neurological function between episodes of headache (Katsarava, 2012).

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 sensory processing (Durham, 2004). Interactions between the 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 synapsing in the Trigeminal Nucleus Caudalis ultimately lead to a state of central sensitization as third order neurons in the thalamus become sensitized (Cady, 2012). Clinically, during a fully developed attack of migraine, central sensitization can be observed as sensory allodynia.

Central to this model of migraine pathophysiology 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 abundantly stored in trigeminal afferents and when released during migraine leads to vasodilation, the release of inflammatory peptides, and increased sensory transmission. In both peripheral and central pain pathways, CGRP is associated with pain transmission and neuronal sensitization (Durham, 2006). Intravenous (IV) infusions of CGRP can cause a migraine-like headache in susceptible individuals with migraine (Hansen, 2010). 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.

The pharmacological treatment of migraine can be divided into two categories: one is to reverse or abort an attack of migraine after it is initiated and the second class is to protect the nervous

system from generating future migraines. Preventive treatments generally do not abort a migraine that has already began.

Intercurrent migraine is defined as an active migraine that occurs in a patient population that are candidates for preventive therapy. While intercurrent migraine is not explicitly defined by the IHS, medications for active migraine such as triptans have been previously been studied (MacGregor, 2009). While generally quite effective, excessive use of acute treatments for active migraine can actually worsen the severity and frequency of migraine causing a secondary headache condition called medication overuse headache (MOH) (Headache Classification Committee, 2018). MOH is common in populations with chronic migraine (Schmid, 2013). Thus, it is critical to initiate preventive treatment before medication overuse is established.

5.2. Eptinezumab Background Information

A significant unmet treatment need for subjects with migraine is for an effective treatment that can abort an existing migraine and at the same time prevent future migraine from occurring. Eptinezumab is currently being reviewed by the Food and Drug Administration (FDA) for an indication in migraine prevention. Unique to its profile is that it is administered as an intravenous infusion and throughout its Phase 2 and Phase 3 development programs, it has consistently demonstrated preventive efficacy as soon as the first day following infusion. This raises the possibility that eptinezumab has the potential to be a treatment intervention for active migraine and at the same time, provide a sustained preventive benefit. In a key secondary endpoint for the percentage of patients with a migraine after dosing, there was a statistically significant reduction in Day 1 migraine frequency for both the 100 and 300 mg groups relative to placebo in ALD403-CLIN-011; in ALD403-CLIN-006, the results were not significant after multiplicity adjustments.

Eptinezumab 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. Eptinezumab is being developed by Lundbeck Seattle BioPharmaceuticals, Inc. (Lundbeck Seattle) for the prevention of migraine. However, as an intravenous infusion (IV) with 100% bioavailability, a T-max of 30 minutes, rapid engagement and high affinity for CGRP, eptinezumab may also be suitable as a treatment for active migraine.

5.2.1. Summary of Clinical Studies

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

A summary of the migraine studies completed and ongoing eptinezumab clinical studies is shown in Table 3.

Table 3: Eptinezumab Clinical Studies

Study ID	Phase/Objective	Study Subject Population	Total Number of Subjects in the Study	Number of Subjects Randomized and Dosed with Eptinezumab	Number of Subjects Randomized and Dosed with Placebo
ALD403-CLIN-002 (completed)	Phase 1b Safety & Efficacy	Frequent Episodic Migraine	163	81	82
ALD403-CLIN-005 (completed)	Phase 2 Safety & Efficacy	Chronic Migraine	616	495	121
ALD403-CLIN-006 (completed)	Phase 3 Safety & Efficacy	Frequent Episodic Migraine	888	666	222
ALD403-CLIN-011 (completed)	Phase 3 Safety & Efficacy	Chronic Migraine	1072	706	366
ALD403-CLIN-013 (completed)	Phase 3 Safety, Open Label	Chronic Migraine	128	128	No Placebo

5.2.2. Dose Justification

Since the objective of this study is to assess treatment of active migraine in patients who require preventive therapy, 100 mg is deemed to be the lowest effective dose. This is based on the ALD403-CLIN-006 and ALD403-CLIN-011 studies in prevention, where 100 mg dose group provided benefit as early as Day 1 and conferred efficacy out to Week 12.

5.3. Risks and Benefits

Eptinezumab may be effective as a treatment for active migraine as well as providing preventive benefit for 12 weeks.

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 both non-serious and serious allergic reactions. Please refer to the Investigator Brochure (IB) for additional details.

In the completed eptinezumab clinical studies, the most common adverse reaction in ≥ 2% of treated patients and ≥ 2% of placebo patients was nasopharyngitis. The majority of these adverse events were categorized as mild to moderate.

The safety of eptinezumab has been evaluated in 2,076 patients with migraine who received at least one dose of eptinezumab, representing 1615 patient-years of exposure. Long term data with eptinezumab is limited; however, 128 subjects have been treated with up to 2 years of exposure.

- Healthy volunteer studies have included limited dosing, with follow-up limited to 3-4 months post last dose.
- Studies in migraine subjects have also included up to 20 weeks of follow-up for Safety. No new significant adverse safety findings were noted during the follow-up period.
- An open label long term follow-up safety study included no new significant findings identified during the long-term follow-up period.

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

5.4. Compliance Statement

This clinical study 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. Primary Objective

The primary objective is:

To evaluate the effect of eptinezumab compared to placebo with respect to time to headache pain freedom AND time to absence of most bothersome symptom during an intercurrent migraine that occurs in subjects who are candidates for preventive therapy.

6.2. Secondary Objectives

The secondary objectives are to evaluate the efficacy of eptinezumab vs. placebo on:

- Headache pain freedom
- Absence of most bothersome symptom
- Time to headache pain relief
- Sustained headache pain freedom from 2 – 48 hours
- Acute rescue medication use
- Effect on symptoms of the qualifying migraine
- Effect on patient-reported outcomes

7. STUDY DESIGN

7.1. Clinical Study Endpoints

Detail regarding the clinical study endpoints and their derivation can be found in Section 12. Migraine headaches are defined as migraines as outlined in the International Headache Society (IHS) International Classification of Headache Disorders (ICHD, 3rd edition, version 2018), Section 1.3 (Headache Classification Committee, 2018).

