Document Type: Protocol and Statistical Analysis Plan

Protocol Title: An Open-Label Study to Assess the Long-term Safety of AXS-07 (meloxicam and rizatriptan) for the Acute Treatment of Migraine in Adults.

ClinicalTrials.gov Identifier: NCT04068051

Document Date: October 17, 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-07-302
[redacted]	[redacted]
DEVELOPMENT PHASE:	Phase 3
PROTOCOL TITLE:	An Open-Label Study to Assess the Long-term Safety of AXS-07 (meloxicam and rizatriptan) for the Acute Treatment of Migraine in Adults.
PROTOCOL VERSION:	Amendment 2
PROTOCOL DATE:	October 17, 2019

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-07-302
PROTOCOL TITLE:	An Open-Label Study to Assess the Long-term Safety of AXS-07 (meloxicam and rizatriptan) for the Acute Treatment of Migraine in Adults.
Protocol Version:	Amendment 2: October 17, 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.

[redacted]

Study Contact and Details

SPONSORED BY:	Axsome Therapeutics, Inc. [redacted]
[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-07-302
DEVELOPMENT PHASE	Phase 3
PROTOCOL TITLE	An Open-Label Study to Assess the Long-term 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 long term safety of chronic intermittent use of AXS-07. **Secondary Objectives:** To assess the effect of AXS-07 on migraine symptoms following repeated treatment of migraine attacks.
STUDY DESIGN	This study is a Phase 3, multicenter, open-label, trial to evaluate the long-term safety of intermittent chronic dosing with AXS-07 in subjects with migraine attacks. Eligible subjects will take a dose of AXS-07 following the onset of a migraine. Subjects will be enrolled for up to 12 months and encouraged to treat all migraine attacks with AXS-07. Subjects are eligible subjects if they have participated in a prior AXS-07 study for the acute treatment of migraine with no significant changes in medical history since participation. Subjects who meet all eligibility criteria will be enrolled at Visit 1 and will be dispensed AXS-07 for at-home treatment of migraine attacks. Subjects will be instructed to treat each migraine attack with AXS-07 and return for clinic visits at Months 1, 3, 6, 9, and 12 (5 return visits). **Migraine Headache Diary** For the first 4 migraine attacks, the subject will record their headache pain intensity (measured by a 4-point rating scale; 0-none, 1-mild, 2-moderate, or 3-severe), in the Migraine Headache Diary immediately prior to taking study medication, and at the following time points after taking study medication: 30 minutes, and 1, 2, 8, 24, and 48 hours after dosing. Prior to dosing, for the first 4 migraine attacks, the subject will define their most bothersome symptom (nausea, photophobia, phonophobia) and assess the presence or absence of each symptom at the following timepoints: 1 and 2 hours after dosing. The subject will be instructed to report any adverse events which occur following each dose of AXS-07. Use of rescue medications will also be recorded. All migraines which occur during the course of the study, regardless of treatment with study drug or not, will be recorded in the Migraine Headache Log. **Study Visits** Subjects will come to the clinic for the enrollment visit (Visit 1, Day 1), Month 1, Month 3, Month 6, Month 9, and Month 12. At each in clinic study visit, the subject will undergo the following safety assessments: assessment of adverse events, review of concomitant medications, vital signs, urine pregnancy test (if applicable), clinical laboratory tests and an electrocardiogram. Additionally, the following patient-reported scales will be completed at every visit: Headache Impact Test-6 (HIT-6), Migraine Disability Assessment Score (MIDAS, not conducted at Month 1), and Migraine-Specific Quality of Life Questionnaire (MSQ).

PLANNED NUMBER OF SUBJECTS	The study will end when there are at least 300 subjects that complete the Month 6 visit and at least 100 subjects that complete the Month 12 visit, treating a minimum of 2 migraines a month. At that time, all remaining uncompleted subjects (those in various interim visits of the study) will be scheduled to come to the site to complete the Month 12 visit procedures. These subjects are considered completing the study.
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. Participated in a prior study with AXS-07 for the acute treatment of migraine. 4. 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 Day 1), 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), abstinence, vasectomized partners and intrauterine devices. 5. Is willing and able to complete the Migraine Headache Diary. **Exclusion criteria**: A subject will be excluded from the study if the subject meets any of the following criteria: 1. Significant change in medical history or concomitant medications since enrolling in the prior AXS-07 study. 2. Initiation of or a change in concomitant medication to reduce the frequency of migraine episodes since completing the prior AXS-07 study. 3. 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 AXS-07. 4. Is currently receiving propranolol or has received propranolol within 2 weeks prior to enrollment or plans to use during the study. Participation in any clinical trial of an experimental drug or device since completing the prior AXS-07 study.
INVESTIGATIONAL PRODUCT	AXS-07 (20 mg meloxicam/10 mg rizatriptan) tablet for oral administration.
TREATMENT REGIMENS	AXS-07 is to be taken orally with water at the onset of a migraine attack.
PRINCIPAL INVESTIGATOR	Multi-center
PLANNED STUDY SITES	Up to approximately 80 study sites in North America
CRITERIA FOR EVALUATION	**Primary Outcome Measures** • The primary safety outcome is long-term safety as evaluated by the incidence, severity, and relatedness of AEs following dosing with AXS-07. **Efficacy Outcome Measures** • Proportion of subjects with headache pain freedom at Hour 2, with headache pain freedom defined as pain intensity = none. • Proportion 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.

	• Proportion of subjects with headache pain relief at Hour 2 • Sustained headache pain freedom between Hours 2 and 24, defined as having no headache pain at Hour 2, with no use of rescue medication and no relapse of headache pain through Hour 24. • Change from baseline in the MIDAS total score • Change from baseline in HIT-6 total score • Change from baseline in the scores of each of the three domains of the MSQ v2.1 • Proportion of subjects with headache pain freedom at Hour 0.5, 1, 8, 24 and 48, with headache pain freedom defined as pain intensity = none. • Proportion of subjects with headache pain relief at Hour 0.5, 1, 8, 24 and 48.
STATISTICAL METHODS	**Analysis Populations:** The following analysis populations are planned for this study: • Safety Population: The Safety Population will include all subjects who take at least one dose study medication. • Intent-to-treat (ITT) Population: The ITT Population will include all subjects who take at least one dose of study medication and report at least one efficacy measurement. Descriptive statistics will be used for all variables and all data over time.
SAMPLE SIZE DETERMINATION	To assess for long-term safety, this study will enroll enough subjects to ensure that 300 subjects are treated for at least 6 months and 100 for 12 months, treating at least 2 migraines a month. Up to 875 subjects may be enrolled to achieve this sample size.
STUDY AND TREATMENT DURATION	The duration of participation will be up to 12 months. Subjects will be allowed to treat each migraine with AXS-07 for up to the 12 months following enrollment. Up to six planned study visits will occur over the 12 months.