CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505 (b)(2) Resubmission
Application Number(s)	NDA 215431
Priority or Standard	Standard
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Division/Office	Division of Neurology 2 / Office of Neuroscience
Reviewer Name(s)	Shawna Cutting, MD
Review Completion Date	January 30, 2025
Established/Proper Name	Meloxicam and rizatriptan
(Proposed) Trade Name	Symbravo
Applicant	Axsome
Dosage Form(s)	One tablet for oral use, containing meloxicam 20 mg and rizatriptan 10 mg
Applicant Proposed Dosing Regimen(s)	One tablet (containing meloxicam 20 mg and rizatriptan 10 mg) at the onset of migraine
Applicant Proposed Indication(s)/Population(s)	Acute treatment of migraine with or without aura in adults
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Acute treatment of migraine with or without aura in adults

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics

PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Axsome Therapeutics, Incorporated (hereafter referred to as the Applicant) developed AXS-07 (SYMBRAVO) as a fixed-dose combination product. Each tablet contains 20 mg meloxicam and 10 mg rizatriptan (equivalent to 14.5 mg rizatriptan benzoate). Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID), currently approved for the relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis, and for the management of moderate-to-severe pain. Rizatriptan is a 5-HT$1_{B/D}$ agonist (triptan) currently approved for the acute treatment of migraine. The combination product, referred to as Symbravo in this document, is delivered as an orally administered tablet for the proposed indication of the acute treatment of migraine with and without aura.

The Applicant is using a 505(b)(2) regulatory pathway, using the listed drugs (LD) Mobic (oral meloxicam), Anjeso (intravenous meloxicam), and Maxalt (rizatriptan), along with data from several trials, to support this marketing application. A pivotal efficacy trial was assessed as adequate to demonstrate efficacy based on the approved indication of rizatriptan (Maxalt) for the acute treatment of migraine and the known analgesic effect of meloxicam (Mobic); a second trial was submitted to support efficacy, although not required for marketing consideration. Since the maximum dose of oral meloxicam (Mobic) was lower than in Symbravo, and since the long-term exposure of meloxicam in Symbravo was not supported by intravenous meloxicam (Anjeso), a long-term safety trial was required to bridge the gap and demonstrate safety of Symbravo administration for up to 12 months. These trials are discussed briefly below.

The Applicant submitted data from a trial intended to demonstrate efficacy and safety of Symbravo (Study AXS-07-301), which utilized the established co-primary endpoints of pain and most bothersome symptom (MBS) freedom at 2 hours to demonstrate efficacy. Since Symbravo is a fixed-dose combination of two products, the approach to the evaluation of efficacy also involved a factorial design to establish the contribution of each individual product to the overall efficacy as per 21 Code of Federal Regulations (CFR) § 300.50. The Applicant utilized Study AXS-07-301 to demonstrate component contribution (of meloxicam and rizatriptan separately, compared to Symbravo) using the endpoint of 24-hour sustained pain freedom. Additionally, the Applicant submitted the results of AXS-07-303 (studying the effect of Symbravo on the acute treatment of a mild migraine attack) and AXS-07-302 (a long-term safety study), which contribute to the overall understanding of the efficacy and safety profile of this product.

The Applicant previously submitted a new drug application (NDA) on June 30, 2021. In addition to the three clinical trials described above, the initial submission included two single dose clinical pharmacology studies (AXS-07-102 and AXS-07-103) to evaluate the relative

bioavailability of the rizatriptan component of Symbravo compared to Maxalt tablets, the relative bioavailability of the meloxicam component of Symbravo compared to Anjeso, and the impact of high fat high calorie meal intake on the pharmacokinetics of each component of Symbravo. These two bioavailablity trials provided the bridge to support the nonclinical chronic toxicity data of rizatriptan needed for this application; since Anjeso is intended for short term use, and since Mobic (oral meloxicam) was not included in the initial submission as a bridging LD, these bioavailability studies did not allow for use of nonclinical chronic toxicity data of meloxicam to support chronic oral administration.