7.1.1. Co-Primary Efficacy Endpoints

- Time to headache pain freedom
- Time to absence of most bothersome symptom

7.1.2. Key Secondary Endpoints:

- Headache pain freedom at 2 hours
- Absence of most bothersome symptom at 2 hours

7.1.3. Secondary Endpoints

- Absence of headache pain at 4 hours
- Absence of most bothersome symptom at 4 hours
- Use of rescue medication within the first 24 hours

7.1.4. Exploratory Endpoints

- Time to headache pain relief
- Headache pain freedom at 2 hours with sustained headache pain freedom for 24 and 48 hours
- Use of rescue medication within the first 48 hours
- Absence of photophobia at all timepoints
- Absence of phonophobia at all timepoints
- Absence of nausea at all timepoints
- Change from Baseline in Headache Impact Test (HIT-6) at Week 4
- Change from Baseline in Migraine Treatment Optimization Questionnaire-6 (mTOQ-6) at Week 4
- Absence of headache pain at all timepoints other than 2 and 4 hours
- Patient Global Impression of Change (PGIC) at Week 4
- Time to next migraine
- Time to first rescue medication

7.1.5. Safety Endpoints

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

7.2. Clinical Study Design

This will be a parallel group, double-blind, randomized, placebo-controlled study assessing the efficacy of eptinezumab for acute migraine. Acute migraine for this study will be defined as an active intercurrent migraine occurring in those patients who are candidates for preventive therapy. Subjects will be randomized to receive either 100 mg eptinezumab or placebo in a 1:1 ratio. Randomization will be stratified by concomitant migraine preventive treatment and region.

The total study duration will be approximately 4 to 12 weeks, including up to 8-week screening period, with clinic visits occurring on Screening, Day 0 (dosing day), and Week 4. Weekly site/subject contact attempts via a mobile application or phone call will occur between screening and Day 0. The number of weekly contacts will be based on the length of time from the Screening visit to Day 0. Randomization and dosing will be triggered by a qualifying migraine and will occur on Day 0. Study design requires that study drug administration be initiated within 1 to 6 hours of migraine onset, and subjects must be willing and able to travel to the site for study drug administration within this time frame. Subjects must remain at the site for 4-hours post start-of-infusion for observation. Subjects may be followed longer than 4 weeks, if necessary, for safety follow-up as described in the protocol. An eDiary will be assigned prior to dosing at the Day 0 visit and dosed subjects must complete the eDiary at the prescribed intervals through 48 hours after start of infusion (t=0). Additionally, subjects will complete eDiary data entry from Day 3 until a new migraine is reported.

Approximately 450 subjects will be randomized and treated. Efficacy and safety assessments will be conducted according to the Schedule of Events and Assessments presented in Section 2.

7.3. Methods to Minimize/Avoid Bias

To minimize bias, this clinical study is randomized, double-blinded, and placebo controlled.

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 study:

1. Male or female subjects 18 – 75 years of age, inclusive, at time of informed consent.
2. Willing and able to read, understand, and sign the Informed Consent Form (ICF) for the clinical study approved by the investigator's local Review Board or a central Institutional Review Board (IRB) or Ethics Committee (EC).
3. Has adequate venous access for administration of study drug and collection of blood samples.
4. Greater than 1-year history of migraine, with or without aura, with onset of first migraine before age 50 as defined by ICHD-3.
5. Migraine on 4 – 15 days per month in the 3 months prior to screening.
6. By history, the subject's typical migraine attacks, if untreated, are associated with headache pain of moderate to severe intensity and a most bothersome symptom of nausea, photophobia, or phonophobia. These migraine attacks must be a minimum duration of 4 hours and maximum duration of 72 hours.
7. History of either previous or active use of triptans for migraine.
8. Headache free for at least 24 hours prior to onset of a qualifying migraine.
9. On Day 0, subjects must have a moderate to severe headache associated with at least one of the following headache characteristics: pulsating quality, unilaterality, and aggravation by or avoidance of routine physical activity. In addition, they must have during the headache at least one of the following:
    a. Nausea and/or vomiting
    b. Photophobia and phonophobia
10. On Day 0, subject must be able to reliably identify the time of qualifying migraine onset.
11. Able and willing to be dosed with study drug during a qualifying migraine attack within 8 weeks of screening visit.
12. Women of child-bearing potential and males with partners of child-bearing potential must agree to use adequate contraception for the duration of the study. 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 with spermicidal gel or diaphragm with spermicidal gel) or vasectomy with use of condom (for male subjects). Females are considered of childbearing potential unless they are permanently sterilized (i.e., bilateral tubal ligation, bilateral salpingectomy, bilateral oophorectomy of hysterectomy) at least 3 months prior to screening or postmenopausal (i.e., no menses for 1 year).

13. Any hormonal therapy (e.g., contraceptives, hormone replacement therapy) use is stable and ongoing for at least 3 months prior to screening and through up to treatment with study drug (Day 0).
14. Willing, committed, and able to comply with scheduled clinic visits and complete all study-related procedures.
15. Subject agrees not to post any personal medical data or information related to the study on any website or social media site (e.g., Facebook, Twitter).
16. Subject is willing to complete the eDiary from Day 0 through the 48-hour period after dosing and from Day 3 until a new migraine is reported.
17. Subject is willing and able to have study drug administration within 1-6 hours of onset of a qualifying migraine and remain at the site for 4 hours post start of infusion for observation.

8.2. Exclusion Criteria

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

1. Unable to differentiate migraine from other headache or pain disorders.
2. Use of the following medication, for any indication, within the **24-hour period** prior to dosing with study drug:
    a. Triptans, ergotamines and ergot-derivatives
    b. Analgesics (including but not limited to acetaminophen, tramadol, nonsteroidal anti-inflammatory drugs [NSAIDs], combination analgesics, caffeine-containing analgesics and opioids/narcotics) and other acute migraine medication(s)
    c. Antiemetic medications (including but not limited to prochlorperazine, promethazine, droperidol, chlorpromazine, metoclopramide)
    d. Antihistamines
    e. Devices, neuromodulation, neurostimulation, or injectable therapy (trigger point injections, extracranial nerve blocks, facet joint injections, spinal manipulation)
3. On Day 0, use of magnesium or cannabis-based products intended for acute treatment of the qualifying migraine.
4. History of new daily persistent headache in any of the 3 months prior to screening.
5. History or diagnosis of chronic tension-type headache, hypnic headache, cluster headache, hemicrania continua, new daily persistent headache, or unusual migraine subtypes such as hemiplegic migraine (sporadic and familial), ophthalmoplegic migraine and migraine with neurological accompaniments that are not typical of migraine aura (e.g., diplopia, altered consciousness, or long duration).
6. History or diagnosis of vestibular migraine.
7. Any changes to preventive migraine treatment(s) within 1 month prior to screening and up to treatment with study drug (Day 0).
8. Use of the following medication, for any indication, in each of the 3 months prior to screening:

a. opioids/narcotics or butalbital containing products (including combinations) on more than 4 days per month; OR
b. triptans, ergotamines, or combination analgesics for 10 or more days per month; OR
c. acetaminophen, aspirin or nonsteroidal anti-inflammatory drugs [NSAIDs] for 15 or more days per month (except if subject is taking 81 mg dose of aspirin for cardiac prophylaxis)

