Document Type: Protocol

Protocol Title: INTERCEPT (Initiating Early Control of Migraine Pain and Associated Symptoms): A Randomized, Double-blind, Single-dose, Placebo-controlled Study to Assess the Efficacy and Safety of AXS-07 (meloxicam and rizatriptan) for the Acute Treatment of Migraine in Adults.

ClinicalTrials.gov Identifier: NCT04163185

Document Date: December 13, 2019

Certain information within this protocol has been redacted to protect either personally identifiable information (PII) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information.
- Other information as needed to protect the confidentiality of Axsome Therapeutics, personal information, or to otherwise protect the integrity of the clinical study.

PROTOCOL

COMPOUND NAME/NUMBER:	AXS-07
PROTOCOL NUMBER:	AXS-07-303
[redacted]	[redacted]
DEVELOPMENT PHASE:	Phase 3
PROTOCOL TITLE:	INTERCEPT (Initiating Early Control of Migraine Pain and Associated Symptoms): A Randomized, Double-blind, Single-dose, Placebo-controlled Study to Assess the Efficacy and Safety of AXS-07 (meloxicam and rizatriptan) for the Acute Treatment of Migraine in Adults.
PROTOCOL VERSION:	Amendment 1
PROTOCOL DATE:	Original: June 24, 2019 Amendment 1: December 13, 2019

AXSOME
THERAPEUTICS

[redacted]

This study will be performed in compliance with Good Clinical Practices and applicable regulatory requirements, including the archiving of essential documents. Information contained in this protocol is confidential in nature, and may not be used, divulged, published, or otherwise disclosed to others except to the extent necessary to obtain approval of the institutional review board or independent ethics committee, or as required by law. Persons to whom this information is disclosed should be informed that this information is confidential and may not be further disclosed without the express permission of Axsome Therapeutics, Inc.

APPROVAL SIGNATURES

PROTOCOL NUMBER:	AXS-07-303
PROTOCOL TITLE:	INTERCEPT (Initiating Early Control of Migraine Pain and Associated Symptoms): A Randomized, Double-blind, Single-dose, Placebo-controlled Study to Assess the Efficacy and Safety of AXS-07 (meloxicam and rizatriptan) for the Acute Treatment of Migraine in Adults.
Protocol Version:	Amendment 1: December 13, 2019

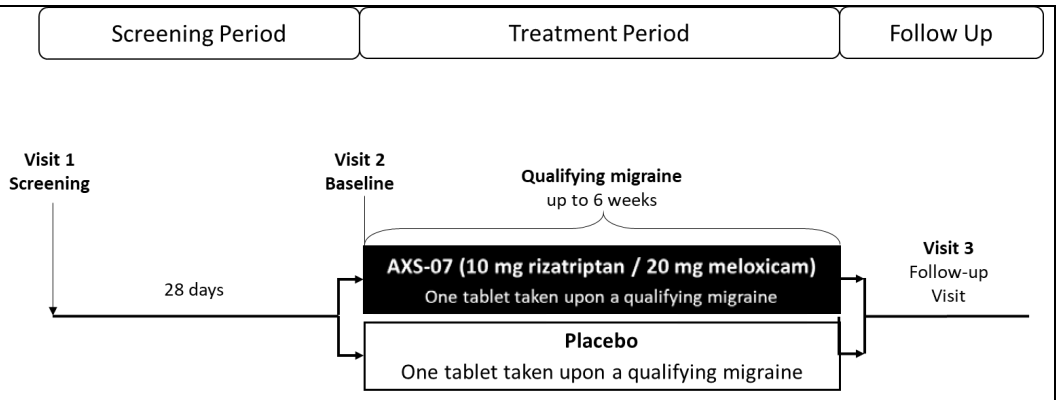
I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

Study Contact and Details

SPONSORED BY:	Axsome Therapeutics, Inc.
[redacted]	[redacted]
INVESTIGATORS:	A current list of clinical investigators will be maintained in the Trial Master File (TMF)

1. SYNOPSIS

PRODUCT NAME/NUMBER	AXS-07
PROTOCOL NUMBER	AXS-07-303
DEVELOPMENT PHASE	Phase 3
PROTOCOL TITLE	INTERCEPT (Initiating Early Control of Migraine Pain and Associated Symptoms: A Randomized, Double-blind, Single-dose, Placebo-controlled Study to Assess the Efficacy and Safety of AXS-07 (meloxicam and rizatriptan) for the Acute Treatment of Migraine in Adults.
INDICATION	Acute treatment of migraine with or without aura in adults.
OBJECTIVES	**Primary Objective:** To evaluate the effect of AXS-07 as compared to placebo in the acute treatment of migraine headache in adults as evaluated by the following two co-primary efficacy variables: 1) pain freedom at Hour 2 and 2) absence of the most bothersome symptom (MBS; nausea, photophobia, or phonophobia) at Hour 2. **Key Secondary Objectives:** To assess the effect of AXS-07 on time to headache pain freedom and functional disability. **Secondary Objectives:** Secondary objectives include assessment of the effect of AXS-07 on: • Percentage of subjects with headache pain relief at Hour 2. • Change from baseline in headache pain relief over time. • Percentage of subjects with headache pain freedom over time. • Time to headache pain relief. • Time to sustained headache freedom through Hour 24. • Percentage of subjects able to perform normal activity over time. • Patient Global Impression of Change (PGI-C) scores at Hour 2. • Percentage of subjects with absence of MBS over time. • Percentage of subjects MBS free over time. • Percentage of subjects with headache pain freedom between Hours 2 and 24 (24-hour sustained pain-free). • Percentage of subjects with headache pain freedom between Hours 2 and 48 (48-hour sustained pain-free). • Percentage of subjects with pain relapse, where relapse is defined as the return of headache within 48 hours after dosing, for subjects who were pain free at Hour 2. • Percentage of subjects using rescue medication. • Time to rescue medication. • Treatment response based on presence of allodynia, BMI, pain intensity, presence of depression, and use of preventive medication.
STUDY DESIGN	The study is a Phase 3, multicenter, randomized, double-blind, single-dose, placebo-controlled trial to evaluate the efficacy and safety of AXS-07 in subjects with migraine attacks. The co-primary efficacy endpoints are the 1) percentage of subjects with headache pain freedom at Hour 2, with headache pain freedom defined as a reduction in headache severity to no pain, and 2) absence of the MBS (nausea, photophobia, or phonophobia) at Hour 2, with the MBS defined at the onset of migraine, prior to drug administration. The key secondary endpoints are the time to headache pain freedom and functional disability at Hour 2.



To qualify for the study, subjects must be 18 to 65 years of age, have an established diagnosis of migraine (history indicating the presence of migraine for at least 1 year) with or without aura as defined by the International Classification of Headache Disorder, 3rd Edition (ICHD-3) and experience an average of 2 to 8 migraine attacks per month (no more than 10 migraine days per month) over the past 3 months.

Screening Period and Randomization

Subjects who successfully complete the Screening visit (Visit 1) will enter into a 28-day Screening Period during which they will record the details (baseline characteristics, headache pain intensity, associated migraine symptoms, and treatments used) of all migraines during this time. The subject must report at least 1 and no more than 8 migraines during the 28-day period in order to continue to be eligible. Subjects who continue to meet all eligibility criteria, will be randomly assigned at Visit 2 (randomization) to receive AXS-07 or placebo, dispensed for at-home treatment of a single migraine attack. Subjects will have 6 weeks to treat a qualifying migraine.

Treatment and Follow-up Periods

After randomization, as soon as possible after the onset of the next migraine, subjects will record baseline headache characteristics in the Headache Diary, and take the study medication, one tablet orally, when prompted by the diary. In the diary, subject will record the headache pain intensity (0-none, 1-mild, 2-moderate, and 3-severe), functional disability, presence or absence of associated symptoms (photophobia, phonophobia, nausea), and Patient Global Impression of Change (PGI-C). Subjects will complete the diary for 48 hours after the onset of the migraine and study drug dosing.

Subjects will be instructed to follow restrictions regarding use of other medications, including rescue medications, and must not sleep or nap for at least 2 hours after taking study drug.

A follow-up visit (Visit 3) will occur after treating one attack. The visit is to be scheduled as soon as possible but within 1 week after dosing, or within 6 weeks after randomization (Visit 2) if the study medication is not used.

Headache Diary Assessments

Diaries will be provided and subjects will be instructed to complete the diary for 48 hours after taking study medication for a migraine.

Headache pain intensity (measured by a 4-point rating scale; 0-none, 1-mild, 2-moderate, or 3-severe), will be recorded by subjects in the diary as soon as possible after the onset of each migraine (prior to dosing in the Treatment Period), and at the following time points: 20, 30 and 45 minutes, and 1, 1.5, 2, 4, 12, 16, 24, and 48 hours.

At the onset of each migraine, and prior to dosing in the Treatment Period, the subject will define their most bothersome symptom (nausea, photophobia, phonophobia) and will assess the presence or absence of it at the following time points 30 minutes and 1, 2, and 4 hours after dosing. In addition, functional disability with regard to daily activities (on a 4-point scale) will be recorded at the following time points: Baseline (prior to dosing during the Treatment Period), 30 minutes, and 1, 2, 4, 12, and 24 hours after dosing. During the Treatment Period, subjects will report PGI-C 2 hours after dosing.

	Safety and Other Assessments A physical examination will be performed at Screening. Samples for clinical laboratory testing (hematology and chemistry) will be collected at Screening. A urine pregnancy test will be performed at Screening, randomization (Visit 2), and Follow-up (Visit 3). ECGs will be performed at Screening and Follow-up (Visit 3). At each visit, vital signs will be assessed and concomitant medications will be reviewed. Presence of allodynia will be collected via the Allodynia Symptom Checklist-12 Item (ASC-12). Baseline assessment of migraine disability will be collected via the Migraine Disability Assessment (MIDAS). Adverse events will be assessed following dosing with study drug. **Concomitant and Rescue Medications** During the Screening Period, subjects can treat each migraine according to their standard-of-care. In the Treatment Period, barbiturates, ergotamine-containing medications, analgesics, and other migraine medications (except prophylactic agents as described below) may not be used 24 hours before, concurrently or within 24 hours after treatment with study drug. The use of MAO-A inhibitors, methylergonovine, or cimetidine are not permitted in the 2 weeks before randomization and for the duration of the study. Migraine prophylactic agents and selective serotonin reuptake inhibitors (SSRIs) / serotonin norepinephrine reuptake inhibitors (SNRIs) are permitted if the subject has been on stable doses for 8 weeks (2 months) prior to randomization; however, subjects taking ergot alkaloids for prophylaxis will be excluded. The use of calcitonin gene-related peptide (CGRP) monoclonal antibodies and onabotulinumtoxinA (Botox®) for migraine prophylaxis is allowed if the subject has been on stable doses for at least 6 months prior to randomization. Propranolol use is not allowed during the study or for 2 weeks prior to randomization. No rescue medication use is allowed prior to 2 hours after the start of the migraine attack. If the subject has inadequate relief from the study medication, they may take an allowed rescue medication after the Hour 2 timepoint. Barbiturates and ergotamine-containing medications are not allowed as rescue medications. Allowed medications include triptans, NSAIDs, antiemetics, non-NSAID analgesics (e.g., acetaminophen), and sedatives.
PLANNED NUMBER OF SUBJECTS	A total of approximately 300 subjects (approximately 150 per group, AXS-07 and placebo) are planned for the trial.
STUDY ENTRY CRITERIA	Inclusion criteria: A subject will be eligible for study participation if the subject meets all of the following criteria: 1. Is male or female 18 to 65 years of age inclusive. 2. Is willing and able to provide written informed consent to participate in the study, and willing and able to understand and comply with the procedures and study requirements. 3. Has an established diagnosis of migraine (history indicating the presence of migraine for at least 1 year) with or without aura as defined by the ICHD-3 criteria. 4. Has a diagnosis of migraine attacks with or without aura, presenting before age 50. 5. Has a history, on average, of 2 to 8 migraine attacks per month over the past 3 months. NOTE: The subject must report at least 1, and no more than 8 migraines during the Screening Period. 6. Has a history of usual migraine duration of > 3 hours untreated (by history) for the 3 months prior to screening. 7. Has the ability to differentiate between migraine and non-migraine headaches. 8. Has a body weight ≥ 45 kg and a body mass index (BMI) ≤ 40 kg/m^2. 9. If receiving a selective serotonin reuptake inhibitor (SSRI) or serotonin norepinephrine reuptake inhibitor (SNRI), the dose has been stable for at least 8 weeks prior to randomization.

10. If female, is either not of childbearing potential (defined as postmenopausal for at least 1 year or surgically sterile [bilateral tubal ligation, bilateral oophorectomy, or hysterectomy]); or is nonlactating and nonpregnant (has negative pregnancy test results at Screening and Baseline), does not plan to get pregnant during the study or for at least one month after, and is using a reliable method of contraception, before study drug administration and for the duration of the trial. Reliable methods of contraception include hormonal, double-barrier methods (e.g., condom and diaphragm, condom and foam, condom and sponge, each with spermicidal jellies or cream), intrauterine devices, vasectomized partners (>6 months prior to Visit 2), and abstinence.
11. Is willing and able to complete the Headache Diary.