In addition to the lack of support for bridging of chronic meloxicam use, there were issues regarding the proposed drug product specification's ability to control potential impurities, the methods to demonstrate levels of potential (b) (4) the ability of the manufacturing controls to ensure consistent product quality, and inadequate data to support the proposed dissolution test method. A Complete Response was issued on April 29, 2022, due to the inadequate reliance on FDA's finding of safety for Anjeso (meloxicam injection), as well as unresolved quality issues. The Applicant submitted a Class 2 resubmission on June 28, 2024; this submission was deemed incomplete due to difficulty with formatting and an inability to ascertain whether previous review issues had been addressed. The Applicant resubmitted the application again on July 31, 2024, and this submission was determined to be complete and is the subject of this review.

1.1. Conclusions on the Substantial Evidence of Effectiveness

All efficacy data were submitted and reviewed within the initial review cycle, for which a Complete Response was issued due to unresolved quality issues and need for information to support the safety of meloxicam for chronic use. A detailed review of the efficacy data in the original submission was completed in the Clinical Review conducted by Viveca Livezey, MD, dated April 11, 2022; these efficacy data are briefly summarized here.

A single adequate and well-controlled Phase 3 trial (AXS-07-301) demonstrated efficacy of Symbravo in treating an acute migraine attack. The trial used well-validated and clinically meaningful endpoints, pain freedom and most bothersome symptoms (MBS) freedom at 2 hours. To satisfy the requirements of 21 CFR § 300.50 Fixed-combination prescription drugs for humans, AXS-07-301 utilized a factorial design to demonstrate superiority of Symbravo versus individual components, rizatriptan and meloxicam. In AXS-07-301, the key secondary endpoints of sustained pain freedom 2-24 hours after study drug administration and percentage of subjects reporting normal function at 2 hours was also met, supporting the robustness of the conclusion that Symbravo demonstrated efficacy over placebo and over each component.

A second well-controlled Phase 3 trial (AXS-07-303) evaluated the effects of Symbravo versus placebo in treating an acute migraine attack. In this study subjects were instructed to treat a mild migraine attack. Trial AXS-07-303 used the same clinically meaningful endpoints as AXS-07-303. This study also demonstrated a benefit of Symbravo compared to placebo on pain freedom

The clinical trials' data presented within this original submission demonstrated persuasive efficacy results which are adequate to support approval for the indication of acute treatment of migraine.

1.2. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

AXS-07 (SYMBRAVO) is a fixed dose combination product; each tablet contains 20 mg meloxicam (a nonsteroidal anti-inflammatory drug (NSAID)), and 10 mg rizatriptan (a 5-HT1B/D agonist (triptan)). Symbravo is intended to be prescribed for the acute treatment of migraine with or without aura. Acute migraine attacks can cause significant disability and impact function for a large percent of the United States population.

As a 505 (b)(2) application, the Applicant is relying on the listed drugs (LDs) meloxicam (both tablet formulation (Mobic) and intravenous formulation (Anjeso)) and rizatriptan (Maxalt). Anjeso is an intravenous formulation of meloxicam indicated for moderate and severe pain. Mobic is an oral tablet approved for relief of signs and symptoms associated with various types of arthritis, at doses up to 15 mg daily. Maxalt is indicated for the acute treatment of migraine in subjects 6 years of age and older. Both Mobic and Anjeso are needed as LDs to provide a pharmacologic cap to meloxicam (with Anjeso) and nonclinical support for long term chronic use of meloxicam (with Mobic).

There are many FDA-approved drugs for the acute treatment of migraine with and without aura in adults, including triptans (5-HT1B/1D receptor agonists), lasmiditan (a 5-HT1F receptor agonist), rimegepant, ubrogepant and zavegepant (CGRP antagonists), dihydroergotamine (DHE), and NSAIDs. NSAIDS can be prescribed alone (diclofenac or celecoxib) or in combination with a triptan (e.g., Treximet). In addition, there are over-the-counter products, including select NSAIDs, approved for the acute treatment of migraine. Symbravo offers another prescription treatment option.