9. Any use of approved devices, neuromodulation, neurostimulation or injectable therapy (trigger point injections, extracranial nerve blocks, facet joint injections) within the 24-hour period prior to treatment with study drug (Day 0).
10. Any use of botulinum toxin for migraine or for any other medical/cosmetic reasons requiring injections within 7 days prior treatment with study drug (Day 0).
11. Any use of systemic corticosteroid for migraine or any other reason within 3 months prior to treatment with study drug (Day 0).
12. Evidence or medical history of clinically significant psychiatric diseases that are uncontrolled and/or untreated.
13. Clinically significant laboratory findings showing evidence of organ dysfunction, any clinically significant deviation from the normal range (abnormal tests may be repeated for confirmation at the discretion of the investigator), or clinically significant physical exam abnormalities at screening, as evaluated by the investigator.
14. Have present or previous malignancies, except:
    - Squamous or basal skin cell carcinoma with excision without evidence of recurrence
    - Malignancy ≥ 5 years since diagnosis/treatment without evidence of recurrence
15. Known history or evidence of hereditary fructose intolerance, severe atopy, or life-threatening allergy (e.g. anaphylaxis). If questions arise, the investigator should contact the medical monitor for guidance.
16. Any clinically significant, concurrent medical condition on the day of infusion.
17. Clinically significant abnormal ECG during the screening period.
18. Positive human immunodeficiency virus (HIV), Hepatitis B surface antigen (HBsAg), and/or Hepatitis C antibody (HCV) at screening.
19. Body Mass Index (BMI) > 35 kg/m2 at screening.
20. Primary or secondary hypertension that is uncontrolled. Note: Mild primary hypertension that is well-controlled for ≥ 6 months prior to screening is allowed.
21. 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), have had any suicidal behavior in the past 5 years (i.e., preparatory acts or behavior), or have 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 visit or phone contact during screening period.

22. 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.
23. Pregnant, breastfeeding, or planning to become pregnant during the study.
24. Receipt of any experimental, unregistered therapy (within or outside a clinical study) within 30 days or 5 plasma half-lives (whichever is longer) prior to screening. Note: Subject use of rimegepant and ubrogepant are allowed to screen provided they have discontinued the drug at a total of 5 half-lives.
25. Receipt of any monoclonal antibody treatment, for migraine or any other indication, (within or outside a clinical study) within 6 months prior to screening.
26. Planned or current participation in any other interventional clinical study during the duration of this clinical study, or within 1 month prior to screening.
27. Any condition that, in the opinion of the investigator, would make the subject unsuitable for the clinical study including but not limited to clinically unstable cardiovascular disease, arteriosclerosis, cardiomyopathy, coronary artery disease, serious heart rhythm abnormalities, neurological disease, cerebrovascular disease, diabetes, Raynaud's disease.
28. Employees of the Sponsor, Clinical Research Organization, or any clinical study site involved in this study 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., 601, 602). At the screening visit, once the subject signs the ICF they are registered in the electronic data capture (EDC), which will assign a unique subject number. The first three digits of the subject number identify the site, and the remaining four digits identify the subject.

Subjects who fail screening may be rescreened if approved in advance by the medical monitor.

8.3.2. Randomization and Treatment Assignment

Randomization and dosing must occur at the dosing visit (Day 0) as specified in the schedule of events and once the eligibility assessments are approved by the medical monitor.

Sites will complete randomization in EDC, and the randomization assignment will be obtained by the clinical study site's unblinded pharmacist or designee in an interactive web/voice randomization system (IxRS). Subjects will be randomized in a 1:1 ratio to one of the treatment groups. Randomization will be stratified by concomitant migraine preventive treatment (concomitant migraine preventive treatment use vs. no concomitant migraine preventive treatment use) and region (North America vs. Rest of World).

Randomized subjects who terminate their clinical study participation for any reason, regardless of whether study drug was administered or not, will retain their randomization assignment and subject number.

8.4. Subject Early Withdrawal

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

8.4.1. Criteria for Withdrawal from the Clinical Study

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

- Withdrawal of consent for the collection of clinical study data including further access to medical records. The reason for withdrawal of consent will be recorded.
- Termination of the study by the sponsor
- Investigator decision (with medical monitor approval)
- Lost to follow-up

The reason for withdrawal and the date of withdrawal must be recorded on the case report form (CRF).

8.4.2. Timing of Withdrawal

Subjects are considered withdrawn from the clinical study at the time that any of the criteria listed in Section 8.4.1 are met and the last study assessment is performed, or at the time of the early termination visit, whichever occurs later.

8.4.3. Follow-up for Early Withdrawal

Subjects who wish to withdraw their consent from study participation will be asked to have an early termination visit with associated visit assessments (see Schedule of Events and Assessments in Section 2). Subjects who withdraw consent before or after randomization but do not receive study drug may discontinue the study without any further procedures.

8.4.4. Replacement Policy

Subjects who are withdrawn from the clinical study after randomization will not be replaced.

8.4.5. Lost to Follow-Up

If the subject fails to attend scheduled study visits or to respond to requests for follow-up, the clinical study 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. STUDY DRUG

9.1. Eptinezumab

Eptinezumab is an anti-calcitonin gene-related peptide humanized monoclonal antibody (anti-CGRP mAb) that is being developed by Lundbeck Seattle BioPharmaceuticals, Inc., for the preventive treatment of migraine. As an intravenous infusion (IV) with 100% bioavailability, a T_{max} of 30 minutes, rapid engagement and high affinity for CGRP, Lundbeck Seattle believes it may be suited for treatment of an active [intercurrent] migraine.

Eptinezumab injection, 100 mg/mL (1 mL per vial), is presented in USP/Ph Eur. Type 1 glass vials as a single-use preservative-free solution for IV administration. Eptinezumab is formulated at a concentration of 100 mg/mL with a pH of 5.8. Those subjects randomized to the eptinezumab treatment group will receive an IV infusion of eptinezumab injection in 100 mL of 0.9% saline.

9.2. Placebo

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

9.3. Study Drug Dosing and Administration

The pharmacist or designee is responsible for receiving, storing and preparing study drug and placebo, as well as transferring study drug or placebo to the blinded staff for administration. Unblinded staff will not be responsible for other aspects of the clinical study where blinding is necessary. Both randomization and dosing must occur on Day 0. Doses of eptinezumab or placebo (total volume of 100 mL) will be administered intravenously over a period of 30 (+15) minutes on Day 0 by the blinded investigator or designee.