Exclusion criteria:

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

1. Has a known history of allergic reaction, hypersensitivity, or clinically significant intolerance to rizatriptan or another triptan, acetaminophen, aspirin, or any NSAIDs, including meloxicam; history of NSAID-induced bronchospasm (subjects with the triad of asthma, nasal polyps, and chronic rhinitis are at greater risk for bronchospasm and should be considered carefully); or hypersensitivity, allergy, or significant reaction to any ingredients of the study drug.
2. Has experienced > 8 migraine attacks monthly during either of the 2 months before screening.
3. Is suffering from cluster headaches (every day or every other day), tension headaches, or other types of migraine.
4. Has experienced chronic daily headache (≥ 15 days per month of non-migraine headaches during each of the 3 months before screening).
5. Has a history of brain stem aura, ophthalmoplegic or hemiplegic migraine headache, or any potentially serious neurological condition that is associated with headache.
6. Has confirmed or suspected cardiovascular or cerebrovascular disease.
7. Has history, symptoms, or significant risk factors for ischemic heart (e.g., silent ischemia, angina, myocardial infarction); coronary artery vasospasm; arrhythmia (e.g., atrial fibrillation or flutter, frequent premature ventricular contractions, atrioventricular block); clinically significant findings on ECG; cardiac accessory conduction pathway disorder (e.g., Wolff-Parkinson-White syndrome); or other cardiovascular disease.
8. Has history of stroke, transient ischemic attack or other cerebrovascular syndrome; peripheral vascular disease; or ischemic bowel disease.
9. Has uncontrolled hypertension (diastolic blood pressure > 95 mm Hg or systolic blood pressure > 160 mm Hg).
10. Is a female subject and is taking estrogenic contraceptives who, in addition, smokes and has experienced migraine attack with aura.
11. Has a concurrent medical condition(s) that requires the chronic (daily or near daily) use of analgesics, narcotic analgesics, steroidal or non-steroidal anti-inflammatory (NSAIDs) agents, tranquilizers, sedatives-hypnotics, antipsychotics, or nitrates or their use for prevention of migraine attacks.
12. Clinically significant abnormalities indicated from the medical history, physical exam, clinical chemistry, hematology, urine drug screen.
13. Had a diagnosis or suspicion of drug induced or chronic daily headaches within 1 year.
14. Has used MAO inhibitor, lithium, methylergonovine, or cimetidine in the 2 weeks before randomization
15. Has a history or current diagnosis of any clinically significant cardiac, pulmonary, neurological, immunological, hematological, gastrointestinal, hepatic, renal, or endocrine disease or any other condition which, in the opinion of the investigator, could compromise

	the subject's welfare, ability to communicate with the study staff, or otherwise contraindicate study participation. 16. Has a history or current diagnosis of schizophrenia or another significant psychiatric disorder which, in the opinion of the investigator, would affect the subject's ability to comply with the study requirements. Stable bipolar disease and stable major depressive disorder is allowed. 17. Is receiving systemic chemotherapy, has an active malignancy of any type, or has been diagnosed with cancer within 5 years before Screening (excluding squamous or basal cell carcinoma of the skin). 18. Has a known or suspected history of alcoholism or drug abuse or misuse within 1 year before Screening or evidence of tolerance or physical dependence before study drug administration. 19. Has, or has had within 1 year, any clinically significant gastrointestinal (GI) disorder, including peptic or gastric ulcers or GI bleeding. 20. Has a medical or surgical condition of the GI system (including motility dysfunction) or renal system that might significantly alter the absorption, distribution, or excretion of any drug substance. 21. Is considered by the investigator, for any reason (including, but not limited to, the risks described as precautions, warnings, and contraindications in the current version of the investigator's brochure for AXS-07 tablets), to be an unsuitable candidate to receive the study drug. 22. Is using or expects to use concurrent analgesic, including NSAIDs (except aspirin at a dose of ≤ 325 mg daily for cardiovascular prophylaxis) during the trial. NOTE: NSAIDs and other analgesics maybe used during the Screening Period. 23. Is currently receiving or expects to use anticoagulants (e.g., heparin, warfarin, nutritional supplements having anticoagulant properties); or has bleeding problems, coagulation abnormalities, active blood dyscrasia, hemorrhagic disease, anemia, porphyria, phenylketonuria, bone marrow suppression, or immunosuppression. 24. Is currently receiving propranolol or has received propranolol within 2 weeks prior to randomization. 25. Has been treated with agents that could affect the analgesic response (such as central alpha agents adrenergic [clonidine and tizanidine]) within 2 weeks before randomization or expects to use such agents during the treatment period. 26. Has tested positive for drugs of abuse on the urine drug screen at randomization (Visit 2). Subjects who test positive at Screening and can produce a prescription for the medication from their physician may be considered for study enrollment at the discretion of the investigator. NOTE: The use of marijuana, medical or otherwise, is not permitted during the study and a positive test for THC will be exclusionary. 27. Has clinically significant abnormalities indicated from the medical history, physical exam, and laboratory findings at Screening that in the investigator's opinion contraindicates study participation. 28. Is HIV positive. 29. Has previously participated in another clinical study of AXS-07 or received any investigational drug or device or investigational therapy within 30 days before Screening. 30. Has significant difficulty swallowing tablets or is unable to tolerate oral medication.
INVESTIGATIONAL PRODUCT	AXS-07 (20 mg meloxicam/10 mg rizatriptan) tablet for oral administration.
REFERENCE PRODUCT	Matching placebo tablets for oral administration.

TREATMENT REGIMENS	The study drug (AXS-07 or placebo) is to be taken orally with water within 30 minutes of onset of a migraine attack.
PRINCIPAL INVESTIGATOR	Multi-center
PLANNED STUDY SITES	Up to 50 study sites in North America
CRITERIA FOR EVALUATION	**Primary Outcome Measures** The primary efficacy variable is the patient reported migraine pain and most bothersome migraine symptom as reported in the Headache Diary. **Co-Primary Endpoints** • Percentage of subjects with headache pain freedom at Hour 2, with headache pain freedom defined as pain intensity = none. • Percentage of subjects with absence of the most bothersome symptom (MBS; nausea, photophobia, or phonophobia) at Hour 2, with the MBS defined at the onset of migraine, prior to drug administration. **Key Secondary Endpoints** • Time to pain freedom. • Percentage of subjects able to perform normal daily activities at Hour 2, defined as a reduction to none on the functional disability scale, for those subjects who report greater than none at baseline. **Secondary Endpoints** *Pain Freedom / Relief* • Percentage of subjects with headache pain freedom over time. • Percentage of subjects with headache pain relief at Hour 2. • Change from baseline in headache pain relief over time. • Time to headache pain relief. • Time to sustained headache freedom through Hour 24. • Time to sustained headache freedom through Hour 48. • Percentage of subjects with headache pain freedom between Hours 2 and 24 (24-hour sustained pain-free). • Percentage of subjects with headache pain freedom between Hours 2 and 48 (48-hour sustained pain-free). • Percentage of subjects with sustained headache pain freedom between Hours 1.5 and 24. • Percentage of subjects with sustained headache pain freedom between Hours 1 and 24. • [redacted] *Functional Disability* • Change from baseline in functional disability to Hour 2. • Change from baseline in functional disability over time. • Percentage of subjects able to perform normal activity (functional disability = none) at Hour 2. • Time to being able to perform normal activity (functional disability = none). • Percentage of subjects able to perform normal activity (functional disability = none) at Hour 1.5. • Percentage of subjects able to perform normal activity (functional disability = none) at Hour 1. • Percentage of subjects able to perform normal activity (functional disability = none) over time. • Sustained ability to function at a normal level (functional disability = none) from Hours 2 to 24.

	• Sustained ability to function at a normal level (functional disability = none) from Hours 2 to 48. *Most Bothersome Symptoms* • Percentage of subjects with absence of MBS over time. • Sustained freedom from MBS from Hour 2 to Hour 24. • Sustained freedom from MBS from Hour 2 to Hour 48. • Absence of photophobia at Hour 2 in the subset of subjects that reported the presence of photophobia at headache baseline. • Absence of phonophobia at Hour 2 in the subset of subjects that reported the presence of phonophobia at headache baseline. • Absence of nausea at Hour 2 in the subset of subjects that reported the presence of nausea at headache baseline. • Absence of photophobia at over time in the subset of subjects that reported the presence of photophobia at headache baseline. • Absence of phonophobia over time in the subset of subjects that reported the presence of phonophobia at headache baseline. • Absence of nausea over time the subset of subjects that reported the presence of nausea at headache baseline. *Rescue Medication Use* • Percentage of subjects using rescue medication within 24 hours after administration of study medication. • Time to rescue medication use. *Other Secondary Endpoints* • Patient Global Impression of Change (PGI-C) scores at Hour 2. • PGI-C scores over time. • Treatment response based on presence of allodynia, BMI, pain intensity, presence of depression, and use of preventive medication. **Safety Endpoints:** • Treatment-emergent adverse events (TEAEs) • Vital signs • Physical exam findings • Clinical laboratory parameters • ECG
STATISTICAL METHODS	**Analysis Populations:** The following analysis populations are planned for this study: • Intent-to-Treat (ITT) Population: the ITT population is the primary analysis population and will include data from all subjects who are randomized and have a qualifying migraine episode. • Safety Population: The Safety Population will include all subjects who receive study medication. Membership in the analysis populations will be determined before unblinding. There are two co-primary efficacy variables, percentage of subjects with pain freedom at Hour 2 and percentage of subjects with absence of MBS at Hour 2. To establish the efficacy, AXS-07 must be significantly better than placebo at a two-sided significant level of 0.05 for each of the two co-primary efficacy variables. The variables related to the percentages will be analyzed via chi-square tests. The percentages, differences in the percentages as well as the two-sided 95% confidence intervals of the differences will be presented. The confidence intervals will be constructed using normal approximations.
SAMPLE SIZE DETERMINATION	In this study, approximately 300 subjects will be randomized 1:1 to either AXS-07 or placebo group.

	For the primary endpoint, approximately 150 subjects per group will provide 90% power to detect a treatment difference at a two-sided significance level of 0.05, assuming that the responder rate for pain freedom at Hour 2 is ≤15% for placebo and ≥29% for AXS-07.
STUDY AND TREATMENT DURATION	The duration of participation will be up to 10 weeks as follows: Screening Period: 28 days. Treatment Period: up to 6 weeks.

Schedule of Assessments

	Visit 1	Visit 2	Visit 3
	Screening	**Randomization**	**Follow-up[d] / EOS**
	Day –28	**Day 1**	**Within 7 days of dosing**
Informed Consent	X		
Inclusion/Exclusion Criteria	X	X	
Demographics	X		
Medical History	X		
Migraine Headache History	X	X	
Medications, Prior and Concomitant, or Non-drug Therapy	X	X	X
Physical Examination, including height and weight	X		X
Vital Signs (seated blood pressure, pulse, oral body temp.)	X	X	X
ECG	X		X
Clinical Laboratory Tests	X		X
Urine Pregnancy Test[a]	X	X	X
Urine Drug Screen	X	X	
ASC-12		X	
MIDAS		X	
Randomization		X	
Dispense Headache Diary and Instruct on Use	X	X	
Review Compliance with Headache Diary		X	X
Dispense Study Drug & Provide Dosing Instructions		X	
Subject Completes Diary Data[b]		X	
Phone call contact[c]		X	
Return Headache Diary			X
Collect/Inventory Study Medication			X
Adverse Events[e]		X	X

Abbreviations: ASC-12 = 12-item Allodynia Symptom Checklist; ECG = electrocardiogram; MIDAS = Migraine Disability Assessment; PGI-C = patient global impression of change.

a. For women of child-bearing potential only. Test results must be negative at Screening and Randomization for the subject to continue in the study.
b. Headache Diary data will be collected at the following times: Baseline (pre-dose during Treatment Period) and 20, 30 and 45 minutes, and 1, 1.5, 2, 4, 12, 16, 24, and 48 hours after dosing
c. The subject should be contacted within 24 hours after administering study medication. During the post-dose call, the site should re-confirm study drug dosing instructions and check for changes in concomitant medications. Following the onset of a qualifying migraine, assess compliance with migraine pain diary, rescue medication use, and to schedule the follow up appointment.
d. Final visit after treating one attack (to be scheduled as soon as possible but within 7 days of dosing), or within 6 weeks after Visit 2 if the study medication not used.
e. Adverse events are not required to be collected if subjects do not receive a dose of study medication.

2. TABLE OF CONTENTS

3. LIST OF ABBREVIATIONS

ADR	adverse drug reaction
AE	adverse event
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CFR	Code of Federal Regulations
CRA	clinical research associate
CGRP	calcitonin gene-related peptide
eCRF	electronic case report form
CSR	clinical study report
DSMB	Data Safety Monitoring Board
EDC	electronic data capture
EOS	End of Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICHD-3	International Classification of Headache Disorder, 3rd Edition
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web response system
MBS	most bothersome symptom
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	nonsteroidal anti-inflammatory drug
PGI-C	Patient Global Impression of Change
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class
SNRI	serotonin norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TEAE	treatment-emergent adverse event
UADR	unexpected adverse drug reaction
UAE	unexpected adverse event
US	United States
WHO	World Health Organization

4. INTRODUCTION

4.1 Background and Rationale

AXS-07 is a novel, oral, rapidly absorbed, investigational medicine consisting of MoSEIC™ meloxicam and rizatriptan being developed for the acute treatment of migraine with or without aura in adults. Rizatriptan is a 5-HT1$_{B/D}$ agonist (triptan) currently approved for the acute treatment of migraine, and meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) currently approved for the relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis [1,2]. The MoSEIC™ meloxicam formulation in AXS-07 tablets provides faster dissolution and absorption of meloxicam as compared to standard preparations, enabling its use for the treatment of migraine.

Migraine is a disorder characterized by recurrent attacks of pulsating, unilateral or bilateral head pain, often associated with nausea, photophobia, and phonophobia [3]. Migraine attacks may occur with or without an aura, which is a focal neurological symptom (e.g. vision changes) that typically precedes other symptoms. Migraine attacks generally last from 4 to 72 hours and are often severe and disabling, requiring bed rest [3].

The rationale for the development of AXS-07 in the treatment of migraine is based on the rapid absorption and long half-live of MoSEIC™ meloxicam in AXS-07 and the potential additive efficacy of MoSEIC™ meloxicam and rizatriptan. The MoSEIC™ meloxicam in AXS-07 contributes a distinct mechanism of action, and reaches C_{max} in approximately one hour after oral administration, thereby providing the potential for greater efficacy and a more rapid onset of action as compared to rizatriptan alone. In addition, the MoSEIC™ meloxicam in AXS-07 maintains an approximately 20-hour half-life, which may provide more sustained efficacy with less recurrence of symptoms as compared to rizatriptan alone.

