Document Type: Protocol

Protocol Title: MOMENTUM (Maximizing Outcomes in Treating Acute Migraine): 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: NCT03896009

Document Date: January 16, 2019

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- 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-07-301
[redacted]	[redacted]
DEVELOPMENT PHASE:	Phase 3
PROTOCOL TITLE:	MOMENTUM (Maximizing Outcomes in Treating Acute Migraine): 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:	Original
PROTOCOL DATE:	January 16, 2019

APPROVAL SIGNATURES

PROTOCOL NUMBER:	AXS-07-301
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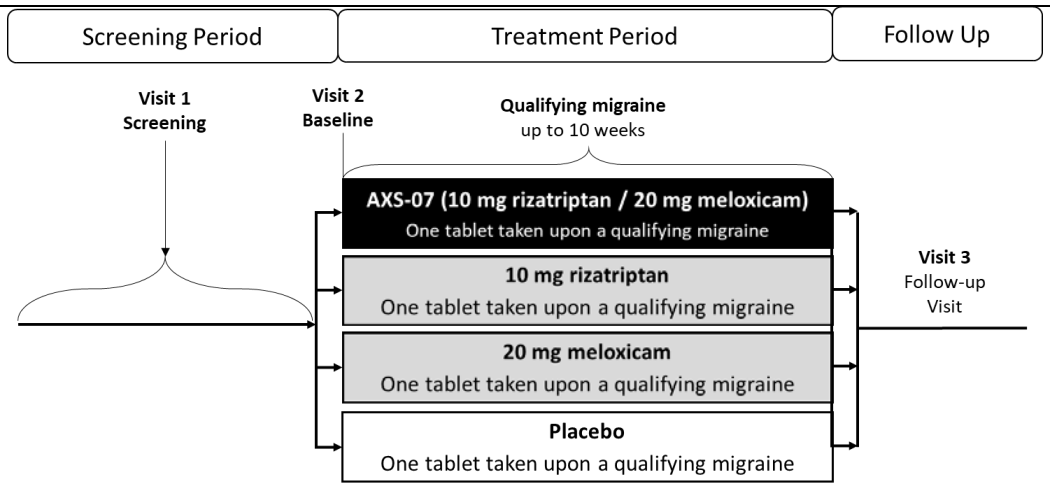
I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

Study Contact and Details

SPONSORED BY:	Axsome Therapeutics, Inc. [redacted]
[redacted]	[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-07-301
DEVELOPMENT PHASE	Phase 3
PROTOCOL TITLE	MOMENTUM (Maximizing Outcomes in Treating Acute Migraine): 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 with Inadequate Response to Prior Acute Treatments.
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 sustained headache pain freedom between Hour 2 and Hour 24. **Secondary Objectives:** To assess 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 freedom. • 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 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	This study is a Phase 3, multicenter, randomized, double-blind, 4-arm, parallel group, 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 from moderate or severe pain 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 endpoint, which will be used to establish contribution of the individual components of AXS-07 to efficacy, is sustained freedom from headache pain between Hour 2 and 24.



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), experience an average of 2 to 8 moderate or severe migraine attacks per month (no more than 10 migraine days per month) over the past 3 months, and have a history of inadequate response to prior acute migraine treatments. An inadequate response is defined as a score of ≤7 on the Migraine Treatment Optimization Questionnaire (m-TOQ-4), corresponding to moderate or worse response to prior treatments over the preceding 4 weeks.

Subjects who successfully complete the Screening visit (Visit 1) and continue to meet all entry criteria, will be randomly assigned at Visit 2 (randomization) to receive, in a 2:2:2:1 ratio, AXS-07, rizatriptan 10 mg, meloxicam 20 mg, or placebo, dispensed for at-home treatment of a single migraine attack. Subjects will have approximately 12 weeks to complete the study, which consists of a 14-day screening period followed by 10 weeks to complete treatment. A follow-up visit (Visit 3) will occur after treating one attack (to be scheduled as soon as possible but within 1 week after dosing), or within 10 weeks after randomization (Visit 2) if the study medication is not used.

Treatment and Assessments:

After randomization, upon the occurrence of the next qualifying migraine attack (defined as the onset of moderate or severe pain intensity) subjects will take the study medication (one tablet). The study medication is to be taken orally with water.

Headache Diary

Headache pain intensity (measured by a 4-point rating scale; none, mild, moderate, or severe), will be recorded by subjects in the Headache Diary immediately prior to taking study medication, and at the following time points after taking study medication: 15, 30 and 45 minutes, and 1, 1.5, 2, 4, 12, 16, 24, and 48 hours after dosing.

Prior to dosing, the subject will define their most bothersome symptom (nausea, photophobia, phonophobia) and assess the presence or absence of each symptom at the following timepoints: 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 pre-dose and at 30 minutes, 1, 2, 4, 12, and 24 hours after dosing. Subjects will assess PGI-C 2 hours after 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 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 and randomization (Visit 2). At each visit, vital signs will be assessed and concomitant medications will be reviewed. Adverse events will be assessed following dosing with study drug.

	Concomitant and rescue medications: 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. Headache Diary Diaries will be provided to subjects to record the severity of the headache (mild, moderate, severe or none), functional disability, presence or absence of associated symptoms (photophobia, phonophobia, nausea), and Patient Global Impression of Change (PGI-C). Subjects will be instructed to complete the diary for 48 hours after taking study medication for a qualifying migraine.
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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 experienced an inadequate response to prior acute treatments over the preceding 4 weeks, defined as a score of ≤ 7 on the Migraine Treatment Optimization Questionnaire (m-TOQ-4) at Screening. 5. Has a diagnosis of migraine attacks with or without aura, presenting before age 50. 6. Has a history, on average, of 2 to 8 moderate or severe migraine attacks per month over the past 3 months. 7. Has a history of usual migraine duration of > 3 hours untreated (by history) for the 3 months prior to screening. 8. Has the ability to differentiate between migraine and non-migraine headaches. 9. Has a body weight ≥ 45 kg and a body mass index (BMI) ≤ 40 kg/m^2. 10. 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. 11. 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) and intrauterine devices. 12. 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), 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 use of analgesics, narcotic analgesics, steroidal or non-steroidal anti-inflammatory 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, NSAIDs (except aspirin at a dose of ≤ 325 mg daily for cardiovascular prophylaxis) during the trial. 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 propanol 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 (including medical marijuana) 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. 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 meloxicam, rizatriptan, and placebo tablets for oral administration.
TREATMENT REGIMENS	The study drug (AXS-07, meloxicam, rizatriptan, or placebo) is to be taken orally with water within 30 minutes of onset of a migraine attack of moderate to severe pain intensity.
PRINCIPAL INVESTIGATOR	Multi-center
PLANNED STUDY SITES	Up to 100 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 Endpoint (for Component Contribution)** • 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. **Additional Key Secondary Endpoints** • Percentage of subjects with pain relief at Hour 2 (AXS-07 versus placebo). • Time to pain relief (AXS-07 versus placebo). • 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. • Percentage of subjects with pain relief at Hour 2 (AXS-07 versus rizatriptan).
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. In addition, to establish the contribution of the individual components of AXS-07, AXS-07 must also be significantly better than each of the components (meloxicam, rizatriptan) at a two-sided significant level of 0.05 for the key secondary efficacy variable, percentage of subjects with sustained pain freedom from Hour 2 through Hour 24. 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.
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STUDY AND TREATMENT DURATION	The duration of participation will be up to 12 weeks as follows: Screening Period: 14 days. Treatment Period: up to 10 weeks.