The study drug administration must be initiated within 1 to 6 hours of onset of the qualifying migraine. Subjects must remain at the site and be monitored by site staff for at least 4 hours post-dose. The investigator must be immediately available during the infusion and for at least 4 hours post start of infusion to assess each subject for the occurrence of adverse events. Subjects will be requested to stay longer than 4 hours after dosing should the investigator determine this is clinically warranted (e.g., subjects should be observed until all AEs are resolved or clinically stable). The timeframe for the post-dose observation period must be documented in the source record.

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

9.3.1. Packaging and Labeling

Before the shipment to the sites, study drug will be labeled with information (protocol number, contents, concentration, storage instructions and any other information), required by regulatory agencies and a statement that it is limited to investigational use. Study drug to be administered to the subject will be labeled after dose preparation by the unblinded pharmacist or designee as specified in the Pharmacy Manual in a manner that protects the blind.

9.3.2. Blinding

This clinical study is double-blinded, meaning the subjects, investigator and site personnel are blinded to treatment assignment, except for the site's unblinded pharmacist or designee. The site must have a written plan in place, site blinding plan, to ensure blinding is adequately maintained for the study. If the blind is broken, the date, time, and reason must be recorded in the source. The blind should only be broken for reasons in which knowledge of the treatment assignment is critical to the management of subject safety. Medical monitor approval should be obtained prior to breaking the blind if possible. The principal investigator will report any cases of unblinding to the Sponsor within 24 hours of the incident. Please refer to the site blinding plan and the infusion guidelines for additional details regarding breaking the study blind.

9.3.3. Storage and Handling of Study Drug

Eptinezumab will be stored at the site at 2°C to 8°C in accordance with any accompanying instructions.

Placebo will be stored at the 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 eptinezumab and placebo in a securely locked, substantially constructed cabinet or other securely locked, substantially constructed enclosure, access to which is limited to maintain blind, prevent theft or diversion of the substance into illegal channels of distribution.

9.3.4. Accountability and Disposition of Investigational Product

The investigator is responsible for maintaining accurate study drug accountability records throughout the clinical study. The site must maintain a Study Drug Accountability Log, on which the unblinded pharmacist or designee will record the receipt, lot number, quantity and dispensation of study drug. Please refer to the Pharmacy Manual for additional details regarding study drug accountability.

Where more than one secure area is being used for storage at a site, all movement of study drug through the chain of custody must be recorded in accountability records such that full reconciliation may be completed at the end of the study.

Included with each study drug shipment is a form listing lot numbers and quantity shipped. The unblinded pharmacist or designee will acknowledge receipt and integrity of these supplies. A copy will be retained in the site's pharmacy binder during study conduct.

9.3.5. Disposition of Study Drug

After completion of the clinical study, the investigator is responsible for either returning or destroying all unused study drug. 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 Lundbeck Seattle directive. Destruction must be in accordance with local regulations for the product type.

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

9.4. Concomitant Medications

Any concomitant therapy used from the time the subject signs the informed consent form through study completion 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.

9.4.1. Prohibited Medications/Treatments

Anti-CGRP treatments are prohibited for the duration of the study.

9.4.2. Restricted Medications/Treatments

Medications which are not prohibited specifically are allowed during the study.

The following medications must be avoided for 2 hours after start of study drug administration:

- Triptans, ergotamines and ergot-derivatives
- Analgesics (including but not limited to acetaminophen, tramadol, nonsteroidal anti-inflammatory drugs [NSAIDs], combination analgesics, caffeine-containing analgesics and opioids/narcotics) and other acute migraine medication(s)
- Antiemetic medications (including but not limited to prochlorperazine, promethazine, droperidol, chlorpromazine, metoclopramide)
- Antihistamines (except if required to treat allergic reactions)
- Any form of magnesium or cannabis-based products
- Devices, neuromodulation, neurostimulation, or injectable therapy (trigger point injections, extracranial nerve blocks, facet joint injections, spinal manipulation)

Botulinum toxin for migraine or any other medical/cosmetic reasons is prohibited for the 48 hours after start of study drug administration.

Systemic corticosteroids for migraine or for any other reason are prohibited for 48 hours after start of study drug administration except if required to treat life threatening allergic reactions.

Any hormonal therapy (e.g., contraceptives, hormone replacement therapy) use must be stable and ongoing for at least 3 months prior to screening and for the duration of the study.

Any migraine preventive treatment use must be stable and ongoing for at least 1 month prior to screening and for the duration of the study.

At the discretion of the investigator, on a case by case basis, changes to the treatment regimen that might be clinically warranted may be made prior to Week 4 after consulting with the medical monitor and obtaining approval.

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 investigator should re-evaluate the subject's risk factors relative to the prescribing information for both prophylactic and acute treatments that the subject is using, and judge that the use of these medications continues to be considered safe.

The Medical Monitor should be contacted for any questions regarding restricted medications.

9.4.3. Rescue Medications

Rescue medication is defined as any medication to treat migraine or migraine associated symptoms. Two hours after start of study drug administration, subjects who did not adequately respond may take their own rescue medication or may elect to take no further medication. Inadequate response is defined as meeting 1 of the following:

- Continues to experience moderate or severe headache pain; OR
- Continues to experience significant migraine associated symptoms; OR
- After initial migraine relief at 2 hours, headache or migraine associated symptoms returns within 2 to 48 hours after the dose of study drug

At the discretion of the investigator, additional rescue medication may be provided to the subject 2 hours post start of infusion if their own rescue medication is inappropriate or does not provide adequate relief. Common examples of rescue medications include ketorolac, injectable or intranasal triptans, antiemetics, diphenhydramine, or in extreme cases, opioids.

9.4.4. Contraceptives

All women are required to have a negative pregnancy test at the Screening Visit and on Day 0 prior to dosing. Women of child-bearing potential and males with partners of child-bearing potential must agree to use adequate contraception during the screening period of the study and for the duration of the study. Abstinence is not an acceptable form of contraception for this study. Acceptable methods of contraception for females of child-bearing potential and males with partners of child-bearing potential are:

- Intrauterine devices
- Double-barrier methods (e.g., condoms and/or diaphragms/cervical cap with spermicidal gel or foam)
- Hormonal contraceptives (oral, depot, patch, injectable, intrauterine devices or vaginal ring), stabilized for at least 3 months prior to screening
- Vasectomy with use of condom (for male subjects)

Females are considered of childbearing potential unless they are:

- Permanently sterilized (i.e., bilateral tubal ligation, bilateral salpingectomy, bilateral oophorectomy or hysterectomy) at least 3 months prior to screening
- Postmenopausal (i.e., no menses for at least 1 year)

10. STUDY ASSESSMENTS AND PROCEDURES

10.1. Schedule of Assessments

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

10.2. Assessments and Procedures

10.2.1. Eligibility Verification

During subject screening, after the ICF is signed and subject is determined by the site to be eligible, the site will submit an Eligibility Verification Packet to the PRA Medical Monitor via the Clinical6 portal, see the Clinical6 training materials for additional information.