Triptans have been shown to be efficacious for moderate to severe migraine [1,4] and are considered by many the drugs of choice for the abortive treatment of attacks. However, triptans, including rizatriptan, suffer from several limitations. Firstly, they do not successfully treat all patients or all attacks. Secondly, they do not work as quickly as patients require. Thirdly, migraine recurrence within 24 hours after treatment with triptans is common. Meloxicam is a potent and well characterized NSAID whose utility has been limited by slow absorption resulting in a delayed Tmax [2]. Results of completed Phase 1 trials of AXS-07 revealed a faster Tmax after oral administration, making this formulation more suitable for the treatment of migraine [2]. By combining rizatriptan with MoSEIC™ meloxicam, AXS-07 may overcome these limitations.

4.2 Clinical Experience with Rizatriptan

The efficacy of rizatriptan in the acute treatment of migraine in adults was established in four multicenter, randomized, placebo-controlled trials. In all studies, the percentage of patients achieving headache response 2 hours after treatment was significantly greater in patients who received either 5 or 10 mg rizatriptan as compared to those who received placebo. Headache response, defined as a reduction of moderate or severe headache pain to no or mild headache pain, was experienced 2 hours after treatment by 67-77% of subjects who received 10 mg rizatriptan versus 35-40% of subjects who received placebo. Rizatriptan treatment was also superior for complete pain relief and demonstrated lower symptom recurrence as compared to placebo. [1]

5. OBJECTIVES

5.1 Primary Objective

To evaluate the effect of AXS-07 as compared to placebo in the acute treatment of migraine headache in adults as evaluated by the following two co-primary efficacy variables: 1) pain freedom at Hour 2, and 2) absence of the most bothersome symptom (MBS; nausea, photophobia, or phonophobia) at Hour 2.

5.2 Key Secondary Objectives

To assess the effect of AXS-07 on time to headache pain freedom and functional disability at Hour 2.

5.3 Secondary Objectives

To assess the effect of AXS-07 on:

Pain Freedom / Relief

- Percentage of subjects with headache pain freedom over time.
- Percentage of subjects with headache pain relief at Hour 2.
- Change from baseline in headache pain relief over time.
- Time to headache pain relief.
- Time to sustained headache freedom through Hour 24.
- Time to sustained headache freedom through Hour 48.
- Percentage of subjects with headache pain freedom between Hours 2 and 24 (24-hour sustained pain-free).
- Percentage of subjects with headache pain freedom between Hours 2 and 48 (48-hour sustained pain-free).
- Percentage of subjects with sustained headache pain freedom between Hours 1.5 and 24.
- Percentage of subjects with sustained headache pain freedom between Hours 1 and 24.
- [redacted]

Functional Disability

- Change from baseline in functional disability to Hour 2.
- Change from baseline in functional disability over time.
- Percentage of subjects able to perform normal activity at Hour 2.
- Percentage of subjects able to perform normal activity at Hour 1.5.
- Percentage of subjects able to perform normal activity at Hour 1.
- Percentage of subjects able to perform normal activity over time.
- Sustained ability to function at a normal level from Hours 2 to 24.
- Sustained ability to function at a normal level from Hours 2 to 48.

Most Bothersome Symptoms

- Percentage of subjects with absence of MBS over time.
- Percentage of subjects with absence of MBS over time.
- Sustained freedom from MBS from Hour 2 to Hour 24.
- Sustained freedom from MBS from Hour 2 to Hour 48.
- Absence of photophobia at Hour 2 in the subset of subjects that reported the presence of photophobia at headache baseline.

- Absence of phonophobia at Hour 2 in the subset of subjects that reported the presence of phonophobia at headache baseline.
- Absence of nausea at Hour 2 in the subset of subjects that reported the presence of nausea at headache baseline.
- Absence of photophobia at over time in the subset of subjects that reported the presence of photophobia at headache baseline.
- Absence of phonophobia over time in the subset of subjects that reported the presence of phonophobia at headache baseline.
- Absence of nausea over time the subset of subjects that reported the presence of nausea at headache baseline.

Rescue Medication Use

- Percentage of subjects using rescue medication within 24 hours after administration of study medication.
- Time to rescue medication use.

Other Objectives

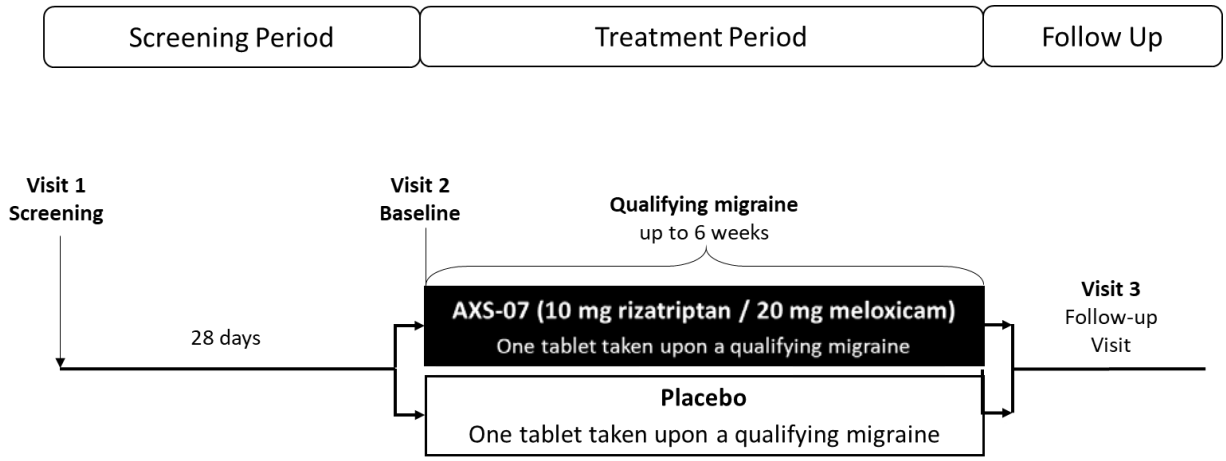
- Patient Global Impression of Change (PGI-C) scores at Hour 2.
- Treatment response based on presence of allodynia, BMI, pain intensity, presence of depression, and use of preventive medication.

6. STUDY DESIGN

6.1 Overall Study Design and Plan

The study is a Phase 3, multicenter, randomized, double-blind, single-dose, placebo-controlled trial to evaluate the efficacy and safety of AXS-07 in subjects with migraine attacks. The co-primary efficacy endpoints are the 1) percentage of subjects with headache pain freedom at Hour 2, with headache pain freedom defined as a reduction in headache severity to no pain, and 2) absence of the MBS (nausea, photophobia, or phonophobia) at Hour 2, with the MBS defined at the onset of migraine, prior to drug administration. The key secondary endpoints are the time to headache pain freedom and functional disability at Hour 2.

Figure 6.1 Study Design



To qualify for the study, subjects must be 18 to 65 years of age, have an established diagnosis of migraine (history indicating the presence of migraine for at least 1 year) with or without aura as defined by the International Classification of Headache Disorder, 3rd Edition (ICHD-3) and experience an average of 2 to 8 migraine attacks per month (no more than 10 migraine days per month) over the past 3 months.

Screening Period and Randomization

Subjects who successfully complete the Screening visit (Visit 1) will enter into a 28-day Screening Period during which they will record the details (baseline characteristics, headache pain intensity, associated migraine symptoms, and treatments used) of all migraines during this time. The subject must report at least 1 and no more than 8 migraines during the 28-day period in order to continue to be eligible. Subjects who continue to meet all eligibility criteria, will be randomly assigned at Visit 2 (randomization) to receive AXS-07 or placebo, dispensed for at-home treatment of a single migraine attack. Subjects will have 6 weeks to treat a qualifying migraine.

Treatment and Follow-up Periods

After randomization, as soon as possible after the onset of the next migraine, subjects will record baseline headache characteristics in the Headache Diary, and take the study medication, one tablet orally, when prompted by the diary. In the diary, subject will record the headache pain intensity (0-none, 1-mild, 2-moderate, and 3-severe), functional disability, presence or absence of associated symptoms (photophobia, phonophobia, nausea), and Patient Global Impression of Change (PGI-C). Subjects will complete the diary for 48 hours after the onset of the migraine and study drug dosing. Subjects will be instructed to follow restrictions regarding use of other medications, including rescue medications, and must not sleep or nap for at least 2 hours after taking study drug.

A follow-up visit (Visit 3) will occur after treating one attack. The visit is to be scheduled as soon as possible but within 1 week after dosing, or within 6 weeks after randomization (Visit 2) if the study medication is not used.

Headache Diary Assessments

Diaries will be provided and subjects will be instructed to complete the diary for 48 hours after taking study medication for a migraine.

Headache pain intensity (measured by a 4-point rating scale; 0-none, 1-mild, 2-moderate, or 3-severe), will be recorded by subjects in the diary as soon as possible after the onset of each migraine (prior to dosing in the Treatment Period), and at the following time points: 20, 30 and 45 minutes, and 1, 1.5, 2, 4, 12, 16, 24, and 48 hours.

At the onset of each migraine, and prior to dosing in the Treatment Period, the subject will define their most bothersome symptom (nausea, photophobia, phonophobia) and will assess the presence or absence of it at the following time points 30 minutes and 1, 2, and 4 hours after dosing. In addition, functional disability with regard to daily activities (on a 4-point scale) will be recorded at the following time points: Baseline (prior to dosing during the Treatment Period), 30 minutes, and 1, 2, 4, 12, and 24 hours after dosing. During the Treatment Period, subjects will report PGI-C 2 hours after dosing.

Safety and Other Assessments

A physical examination will be performed at Screening. Samples for clinical laboratory testing (hematology and chemistry) will be collected at Screening. A urine pregnancy test will be performed at Screening, randomization (Visit 2), and Follow-up (Visit 3). ECGs will be performed at Screening and Follow-up (Visit 3). At each visit, vital signs will be assessed and concomitant medications will be reviewed.

Presence of allodynia will be collected via the Allodynia Symptom Checklist-12 Item (ASC-12). Baseline assessment of migraine disability will be collected via the Migraine Disability Assessment (MIDAS).

Adverse events will be assessed following dosing with study drug.

6.2 Discussion of Study Design

A double-blind design is appropriate for assessing the efficacy and safety of AXS-07. Randomization was included to avoid bias. Placebo was chosen as the primary comparator to show treatment effect of AXS-07.

The use of a single dose to treat an acute migraine is consistent with the FDA guidance on developing drugs for the acute treatment of migraine. The safety and efficacy assessments used in this study are recognized and validated standards of measurement.

6.3 Study Sites

The study will take place at up to 50 study sites in the United States. Each site is anticipated to screen a sufficient number of subjects to be able to randomize approximately 10 subjects. A study site with a high recruitment rate may be allowed to recruit more subjects if other sites have slow enrollment.

6.4 Point of Contact

A point of contact will be identified to provide information to subjects about where to obtain information on the study, the rights of the subject, and whom to contact in case of study-related injury. This information will be provided in the subject information and ICF.

7. SUBJECT POPULATION

7.1 Selection of Study Population and Diagnosis

Eligible subjects must have a confirmed diagnosis of migraine, meeting the ICHD-3 criteria, with an average of 2 to 8 migraines per month, over the past 3 months. Approximately 300 subjects will be enrolled at up to 50 study centers in the US.

Eligible subjects will be otherwise generally healthy, as required by the inclusion and exclusion criteria, documented by medical history, physical examination, and clinical laboratory examinations.

7.2 Study Entry Criteria

7.2.1 Inclusion Criteria

A subject will be eligible for study participation if the subject meets all of the following criteria:

1. Is male or female 18 to 65 years of age inclusive.
2. Is willing and able to provide written informed consent to participate in the study, and willing and able to understand and comply with the procedures and study requirements.
3. Has an established diagnosis of migraine (history indicating the presence of migraine for at least 1 year) with or without aura as defined by the ICHD-3 criteria.
4. Has a diagnosis of migraine attacks with or without aura, presenting before age 50.
5. Has a history, on average, of 2 to 8 migraine attacks per month over the past 3 months. NOTE: The subject must report at least 1, and no more than 8 migraines during the Screening Period.
6. Has a history of usual migraine duration of > 3 hours untreated (by history) for the 3 months prior to screening.
7. Has the ability to differentiate between migraine and non-migraine headaches.
8. Has a body weight ≥ 45 kg and a body mass index (BMI) ≤ 40 kg/m^2.
9. If receiving a selective serotonin reuptake inhibitor (SSRI) or serotonin norepinephrine reuptake inhibitor (SNRI), the dose has been stable for at least 8 weeks prior to randomization.
10. If female, is either not of childbearing potential (defined as postmenopausal for at least 1 year or surgically sterile [bilateral tubal ligation, bilateral oophorectomy, or hysterectomy]); or is nonlactating and nonpregnant (has negative pregnancy test results at Screening and Baseline), does not plan to get pregnant during the study or for at least one month after, and is using a reliable method of contraception, before study drug administration and for the duration of the trial. Reliable methods of contraception include hormonal, double-barrier methods (e.g., condom and diaphragm, condom and foam, condom and sponge, each with spermicidal jellies or cream), intrauterine devices, vasectomized partners (>6 months prior to Visit 2), and abstinence.
11. Is willing and able to complete the Headache Diary.