10.2.2. Randomization and Dosing

Randomization and dosing must occur at the Day 0 visit, once the medical monitor approves the subject's eligibility status.

All subjects will be randomized via EDC after the following:

- Eligibility has been approved by the medical monitor
- Review of all inclusion/exclusion criteria to confirm subject is eligible on Day 0
- Subject confirms continued interest in participating in the study

If > 6 hours has passed since the onset of migraine, the subject will not be dosed with study drug.

10.2.3. Demographics

The year of birth, age, sex, ethnicity and race, will be collected in the source and recorded and in the CRF at Screening.

10.2.4. Medical and Migraine History

Medical history collection will include medical history as well as social and family 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 present at the time of informed consent will be considered medical history.

Migraine history will be collected at the screening visit by the investigator. The data gathered will be collected in the source and recorded in the CRF, including but not limited to:

- Diagnostic criteria for migraine with or without aura as defined by ICHD-3
- Migraine medication use (past and present, acute and preventive)
- Age at diagnosis of migraine, migraine triggers and other details of the subjects' history with migraine

Investigators must demonstrate due diligence in obtaining medical records. All attempts to obtain medical records should be documented. If medical records cannot be obtained, history

may be confirmed via subject interview in order to obtain sufficient information to confirm all eligibility criteria are met.

10.2.5. Physical Examinations

Physical examinations will be performed at the times noted in the Schedule of Events and Assessments 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 physical examination at the screening visit will be comprehensive and appropriate to determine the overall physical health of each subject. Examination of the genitourinary system and rectum may be deferred by the investigator if the subject's related medical history and review of systems are negative. For all other visits that call for a physical examination, the body systems examined will be at the discretion of the investigator.

Physical examinations will also include height, weight and BMI, which can be delegated to other blinded site staff. Weight will be measured at all visits, while height and BMI 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 at subsequent visits will be considered an AE.

10.2.6. Vital Signs

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

When measuring vital signs, the subject should be rested for 5 minutes before obtaining vital signs. Blood pressure may be repeated to confirm measurement if appropriate.

10.2.7. eDiary Assessments

Subjects will be assigned an electronic diary (eDiary) prior to dosing on Day 0 to collect migraine data. At the Screening and Day 0 visits, the site staff will train the subject on eDiary use and educate the subject on the importance of completing the eDiary at all timepoints. Subjects will be instructed to complete the eDiary at all timepoints from pre-dose through 48 hours. Additionally, subjects will complete eDiary data entry from Day 3 until a new migraine is reported (specified in the Schedule of Events and Assessments [Section 2]). The subject will be instructed to return the eDiary at the Week 4 clinic visit. The data collected includes but is not limited to:

- Start of infusion (t=0)
- Headache severity on a four-point Likert scale (0=none, 1=mild, 2=moderate, 3=severe)
- Presence or absence of migraine associated symptoms, including nausea, photophobia or phonophobia, one of which will be identified prior to dosing as the subject's most bothersome migraine-associated symptom
- Use of rescue and acute treatment of migraine medication

10.2.8. Qualifying Migraine Assessment

The Qualifying Migraine Assessment will be completed at the Day 0 visit prior to randomization by an investigator. The data gathered by this questionnaire includes but is not limited to:

- Headache characteristics
- Symptoms of the migraine the subject is currently experiencing to confirm qualifying migraine.
    - Note: Presenting migraine symptoms on the day of study drug administration are not considered adverse events and will be collected and monitored separately.
- Time of migraine onset

10.2.9. Questionnaires

Protocol number, subject number and date of administration must be captured on all questionnaires.

10.2.9.1. Headache Impact Test (HIT-6)

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

Subjects will be given the questionnaire at Screening and Week 4 visits and asked to review the brief instructions and complete. The completed HIT-6 questionnaire 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.

10.2.9.2. Migraine Treatment Optimization Questionnaire-6 (mTOQ-6)

The migraine treatment optimization questionnaire-6 (mTOQ-6) is a tool used to assess response to acute treatment in persons with migraine. The mTOQ-6 is a 6 question, Likert-type, self-reporting questionnaire with responses ranging from “Never” to “Half The Time Or More” with the following response scores: Never=1, Rarely=2, Less Than Half The Time=3, Half The Time Or More=4. The total score for the mTOQ-6 is the sum of each response score and will be treated as missing if the response is missing for one or more questions.

Subjects will be given the questionnaire at Screening and Week 4 visits and asked to review the brief instructions and complete. The completed mTOQ-6 questionnaire 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.

10.2.9.3. 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.

Subjects will be given the questionnaire at the Week 4 visit and asked to review the brief instructions and complete. The completed PGIC questionnaire must be reviewed for completeness and clarity by site staff prior to the subject leaving the clinic.

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

The Columbia–Suicide Severity Rating Scale (C-SSRS) is an assessment tool that evaluates suicidal ideation and behavior. 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 and Assessments in Section 2. 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.

10.2.10. 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 and Assessments in Section 2. ECG data will be transmitted and read centrally by a cardiologist; however, the investigator must review the ECG at screening and Week 4 and ensure there are no clinically significant abnormalities. In addition, all confirmed (i.e., centrally-read) ECGs will be reviewed by the investigator and evaluated for clinical significance to verify eligibility.

All ECGs are expected to be performed on the ECG device provided to the site by the study sponsor. A local ECG device may be used only if there are technical issues with the central ECG device that cannot be resolved while the subject is onsite. If a local ECG device is used, a paper ECG must be submitted to the central ECG reader. All technical issues must be reported immediately to the central ECG help desk.

10.2.11. Laboratory Samples and Testing

10.2.11.1. Urine Drug Screening

A screening test for drugs of abuse will be performed on urine samples during the screening visit and on Day 0 visit prior to dosing. Urine drug screen kits will be provided by the central lab and the test performed on site. If a urine drug screen is positive and there is no medical record documentation of prescribed medications to explain the result, the subject should be considered for exclusion from the study. Questions regarding the eligibility can be addressed with the medical monitor.

10.2.11.2. 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 and Assessments, Section 2. Urine pregnancy test must be performed and reviewed prior to randomization and dosing on Day 0.

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.

10.2.11.3. Clinical Laboratory Testing

Blood samples for clinical laboratory tests, including hematology, serum chemistry and serology [including human immunodeficiency virus (HIV), Hepatitis B and Hepatitis C], will be collected at the time points specified in the Schedule of Events and Assessments in Section 2.