7.2.2 Exclusion Criteria

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

1. Has a known history of allergic reaction, hypersensitivity, or clinically significant intolerance to rizatriptan or another triptan, acetaminophen, aspirin, or any NSAIDs, including meloxicam; history of NSAID-induced bronchospasm (subjects with the triad of asthma, nasal polyps, and chronic rhinitis are at greater risk for bronchospasm and should be considered carefully); or hypersensitivity, allergy, or significant reaction to any ingredients of the study drug.
2. Has experienced > 8 migraine attacks monthly during either of the 2 months before screening.
3. Is suffering from cluster headaches (every day or every other day), tension headaches, or other types of migraine.
4. Has experienced chronic daily headache (≥ 15 days per month of non-migraine headaches during each of the 3 months before screening).
5. Has a history of brain stem aura, ophthalmoplegic or hemiplegic migraine headache, or any potentially serious neurological condition that is associated with headache.
6. Has confirmed or suspected cardiovascular or cerebrovascular disease.
7. Has history, symptoms, or significant risk factors for ischemic heart (e.g., silent ischemia, angina, myocardial infarction); coronary artery vasospasm; arrhythmia (e.g., atrial fibrillation or flutter, frequent premature ventricular contractions, atrioventricular block); clinically significant findings on ECG; cardiac accessory conduction pathway disorder (e.g., Wolff-Parkinson-White syndrome); or other cardiovascular disease.
8. Has history of stroke, transient ischemic attack or other cerebrovascular syndrome; peripheral vascular disease; or ischemic bowel disease.
9. Has uncontrolled hypertension (diastolic blood pressure > 95 mm Hg or systolic blood pressure > 160 mm Hg).
10. Is a female subject and is taking estrogenic contraceptives who, in addition, smokes and has experienced migraine attack with aura.
11. Has a concurrent medical condition(s) that requires the chronic (daily or near daily) use of analgesics, narcotic analgesics, steroidal or non-steroidal anti-inflammatory (NSAIDs) agents, tranquilizers, sedatives-hypnotics, antipsychotics, or nitrates or their use for prevention of migraine attacks.
12. Clinically significant abnormalities indicated from the medical history, physical exam, clinical chemistry, hematology, urine drug screen.
13. Had a diagnosis or suspicion of drug induced or chronic daily headaches within 1 year.
14. Has used MAO inhibitor, lithium, methylergonovine, or cimetidine in the 2 weeks before randomization
15. Has a history or current diagnosis of any clinically significant cardiac, pulmonary, neurological, immunological, hematological, gastrointestinal, hepatic, renal, or endocrine disease or any other condition which, in the opinion of the investigator, could compromise the subject's welfare, ability to communicate with the study staff, or otherwise contraindicate study participation.
16. Has a history or current diagnosis of schizophrenia or another significant psychiatric disorder which, in the opinion of the investigator, would affect the subject's ability to

comply with the study requirements. Stable bipolar disease and stable major depressive disorder is allowed.

17. Is receiving systemic chemotherapy, has an active malignancy of any type, or has been diagnosed with cancer within 5 years before Screening (excluding squamous or basal cell carcinoma of the skin).
18. Has a known or suspected history of alcoholism or drug abuse or misuse within 1 year before Screening or evidence of tolerance or physical dependence before study drug administration.
19. Has, or has had within 1 year, any clinically significant gastrointestinal (GI) disorder, including peptic or gastric ulcers or GI bleeding.
20. Has a medical or surgical condition of the GI system (including motility dysfunction) or renal system that might significantly alter the absorption, distribution, or excretion of any drug substance.
21. Is considered by the investigator, for any reason (including, but not limited to, the risks described as precautions, warnings, and contraindications in the current version of the investigator's brochure for AXS-07 tablets), to be an unsuitable candidate to receive the study drug.
22. Is using or expects to use concurrent analgesic, including NSAIDs (except aspirin at a dose of ≤ 325 mg daily for cardiovascular prophylaxis) during the trial. NOTE: NSAIDs and other analgesics maybe used during the Screening Period.
23. Is currently receiving or expects to use anticoagulants (e.g., heparin, warfarin, nutritional supplements having anticoagulant properties); or has bleeding problems, coagulation abnormalities, active blood dyscrasia, hemorrhagic disease, anemia, porphyria, phenylketonuria, bone marrow suppression, or immunosuppression.
24. Is currently receiving propranolol or has received propranolol within 2 weeks prior to randomization.
25. Has been treated with agents that could affect the analgesic response (such as central alpha agents adrenergic [clonidine and tizanidine]) within 2 weeks before randomization or expects to use such agents during the treatment period.
26. Has tested positive for drugs of abuse on the urine drug screen at randomization (Visit 2). Subjects who test positive at Screening and can produce a prescription for the medication from their physician may be considered for study enrollment at the discretion of the investigator. NOTE: The use of marijuana, medical or otherwise, is not permitted during the study and a positive test for THC will be exclusionary.
27. Has clinically significant abnormalities indicated from the medical history, physical exam, and laboratory findings at Screening that in the investigator's opinion contraindicates study participation.
28. Is HIV positive.
29. Has previously participated in another clinical study of AXS-07 or received any investigational drug or device or investigational therapy within 30 days before Screening.
30. Has significant difficulty swallowing tablets or is unable to tolerate oral medication.

7.3 Premature Subject Withdrawal

All subjects will be advised that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. The investigator should make every reasonable attempt to keep subjects in the study; however, subjects must be withdrawn from the study if they withdraw consent to participate. The investigator or designee must attempt to contact subjects who fail to attend scheduled visits by telephone or other means to exclude the possibility of an adverse event (AE) being the cause of withdrawal. Should this be the cause, the AE must be documented, reported, and followed as described in Section 10.2.

Axsome reserves the right to request the withdrawal of a subject because of protocol violations or other reasons.

The investigator also has the right to withdraw subjects from the study or discontinue study drug treatment at any time for lack of therapeutic effect that is intolerable or otherwise unacceptable to the subject, for intolerable or unacceptable AEs, intercurrent illness, noncompliance with study procedures, administrative reasons, or in the investigator's opinion, to protect the subject's best interest.

If a subject is withdrawn or discontinues treatment before completing the study, the reason and the date of discontinuation will be recorded on the appropriate electronic case report form (eCRF). If the subject received study drug prior to discontinuation, all attempts should be made to complete the end of study evaluations.

7.4 Subject Replacement Criteria

Subjects who are withdrawn will not be replaced. If a substantial number of subjects are withdrawn from the study, then Axsome will evaluate the need for developing replacement criteria.

8. TREATMENTS

8.1 Identification of Investigational Product

The following study medications will be provided:

- **AXS-07**: a fixed-dose combination tablet consisting of 20 mg meloxicam and 10 mg rizatriptan in the form of a single layer tablet for oral administration.
- **Placebo**: a single layer tablet with no active ingredient for oral administration, that matches the appearance of AXS-07.

[redacted]

8.2 Labeling and Packaging

[redacted]

8.2.1 Labeling

The bottles of the study drug will have a label that meets the applicable regulatory requirements and may include the following: subject identifier, dosage strength, lot number, package number, protocol number, specified number of tablets, caution statement, storage, sponsor/manufacturer identification, and dosing instructions.

8.2.2 Packaging

The study drug will be packaged in bottles, which will include 1 tablet and will blinded to the investigator, the study clinic personnel, and subjects.

8.3 Study Medication Administration

Eligible subjects will be randomized and dispensed study drug at Visit 2. At this visit, the site will instruct the subject how to use the Headache Diary and when to take the dose of study medication. Study medication will be taken upon the occurrence of a migraine.

Once a migraine occurs, the subject will be prompted by the Headache Diary to self-administer the dose of study medication with water. The subject must not sleep or nap for at least 2 hours after taking study drug. If the subject reports vomiting within 2 hours of study drug dosing, the exact time of vomiting should be recorded in the eCRF.

8.4 Dispensing and Storage

The study drug is to be used exclusively in this clinical study according to the instructions of this protocol. The investigator or designee is responsible for dispensing the study drug according to the dosage scheme and for ensuring its proper storage.

The investigator or designee must confirm the receipt of the study drug. A copy of this receipt must be kept by the investigator or designee and another copy will be stored at Axsome and/or its designee. The study drug will be dispensed to the subject at Visit 2 (randomization). The study drug will be self-administered by the subject at the onset of a migraine attack. The subject will have up to 6 weeks after being randomized to treat a migraine attack with study drug.

Once study drug has been received on site it must be stored at 25°C (77°F) and in a dry place in a securely locked area that is not generally accessible. Excursions between 15° and 30°C (59° and 86°F) are permitted. The storage area will be accessible only to those persons authorized by the investigator.

8.5 Method of Assigning Subjects to Treatment Groups

In this parallel-group randomized study, subjects who meet study entry criteria will be randomly assigned in a 1:1 ratio to AXS-07 or placebo. The randomization schedule will be computer generated using a permuted block algorithm that will randomly allocate the study drug to randomization numbers. The randomization numbers will be assigned sequentially through a central interactive web response system (IWRS) as subjects are entered into the study. The randomization schedule will not be stratified. Study center will not be a blocking factor in the randomization schedule.

The randomization schedule will be prepared before the start of the study. No one involved in the study performance will have access to the randomization schedule before official unblinding of treatment assignment. No subject will be randomized into this study more than once.

8.6 Blinding and Unblinding Treatment Assignment

All subjects, investigators, and study personnel involved in the conduct of the study, including data management, will be blinded to treatment assignment with the exception of a specified independent unblinded statistician and clinical supply manager who will have access to the randomization code. The unblinded study personnel will not otherwise participate in study procedures or data analysis before unblinding of the study data to all study related personnel.

Study personnel will strive to safeguard the integrity of the study blind to minimize bias in the conduct of the study. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment. Unblinding should be discussed in advance with the medical monitor if possible. For emergency unblinding, the investigator will use the IWRS. If the investigator is not able to discuss treatment unblinding in advance, then he or she must notify the medical monitor as soon as possible about the unblinding incident without revealing the subject's treatment assignment. The investigator or designee must record the date and reason for study discontinuation on the appropriate eCRF for that subject. In all nonemergency cases, the investigator must discuss the event with the medical monitor before unblinding the subject's treatment assignment.

If treatment assignment is unblinded for an individual subject, study personnel will be notified of that subject's treatment assignment without unblinding those of the remaining subjects in the study. Thus, the overall study blind will not be compromised. If a subject's treatment assignment is unblinded, he or she may or may not be asked to withdraw from the study. The investigator will make this decision after consultation with the medical monitor.

Official study unblinding will occur after the last subject has completed and the database has been locked.

8.7 Selection of Doses in the Study

The dose of AXS-07 in this study incorporates a rizatriptan dose (10 mg) which was selected because it is currently approved for the acute treatment of migraine, and because it has been shown to be efficacious in several large controlled clinical trials. The oral meloxicam dose (20 mg) in AXS-07 was selected based on an analysis of the dose-dependent effect of intravenously administered meloxicam in the treatment of acute pain, observed in a large controlled trial.

8.8 Selection of Timing of Dose for Each Subject

A single dose will be taken upon the first onset of migraine pain. The study medication is to be taken orally with water.

8.9 Dose Adjustment Criteria

Dose adjustment is not allowed during this study.

8.10 Drug Accountability

The investigator, or designee, must maintain adequate records showing the receipt, dosing, or other disposition of the study drug provided, including the date, quantity, batch or code number, and identification of subjects (subject number and initials) who received it. The investigator will not supply the study drug to any person except those named as sub-investigators on the Form FDA 1572, designated study personnel, and subjects in this study. The investigator will not dispense the study drug from any study sites other than those listed on the Form FDA 1572. The study drug may not be relabeled or reassigned for use by other subjects. If any of the study drug is not dispensed; is lost, stolen, spilled, unusable; or is received in a damaged container, this information must be documented and reported to Axsome Therapeutics and appropriate regulatory agencies, as required.

Upon completion of the study, the study drug (unused and empty packaging, e.g., study drug bottles) must be left in the original packaging and returned to Axsome or its designee for destruction.

8.11 Treatment Compliance

Study drug will be self-administered by the subject. Dosing details will be recorded in the subject's Headache Diary.

8.12 Permitted and Prohibited Therapies

All concomitant medications and treatments used (including over-the-counter medications and herbal supplements) will be recorded in the source document and on the appropriate eCRF. All effort should be made to record medications taken for migraine over the past 3 months. This includes both current and prior medications.

During the Screening Period, subjects may treat their migraines according to their standard of care. All medications used to treat migraines will be recorded in the Headache Diary.

8.12.1 Rescue Medication

No rescue medication use is allowed within 2 hours after the start of the migraine attack. After the 2-hour diary time point has been recorded, if the subject has inadequate relief from the study medication, they may take an allowed rescue medication. Barbiturates and ergotamine-containing medications are not allowed as rescue medications.

Examples of allowed medications include triptans, NSAIDs, antiemetics, non-NSAID analgesics (e.g., acetaminophen, gabapentin), and sedatives.

8.12.2 Permitted Therapies

Migraine prophylactic agents and selective serotonin reuptake inhibitors (SSRIs) / SNRIs are permitted if the subject has been on a stable dose for 8 weeks (2 months) prior to randomization. The use of calcitonin gene-related peptide (CGRP) monoclonal antibodies and onabotulinumtoxinA (Botox®) for migraine prophylaxis is allowed if the subject has been on stable doses for at least 6 months prior to randomization. No changes in dose will be permitted during the study.

The following medications for acute migraine treatment will be permitted during screening and prior to receiving study drug. These medications may not be used 24 hours before, concurrently or within 24 hours after treatment with study drug.

- Ergotamine-containing medications
- Barbiturates

8.12.3 Prohibited Therapies

The following medications are not permitted in the 2 weeks before randomization and for the duration of the study.

- MAO-A inhibitors
- Methylergonovine
- Cimetidine

- Propranolol
- Opioids

Subjects taking ergot alkaloids for prophylaxis for acute migraine will be excluded from the study.

8.13 Treatment After the End of Study

After the end of the study, each subject will be treated according to standard clinical practice.

9. STUDY PROCEDURES

Subjects will provide written informed consent before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

For the timing of assessments and procedures throughout the study, refer to the schedule of events (Section 17.1). Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the schedule of events for each subject. If a subject misses a study visit for any reason, the visit should be rescheduled within the visit window specified below.