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).

All clinical laboratory blood samples will be initially processed by site staff and shipped to a central laboratory for analysis as specified in the Laboratory Manual. A licensed medical provider 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.

11. ASSESSMENT OF SAFETY

11.1. Adverse Events

11.1.1. Definitions

An adverse event (AE) is any untoward medical occurrence in a subject 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 study drug, whether or not related to the study drug. (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 study. 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 study drug.
- 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 study are part of the patient's medical history and are not considered an adverse event. 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 CRF. A pre-existing or chronic condition that worsens after signing the informed consent is considered an adverse event.

Pre-existing medical conditions of clinical significance must be included in the subject’s medical history and recorded on the medical history CRF page. Presenting migraine symptoms on the day of study drug administration are not considered adverse events.

Progression of treatment indication including new or worsening of anticipated clinical signs or symptoms, which are collected as clinical efficacy variables and assessed as unequivocally associated with the symptom progression and /or lack of efficacy, should NOT be reported as adverse events unless the symptom progression is greater than anticipated in the natural course of the disease.

Each event recorded on the AE CRF is required to be assessed by the investigator with regard to the following; seriousness, severity, and relationship to study drug, as outlined below.

Lack of Efficacy or Worsening of Migraines

Events that are clearly consistent with the expected pattern of progression of the underlying migraine should NOT be recorded as AEs. Migraine activity will be recorded in the eDiary and these data will be captured as effectiveness assessment data only. If there is any uncertainty as to whether an event is due to disease progression or worsening, it should be reported as an AE.

Seriousness

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

- Death
- Is life-threatening (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
- A hospitalization is defined as greater than 24-hour post 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 Study Drug

The investigator is required to assess the causality/relationship between each AE and the study drug as not related or related and record the assessment on the source documents and in the CRF AE page. Medical judgment should be used to determine the likely relationship of the AE to the study drug 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 study drug (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 study drug.

11.1.3. Recording Adverse Events

Event reporting will extend from time of informed consent until completion of the final visit. AEs should be recorded on the AE CRF, whether believed by the investigator to be related or not related to the study drug.

AE reporting should contain:

- A brief description of the event
- Date of onset
- Date of resolution
- Severity
- Actions taken or treatment required
- Relationship to study drug
- 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 study period (beginning with informed consent), whether considered to be related to the study drug or not, must be reported within 24 hours of awareness or knowledge of the event. Serious adverse events occurring within 30 days of the end of the clinical study must be reported regardless of the relationship with the study drug. The SAE Notification Form should be used to report any related SAEs which occur after the end of the clinical study.

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 CRF AE page and indicate the reason for seriousness. The minimum information required for an initial report is:

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

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

The sponsor will determine if an SAE requires expedited reporting to regulatory agencies. The clinical study site personnel are responsible for reporting these events to their IRB according to the institution's 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 eptinezumab, as referenced in the Investigator's Brochure.
- May be symptomatically and pathophysiologically related to an AE listed in the Investigator's Brochure, but differ from the event due to greater severity, frequency or specificity.

The sponsor or designee will report, to the appropriate regulatory authorities according to local and regulatory requirements, unexpected SAEs which are considered related to eptinezumab (suspected unexpected serious adverse reactions [SUSARs]). The clinical study 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 completes the study, is lost to follow up or withdraws from the study.

The investigators must report new significant follow-up information to the Sponsor within 24 hours of becoming aware of the event for SAE's and enter into EDC Rave within 5 business days for AE's. New significant information includes the following:

- new signs or symptoms or a change in the diagnosis
- significant new diagnostic test results
- change in causality based on new information
- change in the event's outcome, including recovery
- additional narrative information on the clinical course of the event

11.1.7. Pregnancy

In the event that a female subject becomes pregnant following administration of study drug or may have been pregnant at the time of study drug exposure, or the partner of a male subject becomes pregnant following administration of study drug, the pregnancy must be reported to the sponsor within five business days of the Investigator becoming aware of the pregnancy. Pregnancy information will be reported to the Sponsor using the Exposure In-Utero Forms in EDC.

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

Follow-up information is to be collected by the Investigator and provided to the sponsor regarding:

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

All pregnancies that occur after a subject completes the study and up to 6 months after study drug administration should be reported by the subject to the investigative site. The investigator must report it to the Sponsor within five business days of awareness or knowledge of the pregnancy.

11.1.8. Suicidal Ideation and Behavior

Recent meta-analyses, spontaneous reports, and published case reports regarding suicidal ideation and behavior arising from drugs tested in clinical studies 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 studies to ensure that subjects in clinical studies 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 (FDA, 2012). 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 study after dosing, any subject who answers "yes" to questions 4 or 5 of the Suicidal Ideation section or answers "yes" to any question in the Suicidal Behavior section of the C-SSRS will be 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 Study Drug

There are no specific antidotes to an infusion of eptinezumab.

A medical emergency should be treated appropriately by the investigator using proper standard of care, according to their typical clinical practice and local guidelines for that emergency condition. Emergency equipment and medication for the treatment of these potential adverse events must be available for immediate use.

Should a medical condition arise that the investigator believes is related to the study drug, clinical judgment should be used to provide the appropriate response including the consideration of discontinuation of study drug. Any events believed to be allergic reactions should be discussed with the medical monitor.

If a subject experiences an allergic reaction, as assessed by the Investigator, that necessitates intervention including study drug interruption or discontinuation and/or the administration of standard medical treatment, the site will collect additional blood specimens using the immune response lab kit, per the laboratory manual, at the time of the event and again at the next scheduled visit. This assessment includes serum histamine, serum tryptase, immunoglobulin E, and complement components.

12. ASSESSMENT OF EFFICACY

The data collected will be used to assess the following endpoints:

12.1. Headache Pain Freedom

Headache pain will be collected on a 4-point scale with 3 being severe, 2 being moderate, 1 being mild, and 0 being no pain. Headache pain freedom is defined as no pain (0) with the absence of rescue medication (note that rescue medication is prohibited for 2 hours post start of infusion). Assessment of headache pain will be taken at all selected timepoints up to 48 hours. Time to headache pain freedom, which is one of the co-primary endpoints, is the first timepoint post start of infusion at which the subject reports freedom of pain meaning their headache pain has gone from moderate or severe (2 or 3) at baseline to no pain (0) with no administration of rescue medication. Headache pain freedom at 2 hours post start of infusion is one of the key secondary endpoints of this study; evaluation at all other timepoints are secondary (at 4 hours) and exploratory endpoints.

12.2. Most Bothersome Migraine-Associated Symptom

MBS is the symptom (from among nausea, photophobia, or phonophobia) that has been identified by the subject on Day 0 prior to dosing as being the most bothersome one for the migraine being treated. Absence of MBS is defined as freedom from the migraine-associated symptom with no administration of rescue medication. Assessment of MBS will be taken at all selected time points from pre-dose to 48 hours. Time to absence of MBS, which is one of the co-primary endpoints, is the first timepoint post start of infusion at which the subject reports absence of MBS with no administration of rescue medication. Absence of MBS at 2 hours post start of infusion is one of the key secondary endpoints of this study; evaluation of absence of migraine associated symptoms at all other timepoints are secondary (at 4 hours) and exploratory endpoints.

12.3. Sustained Pain Freedom

Freedom from headache pain (0) at 2 hours and sustaining this pain-free status to 24 and 48 hours (i.e. pain free 2 - 24 and 2- 48 hours) with no administration of rescue medication.

12.4. Rescue Medication

Use of rescue medication at any time, which is defined as any intervention (medical or device) provided to the subject to provide relief of migraine. This should not be provided sooner than 2 hours following start of the study drug administration.

13. STATISTICAL CONSIDERATIONS

13.1. Decision Rule

Pair-wise testing of each eptinezumab group vs. placebo will be performed. The testing procedure will start with primary endpoints. The result that is considered a study success is when both time to headache pain freedom and time to absence of MBS are statistically significant at the 5% significance level. If this occurs, testing will continue to key secondary endpoints.

The key secondary endpoints will be tested hierarchically at a 5% significance level (pain freedom at 2 hours, followed by absence of most bothersome symptom at 2 hours). If both key secondary endpoints achieve statistical significance, the secondary endpoints will be tested hierarchically at 5% level of significance (pain freedom at 4 hours, followed by absence of most bothersome symptom at 4 hours, followed by use of rescue medication within 24 hours).

13.2. Sample Size

The planned sample size for this study is 450 randomized and dosed subjects. These subjects will be allocated into 2 treatment groups, eptinezumab vs. placebo, in a 1:1 ratio. Two hundred twenty-five subjects per group provides at least 90% power to detect a 0.736 hazard ratio favoring eptinezumab at the 5% significance level for both co-primary endpoints. In addition, this sample size also provides 90% power for the key secondary endpoints, assuming that each at 5% significance level eptinezumab increases response rates for both 2-hour endpoints by at least 14.5 percentage points and that the correlation between these two endpoints is 0.8.

13.3. General Considerations

13.3.1. Definition of Baseline

The baseline assessment will be the latest available valid measurement taken prior to the administration of study drug on Day 0 (an eDiary will be assigned before dosing on the day of treatment visit).

13.3.2. Handling of Missing Data

Summary statistics will be reported based upon observed data. Subjects with missing data for the time-to-event co-primary endpoints will be considered to be censored at the last timepoint prior to the missing assessments. In the case of subjects having missing headache eDiary data at the 2-hour assessment, they will be assigned as non-responders for the key secondary endpoints, regardless of treatment arm. Additionally, if the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study medication, except if an incomplete date (e.g., month and year) clearly indicates that the event started prior to treatment.

13.3.3. Populations to be Analyzed

The populations to be analyzed are as follows:

Full Analysis Population: Randomized subjects who received eptinezumab/placebo. Subjects will be summarized within the treatment group to which they were randomized. This population will be used for efficacy analyses.

Safety Population: Includes all subjects who received eptinezumab or placebo infusions. Subjects will be summarized within the treatment group for which they actually received treatment. This population will be used for the safety analyses.

13.4. Statistical Methods

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

13.4.1. Subject Disposition, Demographics and Baseline Characteristics

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

13.4.2. Efficacy Analyses

Primary Efficacy Analyses

The analysis of the time to pain freedom will be based upon Kaplan-Meier method. The treatment difference will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., hazard ratio) between the treatment arms. The median estimate for each treatment group, hazard ratio and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The analysis of the time to absence of MBS will be conducted similarly.

Key Secondary Efficacy Analyses

For each of the 2-hour endpoints, the treatment groups will be compared using a Cochran-Mantel-Haenszel (CMH) test, adjusting for the study’s stratification factors. The treatment difference estimation, odds ratio, and associated confidence intervals will be provided.

Secondary Efficacy Analyses

The absence of headache pain (headache pain freedom) at 4 hours, and the absence of most bothersome symptom at 4 hours will be analyzed similarly to the key secondary endpoints.

The use of rescue medication within 24 hours will be analyzed similarly to the key secondary endpoints. In case of a missing assessment, it will be assumed that no rescue medication was taken in connection with that assessment.

Exploratory Efficacy Analyses

Additional exploratory efficacy endpoints will be assessed.

13.4.3. Safety Analyses

13.4.3.1. Adverse Events

The incidence of all AEs will be tabulated by treatment received. These AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). For incidence reporting, if a subject reported more than one 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 study drug administration will be provided as part of a listing.

An overview of AEs, which includes subject incidence of AEs, SAEs, deaths will be presented. For AEs presented by severity, the worst severity during the clinical study will be presented for each subject.

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

13.4.3.2. Serious Adverse Events

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

13.4.3.3. 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 and will be tabulated.

13.4.3.4. Electrocardiogram (ECG) Results

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

13.4.3.5. Vital Signs

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

13.4.3.6. C-SSRS

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

14. ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

14.1. Data Quality Assurance

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

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the clinical study for each clinical study subject. All information recorded on the CRFs for this clinical study 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 subjects treated as part of the research under this protocol. The principal investigator or sub-investigator agrees to maintain accurate CRFs and source documentation as part of the case histories. These source documents include, but are not limited to, eDiary archives, laboratory reports and original ECGs.

14.3. Study Documentation

Source document is defined as any hand written or computer-generated document that contains medical information or test results that have been collected for or are in support of the protocol specifications, 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.

14.4. Data Collection and Electronic Data Capture (EDC)

The data collected during the study (except clinical laboratory test results, ECG results) will be recorded in the subject's CRF. The study site(s) will use an EDC system that is compliant with relevant FDA regulatory requirements per 21 CFR Part 11. Data queries and data corrections will be handled through the same system. All transactions within the EDC system are fully documented within an electronic audit trail. Each set of completed CRFs must be reviewed after being source verified by monitor and electronically signed and dated by the investigator. The mTOQ-6, HIT-6, PGIC and C-SSRS questionnaires will be completed on paper. The eDiary assessments will be collected on the electronic diary (eDiary).

14.5. Archiving Clinical Trial Records

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

these documents should be retained for a longer period if required by applicable legal requirements.