9.1 Study Periods, Visits, and Procedures

9.1.1 Visit 1: Screening (Day -28)

Subjects will sign an ICF before any screening-related procedures are performed. The following procedures will be performed at the Screening:

- Obtain written informed consent.
- Assign an enrollment number.
- Review inclusion/exclusion criteria.
- Confirm diagnosis of migraine with or without aura as defined by the ICHD-3 criteria.
- Record demographics and detailed medical history, including history of depression, a review of medications taken within 30 days before Screening, and migraine medications taken for the last 3 months.
- Record concomitant medications, including planned medications to treat acute migraines during the Screening Period.
- Perform a complete physical examination (excluding breast and genitourinary examination) with review of body systems.
- Record vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature) after the subject has been in a seated position for at least 5 minutes.
- Measure height and weight.
- Collect ECG.
- Collect blood and urine samples for clinical laboratory tests (hematology, biochemistry, and urinalysis); see Section 9.3.3.2.1 for a complete list of required laboratory tests.
- Conduct onsite urine analysis for the following:
  - Pregnancy test for females of childbearing potential.
  - Drug screen.

- Review the use of a Headache Diary and confirm subject will be willing and able to complete diary assessments.
- Dispense Headache Diary and train on diary completion.

9.1.2 Screening Period (Day -28 to Day -1)

The Screening Period is a fixed 28 days prior to randomization, if needed to accommodate scheduling the Screening period can be ± 3 days.

During the Screening Period, the subjects will record and complete the Headache Diary in a similar manner that they will during the Treatment Period. Subjects must have at least 1 migraine and no more than 8 migraines during this period in order to be eligible for the study. Additionally, subjects must report at an average of at least 80% compliance of timepoints on the Headache Diary to be eligible.

Subjects will treat all migraines according to their standard of care during the Screening Period and all medications will be recorded.

9.1.3 Visit 2: Randomization (Day 1)

Day 1 (Visit 2) is the randomization visit. The following procedures will be performed at Visit 2:

- Confirm subject continues to meets all inclusion/exclusion criteria.
- Record vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature) after the subject has been in a seated position for at least 5 minutes.
- Record weight.
- Conduct onsite urine analysis for the following:
  - Pregnancy test for females of childbearing potential.
  - Drug screen.
- Review instructions with the subject on how to use the electronic diary.
- Complete ASC-12 and MIDAS.
- Randomize and dispense study medication.
- Train subject on when to take study medication.
- Record new or changes to concomitant medications.

Following the Baseline visit and prior to treating a migraine, the subject should be contacted regularly to review the following:

- Record new or changes to concomitant medications.
- Review instructions completion of the Headache Diary.
- Review when to take study medication.

Once the subject has a qualifying migraine, the subject should be contacted as soon as possible, within 24 hours, following study drug administration. During the call, the following should be reviewed:

- Record AEs and rescue medication use.

- If study drug was taken on an empty stomach. If not, the type of food and timing relative to study drug should be recorded.
- If applicable, timing of migraine related to menstrual cycle.
- Ensure subject is completing migraine pain diary and questionnaires & assess compliance.
- Schedule Visit 3, within 7 days of dose.

9.1.4 End of Study: Visit 3 (within 7 days of study drug administration)

The following procedures should be conducted at the End of Study visit:

- Record AEs and concomitant medications.
- Record vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature) after the subject has been in a seated position for at least 5 minutes.
- Record weight.
- Perform a physical examination.
- Collect ECG.
- Collect blood and urine samples for clinical laboratory tests (hematology, biochemistry, and urinalysis); see Section 9.3.3.2.1 for a complete list of required laboratory tests.
- For females of childbearing potential, conduct a urine pregnancy test.
- Collect Headache Diary from subject.
- Collect study drug.

9.1.5 Early Termination Visit

An early termination visit will occur if the subject is randomized, but does not receive study drug. During the visit, the following will occur.

- Record reason for early termination.
- Collect Headache Diary from subject.
- Collect study drug.

9.2 Study Duration

The study will last up to approximately 10 weeks for an individual subject.

9.3 Assessments

9.3.1 Efficacy

9.3.1.1 Headache Diary

A Headache Diary will be provided to subjects who will be trained by study personnel on how to use the diary at Screening.

The Headache Diary will be completed for 28 days during the Screening Period to record each migraine. After randomization, the subject will log the migraine in the diary, which will prompt the subject when to take the dose.

The diary will be used to record baseline headache characteristics (eg, severity, location, and quality of pain), and the ongoing severity of the headache pain (0-none, 1-mild, 2-moderate, 3-severe), presence or absence of associated symptoms (photophobia, phonophobia, nausea), functional disability (none, mild, moderate, or severe), and Patient Global Impression of Change (PGI-C). Subjects will be instructed to complete the diary at the specified time points for 48 hours after a migraine.

9.3.1.1.1 Headache Pain Intensity

Headache pain intensity (measured by a 4-point rating scale; 0-none, 1-mild, 2-moderate, or 3-severe), will be recorded by the subject in the Headache Diary.

Pain intensity will be collected at the following time points: baseline, 20, 30 and 45 minutes, and 1, 2, 4, 12, 16, 24, and 48 hours after dosing.

9.3.1.1.2 Most Bothersome Symptom Reporting

The presence or absence of the following migraine symptoms will be recorded by the subject in the Headache Diary: nausea, photophobia, phonophobia. At the beginning of each migraine, (and prior to dosing in the Treatment Period) the subject will define the most bothersome symptom and will assess the presence or absence of each symptom at the following time points: 30 minutes, and 1, 2, and 4 hours after dosing.

9.3.1.1.3 Functional Disability

Patient-reported level of functional disability (degree of interference with normal activities) will be measured using a 4-point rating scale. Functional disability will be recorded by the subject in the Headache Diary at the beginning of each migraine (prior to dosing during the Treatment Period), and at 30 minutes, and 1, 2, 4, 12, and 24 hours after dosing.

9.3.1.1.4 Patient Global Impression of Change

The PGI-C is 7-point scale completed by a patient. It measures a general assessment of the improvement or worsening of the underlying disease (migraine headache). Subjects will complete the PGI-C at 2 hours following reporting a migraine.

9.3.1.2 Allodynia Symptom Checklist (ASC-12)

The ASC-12 is a validated checklist to assess the degree of allodynia in migraine sufferers [8, 9]. Sum scores on the ASC-12 range from 0 to 24 and are divided into no allodynia (0-2), mild allodynia (3–5), moderate allodynia (6–8), and severe allodynia (≥9).

Allodynia will be assessed at Baseline using the ASC-12.

9.3.1.3 Migraine Disability Assessment (MIDAS)

The MIDAS questionnaire is a validated 5-item questionnaire developed to assess headache-related disability [10, 11,12]. The MIDAS score is based on five disability questions in three dimensions: school/job, housework, and social. Each of the 5 questions is answered based on the number of days, in the past 3 months, of activity limitations due to migraine. The score is the sum of responses which are categorized in to the following categories: little or no disability (0 – 5), mild disability (6 - 10), moderate disability (11 – 20), and severe disability (21+). Two

supplemental non-scored questions provide additional clinical information about headache frequency and the average pain intensity of headaches over the previous three months.

The MIDAS questionnaire will be administered at Baseline.

9.3.2 Clinical Pharmacology

Not applicable for this study.

9.3.3 Safety

Safety assessments will include the evaluation of treatment emergent adverse events (TEAEs); clinical laboratory test results; vital sign measurements; and physical examination findings.

9.3.3.1 Adverse Events

The definitions and management of and special considerations for AEs are provided in Section 10.

9.3.3.2 Clinical Laboratory Safety Assessments

9.3.3.2.1 Clinical Laboratory Tests to be Performed

Samples for the following laboratory tests will be collected at the time points specified in the schedule of events (Section 17.1).

Hematology	Hemoglobin, hematocrit, red blood cell count, red blood cell indices, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count (or estimate), and white blood cell count, including differential
Serum Chemistry	Albumin, total bilirubin, direct bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, glucose, sodium, potassium, and chloride.
Urinalysis	Sp. gravity, pH, glucose, total protein, ketones, color, sample aspect (appearance)
Pregnancy Test	For women of childbearing potential only. A urine test will be performed at screening, randomization, and end of study.
Urine Drug Screen	Amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, and tetrahydrocannabinol (THC).

Blood samples for hematology, serum chemistry, and urine samples for urinalysis will be sent to a central laboratory for analyses. Urine drug screens and urine pregnancy tests will be conducted at the study sites.

9.3.3.2.2 Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be employed by all study personnel involved in the collection of blood and handling of specimens in both the clinic and laboratory settings. Refer to current recommendations of the appropriate authorities.

In addition to appropriate handling of subject samples, specific regulations exist about the shipment of biologic/etiologic samples. Procedures and regulations for the packaging and shipping

of infectious samples are outlined in the study laboratory manual. The investigator or designee is responsible for ensuring that all study samples that are to be transported to another location are appropriately packed and shipped according to the applicable regulations.

9.3.3.2.3 Evaluation of Clinical Laboratory Values

The normal ranges of values for clinical laboratory assessments in this study will be provided by the responsible laboratory and submitted to Axsome or its designee before the start of the study. These will be regarded as the reference ranges on which decisions will be made.

If a clinical laboratory value is out of the reference range, it is not necessarily clinically relevant. The investigator is responsible for determining whether these occurrences are considered as AEs.

All clinical laboratory values that in the investigator's opinion show clinically relevant or pathological changes during or after termination of the treatment must be reported as AEs and followed as described in Section 10.2.5.

All measurements described in this section are recognized standard methods.

9.3.3.3 Clinical Examinations

9.3.3.3.1 Vital Signs

Vital signs will include blood pressure, heart rate, respiratory rate, and oral body temperature. Blood pressure will be measured after the subject has been in a sitting position for 5 minutes. Height will be measured at Visit 1, and weight will be measured at all visits.

9.3.3.3.2 Physical Examination

A complete physical examination (excluding breast and genitourinary examination) will be performed at screening and end of study.

9.3.3.3.3 Electrocardiogram (ECG)

A 12-lead ECG will be conducted after the subject has been resting for at least 2 minutes. At a minimum, the following parameters should be collected; heart rate, PR interval, QRS duration, QT interval, and QTcF.

If the subject reports cardiac related adverse events, they should return for an unscheduled visit and an ECG should be conducted.

10. ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease, temporally associated with the product, whether or not related to the product.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. (Worsening of a pre-existing condition is considered an AE.)

Events that occur in subjects treated with placebo or active comparator or during treatment-free periods of the study are also considered AEs.

10.1.2 Adverse Drug Reaction

All noxious and unintended responses to a study drug related to any dose should be considered adverse drug reactions (ADRs).

The phrase "responses to a study drug" means that a causal relationship between a study drug and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a study drug qualify as ADRs.

All AEs for which the judgment of relationship to the study drug is "possible" or higher will be considered ADRs. If a relationship to the study drug is not given, then the AE must be treated as if the relationship to the study drug were "possible."

10.1.3 Unexpected Adverse Event/Adverse Drug Reaction

An expected AE or ADR is an event for which the nature or severity is consistent with the known AE profile of the product. For a study drug, the known information is contained in the IB. For a marketed product, the known information is contained in the current package insert for the product.

An unexpected adverse event (UAE) or unexpected adverse drug reaction (UADR) is an event for which the specificity or severity is not consistent with the current IB. For example, hepatic necrosis would be unexpected (greater severity) if the IB only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected events. Examples would be a) acute renal failure as an expected adverse reaction with a subsequent new occurrence of interstitial nephritis (interstitial nephritis would be unexpected) and b) hepatitis with a first occurrence of fulminant hepatitis (fulminant hepatitis would be unexpected).

10.1.4 Serious Adverse Events/Drug Reaction

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
  NOTE: *The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*
- Requires inpatient hospitalization or prolongation of existing hospitalization.
  NOTE: *Inpatient hospitalization is defined as 24 hours in a hospital or an overnight stay. An elective hospital admission to treat a condition present before exposure to the study drug, or a hospital admission for a diagnostic evaluation of an AE, <u>does not</u> qualify the condition or event as an SAE. Further, an overnight stay in the hospital that is only due to transportation, organization, or accommodation problems and without medical background does not need to be considered an SAE.*
- Results in persistent or significant disability/incapacity.

- Is a congenital anomaly.
  NOTE: *A congenital anomaly in an infant born to a mother who was exposed to the study drug during pregnancy is an SAE. However, a newly diagnosed pregnancy in a subject who has received a study drug is not considered an SAE unless it is suspected that the study drug(s) interacted with a contraceptive method and led to the pregnancy.*
- Is an important medical event.
  NOTE: *Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. The occurrence of malignant tumors is also to be considered serious*

10.1.5 Significant Adverse Events

Other significant AEs are defined as marked hematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including significant additional concomitant therapy.

10.1.6 Treatment-Emergent Adverse Events

An AE is defined as treatment emergent if the first onset or worsening is after the first administration of the study drug and not more than 5 days after the last study visit.

10.2 Management of Adverse Events

Adverse events will be collected after administration of study drug through Visit 3.

10.2.1 Collection of Adverse Events

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described previously. At each visit, the subject will be allowed time to spontaneously report any issues since the last visit or evaluation. The investigator will then monitor and/or ask about or evaluate AEs using nonleading questions, such as:

- "How are you feeling?"
- "Have you experienced any issues since your last visit?"
- "Have you taken any new medications since your last visit?"

Any clinically relevant observations made during the visit will also be considered AEs.

10.2.2 Evaluation of Adverse Events

10.2.2.1 Severity of Adverse Events

The clinical severity of an AE will be classified as:

Mild	Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria, as described in Section 10.1.4.

10.2.2.2 Seriousness

The investigator is to evaluate whether the AE meets serious criteria, as described in Section 10.1.4.

10.2.2.3 Action(s) Taken

Action(s) taken may consist of:

Dose not changed	An indication that a medication schedule was maintained.
Not applicable	Determination of a value is not relevant in the current context.
Unknown	Not known, not observed, not recorded, or refused.

10.2.2.4 Outcome at the Time of Last Observation

The outcome, including Fatal, at the time of last observation will be classified per eCRF completion instructions. Only select fatal as an outcome when the AE results in death. If more than 1 AE is possibly related to the subject's death, the outcome of death should be indicated for each such AE. Although "fatal" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

10.2.2.5 Adverse Event Relationship to the Study Drug

The investigator will also assess the relationship (if any) between the AE and the study treatment (*not related, unlikely, possibly, probably or definitely).*

The investigator will use the following definitions to classify the relationship of an AE to study medication:

Not related: AEs which, after careful consideration, are clearly and undeniably because of extraneous causes (e.g. disease, environment);

Unlikely: This category can generally be considered applicable to those AEs which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the test drug. An AE may be considered unlikely to be related if or when at least two of the following criteria are fulfilled:

1) The event does not follow a reasonable temporal sequence from administration of the test drug;
2) The event could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient;
3) The event does not follow a known pattern of response to the test drug;
4) The event does not reappear or worsen when the drug is re-administered.

Possibly: This category applies to those AEs for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration appears unlikely, but cannot be ruled out with certainty. An AE may be considered possibly related if or when at least two of the following criteria are fulfilled:
1) The event follows a reasonable temporal sequence from administration of the drug;
2) The event could not readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient;
3) The event follows a known pattern of response to the test drug.

Probably: This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the test drug. An AE may be considered probably related if or when least three of the following criteria are fulfilled:
1) The event follows a reasonable temporal sequence from administration of the drug;
2) The event could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient;
3) The event disappears or decreases on stopping or reducing the dose. There are important exceptions when an AE does not disappear upon discontinuation of the drug, but drug-relatedness clearly exists, e.g. bone marrow depression, fixed drug eruptions, tardive dyskinesia;
4) The event follows a known pattern of response to the test drug.

Definitely: This category applies to those AEs, which the investigator feels are undeniably related to the test drug. An AE may be assigned an attribution of definitely related if or when all the following criteria are fulfilled:
1) The event follows a reasonable temporal sequence from administration of the drug;
2) The event could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient;
3) The event disappears or decreases on stopping or reducing the dose and reappears with re-exposure to study medication (Note: this does not mean that the patient is to be re-exposed to study medication, however, a category of definitely related can only be used when recurrence is observed);

4) The event follows a known pattern of response to the test drug.

10.2.3 Documentation

All AEs occurring within the period of observation for the study must be documented in the eCRF with the following information, where appropriate. (The period of observation for the study is described in Section 10.2.)

- AE name or term.
- When the AE first occurred (start date and time).
- When the AE stopped (stop date and time or an indication of "ongoing").
- Severity of the AE.
- Seriousness (e.g., hospitalization or death).
- Actions taken.
- Outcome.
- Investigator opinion regarding the AE relationship to the study drug(s).

10.2.4 Treatment of Adverse Events

Adverse events that occur during the study will be treated if necessary by established standards of care. If such treatment constitutes a deviation from the protocol, the subject may continue in the study at the discretion of Axsome after consultation with the investigator and/or medical monitor.

If AEs occur in a subject that are not tolerable, or for which continued administration of the study drug is not reasonable in view of the potential benefit to the subject, the investigator must decide whether to stop the study and/or treat the subject. Special procedures may be recommended for the specific study drug, such as the collection of a serum sample for blood concentrations of the study drug, specific tapering procedures, or treatment regimens, as appropriate.

For double-blinded studies, it is not necessary to unblind a subject's treatment assignment in most circumstances, even if an SAE has occurred. If unblinding is necessary, see Section 8.6 for a description of the unblinding procedures.

10.2.5 Follow-up of Adverse Events

Any AE will be followed (up to a maximum of 30 days after the subject's last visit in the study) to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause(s) (i.e., concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be reported in the subject's medical record and recorded on the appropriate eCRF.

10.2.6 Notification

10.2.6.1 Serious Adverse Events

The investigator or designee must report all SAEs within 24 hours of first becoming aware of the event by completing the Serious Adverse Event Report Form. [redacted] At the time of first notification, the investigator or designee should provide the following information, if available:

- Protocol number.

- Reporter (study site and investigator).
- Subject's study number and initials.
- Subject's date of birth.
- Subject's gender.
- Date of dose of study drug.
- Adverse event term.
- Time and date of occurrence of the event.
- A brief description of the event, outcome to date, and any actions taken.
- The seriousness criteria(on) that were met.
- Concomitant medication at onset of the event.
- Relevant past history information.
- Relevant laboratory test findings.
- Investigator's opinion of the relationship to the study drug(s). ("Is there a reasonable possibility that the study drug caused the SAE? Yes or No?").
- Whether and when the investigator was unblinded as to the subject's treatment assignment.

The investigator must also promptly provide any available supporting information which is requested after review of the initial SAE Report Form.

Any missing or additional relevant information concerning the SAE should be provided in a follow-up SAE Report Form. Ensure that any additional information requested about the event (e.g., hospital reports, autopsy reports) is provided as soon as it is available.

The investigator is required to comply with applicable regulations (including local laws and guidance's) regarding the notification of his or her health authorities, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), principal and coordinating investigators, study investigators, and institutions. The detailed reporting duties and division of responsibilities between Axsome and designated vendors will be provided in a separate document (see the Safety Management Plan). Each investigator is obligated to learn about the reporting requirements for investigators in his or her country. The study monitor may be able to assist with this.

10.2.6.2 Adverse Drug Reactions

Axsome will report all ADRs related to the study drug to the proper health authorities; serious ADRs will be reported immediately and nonserious ADRs will be reported after completion of the study. Suspected serious adverse drug reactions must be reported to Axsome immediately, regardless of the time that has elapsed since the end of the period of observation.

10.2.6.3 Nonserious Adverse Events

Axsome will review nonserious AEs that are recorded in the eCRF on a regular basis.

10.3 Special Considerations

10.3.1 Adverse Events of Special Interest

No AEs of special interests have been defined for this study.

10.3.2 Pregnancy

All women of childbearing potential who participate in the study should be counseled on the need to practice adequate birth control (from the time of Screening through 30 days beyond the End of Study) and on the importance of avoiding pregnancy during study participation. Women should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted before administration of the study drug on every woman of childbearing potential. A woman who is found to be pregnant at the Screening Visit will be excluded from the study and considered a screen failure.

A woman who becomes pregnant during study drug treatment or within 30 days of discontinuing the study drug will be immediately discontinued from study participation. The investigator must report the pregnancy as if it were an SAE within 24 hours of learning of the pregnancy. The investigator should record information related to the pregnancy on the Pregnancy and Lactation Exposure Form provided by Axsome or its designee.

Early termination visit assessments are required as soon as possible after learning of the pregnancy. The investigator is also responsible for following the pregnancy until delivery or termination. Findings must be reported on the Pregnancy and Lactation Exposure Form and reported to Axsome or its designee. The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly.

10.3.3 Overdose

Subjects should receive no more than one dose of study drug in this study.

Overdose that occurs during the study will be treated and documented as an AE/UAE/SAE if it fulfills the criteria. If the overdose does not result in an AE, it should be reported in written form to the designated individual(s) who receive SAE notification. The information contained therein should include study site identification, reporter identification, subject identification, study drug, dose, action taken (e.g., administration of antidote [if available] or supportive measures or therapy), and any comments.

11. DATA SAFETY MONITORING BOARD

Not applicable.

12. STATISTICS

This section describes the statistical methods to be used to analyze efficacy and safety. These methods may be revised and updated due to reasons such as regulatory requirements or need for further clarifications. The final analysis plan will be documented in a formal statistical analysis plan (SAP) that must be finalized before database lock. The SAP will include details on how variables will be derived, how missing data will be handled, and how data will be presented as

well as the details on statistical methods to be used for safety and efficacy analyses. The final clinical study report will discuss deviations from the SAP, if any.

12.1 Study Endpoints

12.1.1 Primary Endpoints

The co-primary endpoints for this study are:

- Percentage of subjects with headache pain freedom at Hour 2, with headache pain freedom defined as pain intensity = 0 (None).
- Percentage of subjects with absence of the most bothersome symptom (MBS; nausea, photophobia, or phonophobia) at Hour 2, with the MBS defined at the onset of migraine, prior to drug administration.

In the primary analysis, subjects who take rescue medication before Hour 2 or who do not have an Hour 2 value will be treated as non-responders.

12.1.2 Key Secondary Endpoints

The key secondary endpoints are

- Time to headache pain freedom.
- Percentage of subjects able to perform normal daily activities at Hour 2, defined as a reduction to none on the functional disability scale, for those subjects who report greater than none at baseline.

12.1.3 Secondary Endpoints

The secondary endpoints are:

Pain Freedom / Relief

- Percentage of subjects with headache pain freedom over time.
- Percentage of subjects with headache pain relief at Hour 2.
- Change from baseline in headache pain relief over time.
- Time to headache pain relief.
- Time to sustained headache freedom through Hour 24.
- Time to sustained headache freedom through Hour 48.
- Percentage of subjects with headache pain freedom between Hours 2 and 24 (24-hour sustained pain-free).
- Percentage of subjects with headache pain freedom between Hours 2 and 48 (48-hour sustained pain-free).
- Percentage of subjects with sustained headache pain freedom between Hours 1.5 and 24.
- Percentage of subjects with sustained headache pain freedom between Hours 1 and 24.
- [redacted]

Functional Disability

- Change from baseline in functional disability to Hour 2.
- Change from baseline in functional disability over time.

- Percentage of subjects able to perform normal activity (functional disability = none) at Hour 2.
- Time to being able to perform normal activity (functional disability = none).
- Percentage of subjects able to perform normal activity (functional disability = none) at Hour 1.5.
- Percentage of subjects able to perform normal activity (functional disability = none) at Hour 1.
- Percentage of subjects able to perform normal activity (functional disability = none) over time.
- Sustained ability to function at a normal level (functional disability = none) from Hours 2 to 24.
- Sustained ability to function at a normal level (functional disability = none) from Hours 2 to 48.

Most Bothersome Symptoms

- Percentage of subjects with absence of MBS over time.
- Sustained freedom from MBS from Hour 2 to Hour 24.
- Sustained freedom from MBS from Hour 2 to Hour 48.
- Absence of photophobia at Hour 2 in the subset of subjects that reported the presence of photophobia at headache baseline.
- Absence of phonophobia at Hour 2 in the subset of subjects that reported the presence of phonophobia at headache baseline.
- Absence of nausea at Hour 2 in the subset of subjects that reported the presence of nausea at headache baseline.
- Absence of photophobia at over time in the subset of subjects that reported the presence of photophobia at headache baseline.
- Absence of phonophobia over time in the subset of subjects that reported the presence of phonophobia at headache baseline.
- Absence of nausea over time the subset of subjects that reported the presence of nausea at headache baseline.

Rescue Medication Use

- Percentage of subjects using rescue medication within 24 hours after administration of study medication.
- Time to rescue medication use.

Other Secondary Endpoints

- Patient Global Impression of Change (PGI-C) scores at Hour 2.
- PGI-C scores over time.
- Treatment response based on presence of allodynia, BMI, pain intensity, presence of depression, and use of preventive medication.

12.1.4 Safety Endpoints

Safety endpoints will include the following:

- Treatment-emergent adverse events (TEAEs)
- Vital sign measurements
- Physical exam findings
- Clinical laboratory parameters
- ECG

12.2 Sample Size Determination

In this study, approximately 150 subjects will be randomized to the AXS-07 and placebo groups.

Approximately 150 subjects per arm will provide 90% power to detect a treatment difference at a two-sided significance level of 0.05, assuming that the responder rate for pain freedom at Hour 2 is ≤15% for the placebo control and ≥ 29%.

12.3 Analysis Populations

The following analysis populations are planned for this study:

- Intent-to-Treat (ITT) Population: the ITT Population is the primary analysis population and will include data from all subjects who are randomized and treat a migraine episode with study drug.
- Safety Population: The Safety Population will include all subjects who receive at study medication.

12.4 Statistical Analyses

Unless otherwise indicated, all testing of statistical significance will be 2-sided, and a difference resulting in a *P* value of less than or equal to 0.05 will be considered statistically significant. Furthermore, the baseline will be the last assessment before the first dosing of the study medication.

Summary statistics will be provided for the variables described in the following sections. For continuous variables, these statistics will typically include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, these statistics will typically include the number and percentage of subjects in each category.

12.4.1 Study Subjects and Demographics

12.4.1.1 Disposition and Withdrawals

The numbers of subjects completing, withdrawing, and discontinuing treatment, along with reasons for discontinuation or withdrawal, will be tabulated overall, and by treatment group. The number of subjects in each analysis population will be reported.

12.4.1.2 Protocol Deviations

Major protocol deviations will be classified and documented by Axsome before database lock and will be discussed in the clinical study report (CSR). All protocol deviations, both minors and majors, will be presented in a data listing.

12.4.1.3 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics (including age, sex, race, weight, and height) will be summarized for each treatment group and for the overall population by descriptive statistics. Medical history and clinical laboratory tests will be listed.

Prior and concomitant medications will be summarized by treatment group, by the number and percentage of subjects taking each medication, classified using World Health Organization (WHO) Drug Dictionary, Anatomical Therapeutic Chemical (ATC) classes, and preferred terms.

12.4.2 Exposure and Compliance

Study drug administration will be summarized in terms of dose taken (yes / no) by treatment group.

12.4.3 Efficacy Analyses

Efficacy variables will be summarized and analyzed using the ITT population unless otherwise specified.

12.4.3.1 Primary Efficacy Analysis

The co-primary efficacy endpoints are the 1) percentage of subjects with headache pain freedom at 2 hours after dosing, with headache pain freedom defined as a reduction in headache severity to no pain, and 2) absence of the most bothersome symptom (MBS; nausea, photophobia, or phonophobia) 2 hours after dosing, with the MBS defined at the onset of migraine, prior to drug administration. Full details of the analysis will be outlined in the SAP.

12.4.3.2 Secondary Efficacy Analyses

The secondary efficacy endpoints will be analyzed using methods similar to those outlined for the primary efficacy analysis. Full details of the analysis will be outlined in the SAP.