It is the responsibility of the investigator and site 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 Lundbeck Seattle BioPharmaceuticals, Inc. and regulatory authorities. Elements of clinical trial documentation should include:

- Subject files containing the completed CRFs 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 Lundbeck Seattle BioPharmaceuticals, Inc.
- Pharmacy files, containing the Investigational Product Accountability Records or dispensation logs and all clinical trial agent-related correspondence

14.6. Good Clinical Practice

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

14.7. Informed Consent

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

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

14.8. Protocol Approval and Amendment

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

The procedures outlined in the protocol and CRFs will be carefully reviewed by the investigator and staff prior to clinical study 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 Lundbeck Seattle BioPharmaceuticals, Inc., and will be provided to the investigator for submission to his/her ethics committee for their review and approval prior to implementation (if appropriate). It should be noted that when an amendment to a protocol substantially alters the clinical study design or increases potential risk to the clinical study subject, the ICF should be revised and subject's consent to continue participation should be obtained.

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

14.8.1. Premature Termination of the Clinical Study

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

The principal investigator may discontinue participation in the study. If the clinical study is terminated prior to scheduled completion, the investigator will be notified and given any necessary instructions concerning final examinations that are required. If the investigator, the sponsor, or the medical monitor becomes aware of conditions or events that suggest a possible safety hazard to subjects if the clinical study continues, the clinical study may be terminated after appropriate consultation between the relevant parties.

14.9. Confidentiality

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

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

14.10. Publication Policy

By signing the clinical study protocol, the Investigator agrees with the use of results of the clinical study 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 and received written permission by the sponsor in advance. The information provided in support of or generated as a result of this clinical study 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 Lundbeck Seattle BioPharmaceuticals, Inc., for review and approval in accordance with the provisions contained in the clinical study agreement. All publications must acknowledge the sponsorship of Lundbeck Seattle BioPharmaceuticals, Inc.

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

15. APPENDICES

15.1. Migraine preventive therapies with established or probable efficacy (Esternalik, 2013), (Antonaci, 2010), (Pringsheim, 2012)

- Angiotensin converting enzyme inhibitor (ACE inhibitor)
  - Lisinopril
  - Candesartan
- anti-CGRP monoclonal antibody
  - Erenumab
  - Fremanezumab
  - Galacanezumab
- Anti-epileptic drug (AED)
  - Divalproex sodium
  - Valproic Acid
  - Topiramate
  - Gabapentin
  - Lamotrigene
- Beta blocker
  - Metoprolol
  - Propranolol
  - Timolol
  - Atenolol
  - Nadolol
  - Bisoprolol
- Calcium channel blocker
  - Verapamil
- Herbal
  - Butterbur
  - Feverfew
- Selective serotonin norepinephrine reuptake inhibitor (SNRI)
  - Venlafaxine
- Selective serotonin reuptake inhibitor (SSRI)
  - Fluoxetine

- Tricyclic (TCA)
  - Amitriptyline
- Triptan
  - Frovatriptan*
  - Naratriptan*
  - Zolmitriptan*

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

**only considered prophylaxis when specifically used as such (e.g., menstrually-related migraine (MRM))*

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

15.2.1. Baseline/Screening Version

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

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

Disclaimer:

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

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

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

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

 C-SSRS—Baseline/Screening (Version 1/14/09) Page 1 of 2

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) Page 2 of 2

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	____

 C-SSRS—Since Last Visit (Version 1/14/09) Page 1 of 2

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 infered 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* _____

15.3. Migraine Treatment Optimization Questionnaire- 6 (MTOQ-6)

Migraine Treatment Optimization Questionnaire-6 item version

Please answer the following questions the medication(s) that you currently use to treat headaches:

(X ONE Box For Each)	Never	Rarely	Less Than Half The Time	Half The Time Or More
Are you able to quickly return to your normal activities (i.e., work, family, leisure, social activities) after taking your migraine medication?	☐	☐	☐	☐
After taking your migraine medication, are you pain free within 2 hours for most attacks?	☐	☐	☐	☐
Does one dose of your migraine medication usually relieve your headache and keep it away for at least 24 hours?	☐	☐	☐	☐
Is your migraine medication well tolerated?	☐	☐	☐	☐
Are you comfortable enough with your migraine medication to be able to plan your daily activities?	☐	☐	☐	☐
After taking your migraine medication, do you feel in control of your migraines enough so that you feel there will be no disruption to your daily activities?	☐	☐	☐	☐

15.4. Patient Global Impression of Change (PGIC)

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

15.5. 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

16. REFERENCES

Antonaci F, Dumitrache C, De Cillis I, Allena M. A review of current European treatment guidelines for migraine. J Headache Pain. 2010; 11: 13-19.

Cady RJ, Shade CL, Cady RK. Advances in drug development for acute migraine. Drugs. 2012:72(17):1-19.

Durham PL. Calcitonin gene-related peptide (CGRP) and migraine. Headache. 2006; 46(Suppl 1):S3-S8.

Durham PL. CGRP-receptor antagonists—a fresh approach to migraine therapy? N Engl J Med. 2004; 350:1073-1075.

Esternalik E, Tepper S. Preventive treatment in migraine and the new US guidelines. Neuropsychiatr Dis Treat. 2013; 9; 709-720.

Hansen JM, Hauge AW, Olesen J, Ashina M. Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura. Cephalalgia. 2010; 30(10):1179-1186.

Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018, 38(1) 1–211.

Katsarava, Buse D. Defining differences between episodic and chronic migraine. Curr Pain and Headache. 2012; 1:86-92.

Leonardi M, Steiner TJ, Scher AT, Lipton RB. The global burden of migraine: measuring disability in headache disorders with WHO's classification of functioning, disability and health (ICF). J Headache Pain. 2005; 6(6):429-440.

Lipton R, Bigal M, Diamond M, Freitag F, Reed M, Stewart W. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007; 68:343-349.

MacGregor, E. Anne & Brandes, Jan & Silberstein, Stephen & Jeka, Sławomir & Czapinski, Piotr & Shaw, Bob & Pawsey, Stephen. (2009). Safety and Tolerability of Short-Term Preventive Frovatriptan: A Combined Analysis. Headache. 49. 1298-314. 10.1111/j.1526-4610.2009.01513.x.

Pringsheim T, Davenport W, Mackie G, et al. Canadian Headache Society Guideline for Migraine Prophylaxis - Section II. Can J Neurol Sci 2012; 39: Suppl. 2 – S8-28.

Schmid CW, Konrad M, Schmid DM, et al. the Journal of Headache and Pain 2013; 14:4

Stewart WF, Ricci JA, Chee E, et al. Lost productive work time costs from health conditions in the United States: results from the American Productivity Audit J Occup Environ Med 2003; 45(12): 1234-1246.

United States Food and Drug Administration, United States Department of Health and Human Services. Guidance for Industry: Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials, Draft Guidance. August 2012. Revision 1.