12.4.4 Adverse Events

Adverse events will be coded by system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) reporting system. Treatment-emergent AEs are defined as AEs with onset on the date of first dose of treatment with the study drug through Visit 3/End of Study (EOS).

The number and percentage of subjects with TEAEs will be displayed for each treatment group by SOC and preferred term. Additionally, TEAEs will be tabulated for each treatment group by severity and by relationship to the study drug. A listing of SAEs will be provided if applicable.

12.4.5 Vital Signs

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from Baseline will be calculated for systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and oral body temperature.

12.4.6 Physical Examination Findings

Physical examination data will be presented in the listings.

12.4.7 Interim Analysis

None.

13. STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel before the study, periodic monitoring visits, and meticulous data management.

13.1 Sponsor and Investigator Responsibilities

13.1.1 Sponsor Responsibilities

Axsome is obligated to conduct the study in accordance with strict ethical principles (Section 15). Axsome reserves the right to withdraw a subject from the study (Section 7.3), to terminate participation of a study site at any time (Section 13.5.3), and/or to discontinue the study (Section 13.5.2).

Axsome agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study according to the study protocol.

13.1.2 Investigator Responsibilities

By signing the Investigator's Agreement (Section 17.2), the investigator indicates that he or she has carefully read the protocol, fully understands the requirements, and agrees to conduct the study in accordance with the procedures and requirements described in this protocol.

The investigator also agrees to conduct this study in accordance with all laws, regulations, and guidelines of the pertinent regulatory authorities (Section 15.1 and Appendix E). While delegation of certain aspects of the study to sub investigators and study coordinators is appropriate, the investigator will remain personally accountable for closely overseeing the study and for ensuring compliance with the protocol and all applicable regulations and guidelines. The investigator is responsible for maintaining a list of all persons that have been delegated study-related responsibilities (e.g. sub investigators and study coordinators) and their specific study-related duties.

Investigators should ensure that all persons who have been delegated study-related responsibilities are adequately qualified and informed about the protocol, study drugs, and their specific duties within the context of the study. Investigators are responsible for providing Axsome with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by Axsome and the relevant governing authorities.

To ensure compliance with the guidelines, the study will be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

13.2 Site Initiation

Study personnel may not screen or enroll subjects into the study until after receiving notification from Axsome that the study can be initiated at the study site. The study site will not be authorized for study initiation until:

- The study site has received the appropriate IRB/IEC approval for the protocol and the appropriate ICF.
- All regulatory/GCP documents have been submitted to and approved by Axsome.
- The study site has a Clinical Trial Agreement in place.

- Study site personnel, including the investigator, have participated in a study initiation meeting/visit.

13.3 Study Documents

All documentation and material provided by Axsome for this study are to be retained in a secure location and treated as confidential material.

13.3.1 Investigator's Regulatory Documents

The regulatory documents are listed as follows:

- Signed original protocol (i.e., Investigator's Agreement).
- Curricula vitae of the principal investigator and sub investigators.
- Name and address of the laboratories.
- List of laboratory reference ranges, and if available, a quality certificate.
- Form Signature Log/Delegation of Study-related Duties.
- Any other relevant GCP documents.

The regulatory documents must be received from the investigator and reviewed and approved by Axsome before the study site can initiate the study and before Axsome will authorize shipment of study drug to the study site. Copies of the investigator's regulatory documents must be retained at the study site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the AXS-07 IB, eCRF completion guidelines, copies of regulatory references, copies of IRB/IEC correspondence, and study drug accountability records should also be retained as part of the investigator's regulatory documents. It is the investigator's responsibility to ensure that copies of all required regulatory documents are organized, current, and available for inspection.

13.3.2 Case Report Forms

By signing the Investigator's Agreement (Section 17.2), the investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all subjects who sign an ICF.

Case report forms are considered confidential documents and should be handled and stored accordingly. Axsome or its designee will provide the necessary training on the use of the specific eCRF system used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual subject visits should be completed as soon as possible after the visit. All requested information must be entered in the electronic data capture (EDC) system according to the completion guidelines provided by Axsome or its designee.

The eCRFs may be signed by the investigator or a sub investigator. These signatures serve to attest that the information contained in the eCRF is accurate and true.

13.3.3 Source Documents

All information recorded in the EDC system must be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated

instruments, memoranda, and pharmacy dispensing records. Investigators should make attempts to collect outside medical records.

During the study, select eCRF data may be used as original data collection tools as long as a description of this documentation process is maintained in the investigator's study files. Before the study starts, a list identifying any data to be recorded directly on the eCRFs (i.e., no prior written or electronic record of data) and considered to be source data will be provided.

Clinical laboratory data required by the protocol will be electronically transferred from the central laboratory to Axsome as well as the investigator. A copy of the laboratory results should be retained with each subject's source data.

13.4 Data Quality Control

Axsome and its designees will perform quality control checks on this clinical study.

13.4.1 Monitoring Procedures

Axsome will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associate(s) (CRA[s]) will visit the investigator and study site at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRA(s) and other authorized Axsome personnel access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. While on site, the CRA(s) will review the following:

- Regulatory documents, directly comparing entries in the EDC system with the source documents.
- Consenting procedures.
- AE procedures.
- Storage and accountability of the study drug and study materials.

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting the eCRF are described in the CRF completion guidelines. As representatives of Axsome, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (Section 17.2), the investigator agrees to meet with the CRA(s) during study site visits; to ensure that study staff is available to the CRA(s) as needed; to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the investigator agrees to allow Axsome or designee auditors or inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

13.4.2 Data Management

Axsome or its designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and Axsome or its vendors' standard operating procedures. A comprehensive data management plan will be developed including a data management overview, database contents, annotated CRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the

corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries are described in the CRF completion guidelines.

13.4.3 Quality Assurance/Audit

This study will be subject to audit by Axsome or its designee. The audits will be undertaken to check compliance with GCP guidelines and will include a minimum of:

- In-house study file audit.
- Audit of computer database quality control.
- Audit of clinical report quality control.

Axsome or its designee may conduct additional audits on a selection of study sites, requiring access to subject notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB/IEC or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with CRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify Axsome immediately.

13.5 Study Termination

The study may be terminated at Axsome's discretion at any time and for any reason.

13.5.1 Regular Study Termination

The end of this study is defined as the date of the last visit of the last subject (last subject out or last subject last visit) participating in the study. Within 90 days of the end of the clinical study, Axsome will notify the IRBs/IECs and regulatory authorities on the regular termination of the study as required according to national laws and regulations.

13.5.2 Premature Study Termination

The study may be terminated prematurely for any reason and at any time by Axsome, IRBs/IECs, regulatory authorities, respective steering committees, or the coordinating investigator. A decision to prematurely terminate the study is binding to all investigators of all study sites.

Within 15 days of premature termination of a clinical study, Axsome or its designee will notify the IRB/IEC and regulatory authorities as appropriate on the premature termination as required according to national laws and regulations. Axsome or its designee must clearly explain the reasons for premature termination.

If the study is terminated prematurely, all investigators have to inform their subjects and take care of appropriate follow-up and further treatment of the subjects to ensure protection of the subjects' interests. Study sites may be asked to have all subjects currently participating in the study complete all of the assessments for the Early Termination Visit.

13.5.3 Study Site Closure

A study site's participation in the study may be terminated at any time by Axsome. At the end of the study, all study sites will be closed. This will include the Investigators final approval and lock of all patient data, return of unused study material and investigational product unless otherwise provided for in writing by Axsome, and final visits by study monitors.

13.5.4 Record Retention

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be separated into two categories: investigator's study file and patient clinical source documents.

The investigator's study file will contain the protocol and protocol amendments (if applicable), eCRF guidelines, IRB / IEC approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents and correspondence.

Patient clinical source documents (which are usually defined by the project in advance to record key efficacy and/or safety parameters independent of the eCRF) may include patient and/or hospital clinical records, physician's and nurse's notes, appointment book, original laboratory reports, X-ray, pathology and special assessment reports, consultant's letters, screening and enrollment log, etc.

The patient's involvement in the study should be clearly documented in the study site's clinical records. Details should include the study protocol number, the patient's screening and randomization number, the patient's consent to take part in the study (including the date of consent), the dates of all study visits, details of any treatments withdrawn because of study participation, the dates of dispensing study medication, details of any AEs (including any SAEs), and changes in concomitant medications.

Study documents should not be destroyed without prior written agreement between Axsome and the investigator. If the investigator wishes to assign the study records to another party or move them to another location, Axsome must be notified in advance.

If the investigator cannot guarantee this archiving requirement for any or all the documents at the investigational site, arrangements must be made between the investigator and Axsome to store these in a sealed container(s) outside the site. The sealed container(s) can therefore be returned to the investigator in case of a regulatory audit. Where source documents are required for the continued care of the patient, appropriate copies should be made for storing outside the site.

13.6 Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of Axsome. The protocol amendment must be signed by the investigator and approved by the IRB/IEC before it may be implemented at a site. Protocol amendments will be filed with the appropriate regulatory agencies having jurisdiction over the conduct of the study.

13.7 Use of Information and Publication

All information concerning AXS-07, Axsome's operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information supplied by Axsome

or its designee to the investigator and not previously published, is considered confidential and remains the sole property of Axsome. Case report forms also remain the property of Axsome. The investigator agrees to use this information for purposes of study execution through finalization and will not use it for other purposes without the written consent of Axsome.

The information developed in this study will be used by Axsome in connection with the continued development of AXS-07 and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this study is the property of Axsome. Publication or other public presentation of AXS-07 data resulting from this study requires prior review and written approval of Axsome. Abstracts, manuscripts, and presentation materials should be provided to Axsome for review and approval at least 30 days before the relevant submission deadline. Data from individual study sites must not be published separately, unless otherwise agreed to in writing by the Axsome.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition or publication by the investigator until Axsome has reviewed and commented on such a presentation or manuscript for publication.

14. FINAL CLINICAL STUDY REPORT

Axsome will retain ownership of the data generated from the study.

The final clinical study report will be written within 1 year of completion of the clinical part of the study. This report will include a summary of the study results based on a statistical evaluation and clinical assessment of the protocol-defined endpoints.

15. ETHICAL AND LEGAL CONSIDERATIONS

15.1 Declaration of Helsinki and Good Clinical Practice

This study will be conducted in compliance with the April 1996 ICH Guidance for Industry E6 GCP (including archiving of essential study documents), the 1996 Version of the Declaration of Helsinki, and the applicable regulations of the countries in which the study is conducted.

See Appendix E for regulations and guidelines.

15.2 Subject Information and Informed Consent

A properly constituted, valid IRB/IEC must review and approve the protocol, the investigator's informed consent document, and related subject information and recruitment materials before the start of the study.

It is the responsibility of the investigator to ensure that written informed consent is obtained from the subject before any activity or procedure is undertaken that is not part of routine care.

According to the Declaration of Helsinki and ICH GCP, subjects must provide their written informed consent before enrollment in a clinical study and before any protocol-specified procedures are performed. Subjects must declare their consent by personally signing and dating the ICF. The written ICF will embody the elements of informed consent as described in the Declaration of Helsinki and will also comply with local regulations.

Each subject should be made aware by the investigator of the nature of the study (i.e., objectives, methods, and potential hazards and benefits) and the procedures involved, using the information on the ICF. Information should be given in both oral and written form whenever possible and

deemed appropriate by the IRB/IEC. Subjects, their relatives (or if necessary, legal representatives) must be given ample opportunity to inquire about details of the study.

Subject information and the ICF must be in a language fully comprehensible to the prospective subject. The written information must be provided to the subject to give him or her sufficient time to understand the information and to prepare questions before being asked for his or her consent. The investigator must confirm that the text was understood by the subject. The subject will then sign and date the IRB/IEC-approved consent form indicating that he or she has given his or her consent to participate in the study. The signature confirms the consent is based on information that has been understood. The form will also be signed by the investigator obtaining the consent and annotated with the study subject number. Each subject's signed ICF must be kept on file by the investigator for possible inspection by regulatory authorities, Axsome, and/or designated personnel. Collection of informed consent has to be documented on the eCRF.

Furthermore, the subject will be informed that if he or she wishes to dropout or withdraw (see Section 7.3) at any time during the study, this will not have any negative consequences. Subjects may be withdrawn by the investigator if any change related to safety or ethics precludes further participation in the study. Subjects will be asked to agree to a final assessment in the event of an early termination of the study.

Subjects will be informed that data from their case may be stored in a computer without inclusion of their name and such data will not be revealed to any unauthorized third party. Data will be reviewed by the monitor, an independent auditor, and possibly by representatives of regulatory authorities and/or IRBs/IECs. The terms of the local data protection legislation will be applied as appropriate.

15.3 Approval by Institutional Review Board and Independent Ethics Committee

For investigational new drug studies, the minimum standards of conduct and requirements for informed consent are defined in the US FDA regulations.

A valid IRB/IEC must review and approve this protocol before study initiation. Written notification of approval is to be submitted by the investigator to the Axsome monitor before shipment of investigational drug supplies and will include the date of the committee's approval and the chairperson's signature. This written approval must consist of a completed Axsome IRB Approval Form or written documentation from the IRB/IEC containing the same information.

Until written approval by the IRB/IEC has been received by the investigator, no subject may undergo any procedure solely for determining eligibility for this study.

Protocol amendments must also be reviewed and approved by the IRB/IEC. Axsome must receive their written approval before implementation. This written approval will consist of a completed IRB/IEC approval form or written documentation from the IRB/IEC containing the same information.

15.4 Finance and Insurance

Details on finance and insurance will be provided in a separate agreement between the investigator and Axsome.

16. REFERENCES

1. Merck & Co., Inc. Maxalt® (rizatriptan) FDA Package Insert. Revised 3/2015.
2. Boehringer Ingelheim, Inc. Mobic® (meloxicam) FDA Package Insert. Revised 6/2016.
3. Demaagd G. The pharmacological management of migraine, part 1: overview and abortive therapy. P T. 2008 Jul;33(7):404-16.
4. Pernix Therapeutics Limited. Treximet® (sumatriptan and naproxen sodium) FDA Package Insert. Revised 05/2016.
5. Lipton RB, Fanning KM, Serrano D, Reed ML, Cady R, and Buse DC. Ineffective acute treatment of episodic migraine is associated with new-onset chronic migraine. Neurology. 2015 Feb 17; 84(7): 688–695.
6. Lipton RB, Kolodner K, Bigal ME, Valade D, Láinez MJ, Pascual J, Gendolla A, Bussone G, Islam N, Albert K, Parsons B. Validity and reliability of the Migraine-Treatment Optimization Questionnaire. Cephalalgia. 2009 Jul;29(7):751-9.
7. Lipton RB, Manack AN, Serrano D, and Buse DC. Acute treatment optimization for migraine: results of the American migraine prevalence and prevention (AMPP) study. The Journal of Headache and Pain 2013. 14(Suppl 1):P201.
8. Lipton RB, Bigal ME, Ashina S, et al. Cutaneous allodynia in the migraine population. Ann Neurol 2008;63: 148–158.
9. Bigal ME, Ashina S, Burstein R, et al. Prevalence and characteristics of allodynia in headache sufferers: a population study. Neurology 2008;70:1525–1533.
10. Stewart WF, Lipton RB, Kolodner KB, Sawyer J, Lee C, Liberman JN. Validity of the Migraine Disability Assessment (MIDAS) score in comparison to a diary-based measure in a population sample of migraine sufferers. Pain 2000;88:41-52
11. Stewart WF, Lipton RB, Whyte J, Dowson A, Kolodner K, Liberman JN, Sawyer J. An international study to assess reliability of the Migraine Disability Assessment (MIDAS) score. Neurology 1999; 53:988-94
12. Stewart WF, Lipton RB, Kolodner K, Liberman J, Sawyer J. Reliability of the migraine disability assessment score in a population-based sample of headache sufferers. Cephalalgia 1999; 19:107-14

17. ATTACHMENTS

17.1 Schedule of Assessments

	Visit 1	Visit 2	Visit 3
	Screening	Randomization	Follow-up[d] / EOS
	Day -28	Day 1	Within 7 days of dosing
Informed Consent	X		
Inclusion/Exclusion Criteria	X	X	
Demographics	X		
Medical History	X		
Migraine Headache History	X	X	
Medications, Prior and Concomitant, or Non-drug Therapy	X	X	X
Physical Examination, including height and weight	X		X
Vital Signs (seated blood pressure, pulse, oral body temp.)	X	X	X
ECG	X		X
Clinical Laboratory Tests	X		X
Urine Pregnancy Test[a]	X	X	X
Urine Drug Screen	X	X	
MIDAS		X	
ASC-12		X	
Randomization		X	
Dispense Headache Diary and Instruct on Use	X	X	
Review Compliance with Headache Diary		X	X
Dispense Study Drug & Provide Dosing Instructions		X	
Subject Completes Diary Data[b]		X	
Phone call contact[c]		X	
Return Headache Diary			X
Collect/Inventory Study Medication			X
Adverse Events[e]		X	X

Abbreviations: ASC-12 = 12-item Allodynia Symptom Checklist; ECG = electrocardiogram; MIDAS = Migraine Disability Assessment; PGI-C = patient global impression of change.

a. For women of child-bearing potential only. Test results must be negative at Screening and Randomization for the subject to continue in the study.
b. Headache Diary data will be collected at the following times: Baseline (at first onset of migraine pain (pre-dose) and 20, 30 and 45 minutes, and 1, 1.5, 2, 4, 12, 16, 24, and 48 hours after dosing
c. The subject should be contacted within 24 hours after administering study medication. During the post-dose call, the site should re-confirm study drug dosing instructions and check for changes in concomitant medications. Following the onset of a qualifying migraine, assess compliance with migraine pain diary, rescue medication use, and to schedule the follow up appointment.
d. Final visit after treating one attack (to be scheduled as soon as possible but within 7 days of dosing), or within 6 weeks after Visit 2 if the study medication not used.
e. Adverse events are not required to be collected if subjects do not receive a dose of study medication.

17.2 Investigator's Agreement

PROTOCOL NUMBER:	AXS-07-303
PROTOCOL TITLE:	INTERCEPT (Initiating Early Control of Migraine Pain and Associated Symptoms): A Randomized, Double-blind, Single-dose, Placebo-controlled Study to Assess the Efficacy and Safety of AXS-07 (meloxicam and rizatriptan) for the Acute Treatment of Migraine in Adults.
VERSION:	Amendment 1 - December 13, 2019

I have read this protocol and the investigator's brochure and agree to conduct this clinical study as outlined herein. I will ensure that all sub-investigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with Axsome and its designated vendors during the study. I carry out the study in accordance with the revised Declaration of Helsinki 1996. I will adhere to all FDA, ICH, and other applicable regulations and guidelines regarding clinical studies on a study drug during and after study completion.

Having considered fully all the available information, I consider it is ethically justifiable to give the study drug to selected subjects in my care according to the study protocol. I:

- Agree to use the study material, including the study drug, only as specified in the protocol and understands that changes cannot be made to the protocol without prior written approval from Axsome.
- Understand that any violation of the protocol may lead to early termination of the study.
- Agree to report to Axsome within time any clinical AE or abnormal laboratory value that is serious, whether or not considered related to administration of the study drug.
- Agree to comply with Axsome and regulatory requirements for the monitoring and auditing of this study.

I, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct the study.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

APPENDICES

A. Address List

[redacted]

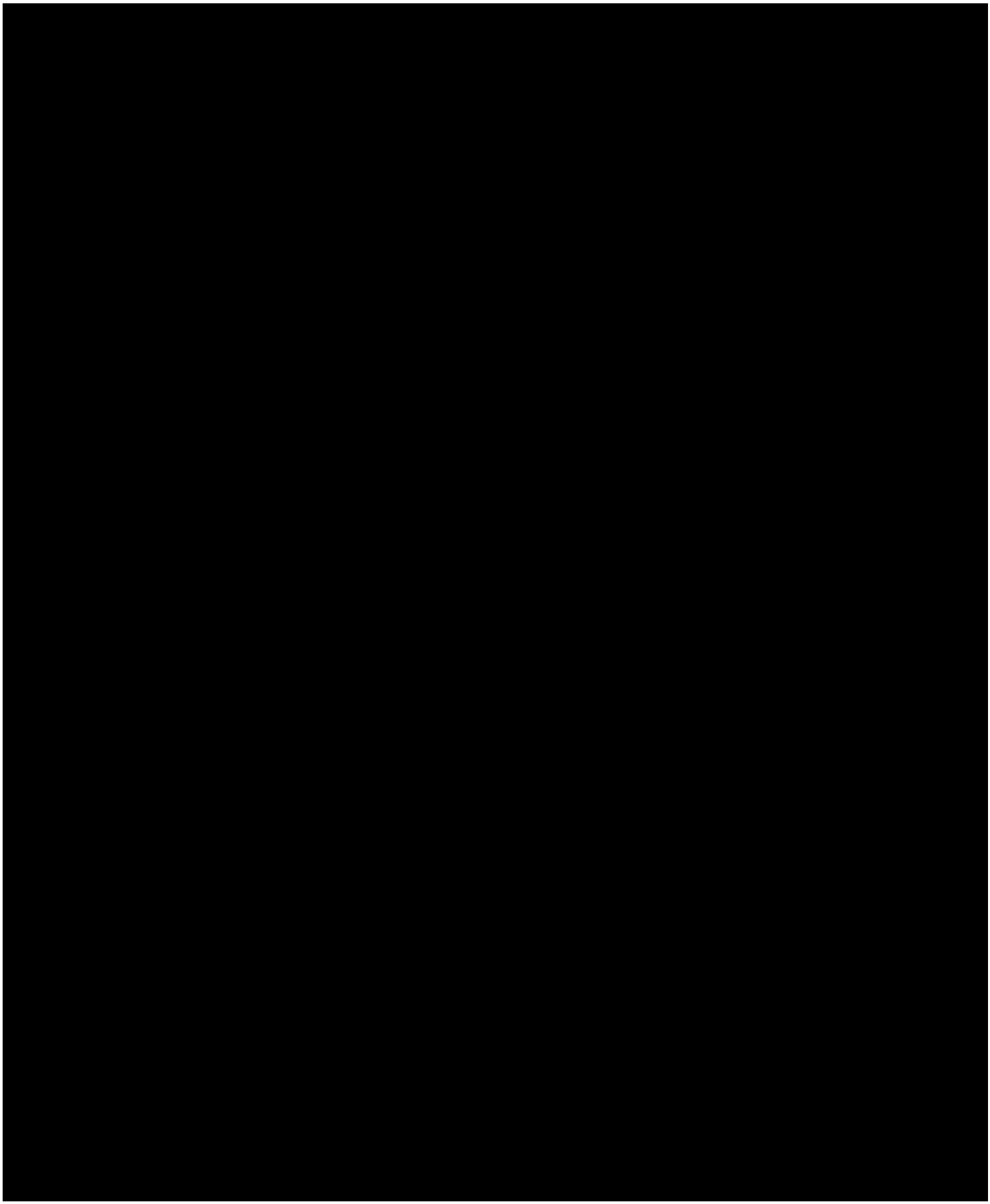
E. Regulations and Good Clinical Practice Guidelines

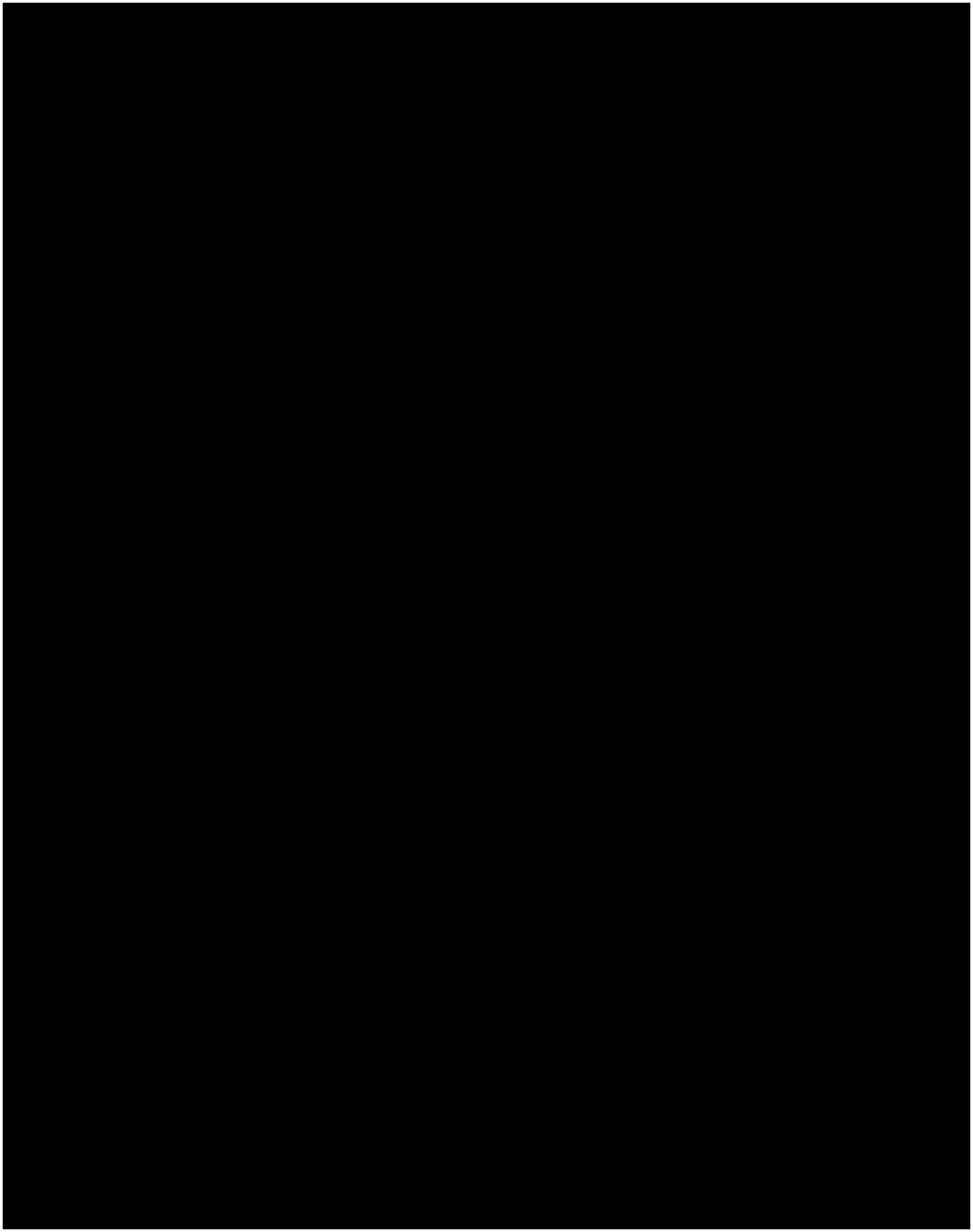
A. Address List

1. Sponsor

Name: Axsome Therapeutics, Inc.

[redacted]





[redacted]

E. Regulations and Good Clinical Practice Guidelines

1. Regulations

Refer to the following United States Code of Federal Regulations (CFR):

- FDA Regulations 21 CFR, Parts 50.20 – 50.27
  Subpart B – Informed Consent of Human Subjects
- FDA Regulations 21 CFR, Parts 56.107 – 56.115
  Part 56 – Institutional Review Boards
  Subpart B – Organization and Personnel
  Subpart C – IRB Functions and Operations
  Subpart D – Records and Reports
- FDA Regulations 21 CFR, Parts 312.50 – 312.70
  Subpart D – Responsibilities of Sponsors and Investigators

2. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URL:
http://www.ich.org/LOB/media/MEDIA482.pdf