The efficacy of Symbravo in the treatment of an acute migraine attack was demonstrated in one adequate and well-controlled trial (AXS-07-301), which used a factorial design to establish contribution by each component. One adequate and well-controlled clinical investigation of Symbravo was assessed as acceptable since rizatriptan is already approved for the acute treatment of migraine, and meloxicam is already approved for a pain indication. AXS-07-301 randomized subjects to Symbravo, meloxicam 20 mg, rizatriptan 10 mg, or placebo and evaluated the effect of treatment on the validated and clinically meaningful co-primary endpoints of the proportion of subjects who were pain and most bothersome symptom (MBS) free at 2 hours after treating a single moderate to severe migraine attack. In Trial AXS-07-301, the therapeutic gain (active drug minus placebo drug effect) comparing Symbravo to placebo was 13.2% on the endpoint of pain freedom at 2 hours, with a p-value of <.001. The therapeutic gain for Symbravo for the endpoint of MBS freedom at 2 hours was 12.5%, with a p-value of 0.002. These results are similar to other contemporary clinical trials in drugs approved for the acute treatment of migraine, with therapeutic gains ranging from 7%-17% for the endpoint of pain freedom at 2 hours and therapeutic gains of 8-16% for the endpoint of MBS freedom at 2 hours.

Symbravo also demonstrated efficacy on several secondary endpoints within Trial AXS-07-301. The Applicant analyzed the key secondary endpoint of sustained pain freedom from 2-24 hours (pain free at 2 hours and through 24 hours without using a rescue medication) to

demonstrate component contribution of both meloxicam and rizatriptan, using a factorial design. This secondary endpoint allowed the Applicant to use Trial AXS-07-301 to establish the contribution of each individual product (meloxicam and rizatriptan) to the overall efficacy of Symbravo as per 21 Code of Federal Regulations (CFR) § 300.50 CFR, by demonstrating a clinically and statistically significant benefit of Symbravo over meloxicam and rizatriptan. The secondary endpoints of pain relief at 2 hours and ability to perform normal daily activities at two hours were also more likely to occur in subjects who took Symbravo compared to placebo.

The Applicant submitted a second randomized, double-blind, placebo-controlled trial (AXS-07-303) that demonstrated the efficacy of Symbravo in the treatment of a mild migraine attack. This trial used the same co-primary endpoints and demonstrated a clinically meaningful effect on pain freedom and MBS freedom at 2 hours. This trial also contributes to the short-term safety of Symbravo. A long-term safety trial (AXS-07-302) was required since the dose of meloxicam in Symbravo (20 mg) is higher than the daily recommended dose of oral meloxicam (15 mg).

The findings from the two placebo-controlled trials indicated an increased frequency of dizziness and somnolence in Symbravo treated subjects. No other new safety signals were detected. The long-term safety trial indicated an increased frequency of dizziness and somnolence, as well as an increased frequency of nausea, vomiting, diarrhea, and upper respiratory tract infection. All of the warnings, precautions, contraindications and boxed warnings that already exist for triptans and NSAIDs should be included in the label for Symbravo. Further, all safety information pertaining to Mobic and Maxalt (the LDs) should also be included in the label, as well as select safety information from Anjeso that is relevant to specific populations. The risks that can occur with this product can be mitigated through labeling. There is no specific pharmacovigilance that should be requested at this time.

From the clinical perspective, the risk/benefit profile of Symbravo is acceptable and supports approval for the acute treatment of migraine with and without aura in adults. The evidence does not suggest that Symbravo is more effective than other FDA-approved drugs for the acute treatment of migraine; however, Symbravo offers another treatment option. Future labeling should clearly convey the safety profile demonstrated with extensive experience with both triptans and NSAIDs and should also describe the increase in the incidence of dizziness and somnolence with the use of Symbravo as compared with placebo. The overall benefit-risk profile of Symbravo is favorable from the clinical perspective, as described in the Benefit-Risk Dimensions below.

The original clinical review by Dr Viveca Livezey noted that the clinical data supported efficacy and safety of Symbravo, but that quality issues precluded approval. As this resubmission addresses quality issues which were raised at the time of initial submission, as well as incorporates nonclinical support by including Mobic as a listed drug, I recommend approval.

Source: modified from Dr. Viveca Livezey's clinical review

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Migraine is a primary headache disorder characterized by recurrent headaches that are moderate to severe, accompanied by associated symptoms of nausea, vomiting, and light and/or sound sensitivity. The typical headache of migraine is throbbing, unilateral, and aggravated by movement. • Migraine attacks typically last 4 to 72 hours when untreated. About one third of people with migraine experience transient neurological symptoms before and/or during an attack, referred to as migraine aura. • Migraine can be very disabling and contribute to loss of productivity and diminished quality of life. • Migraine is more frequent in females than in males. (Lipton, Stewart, Diamond, Diamond, & Reed, 2001) • Migraine prevalence peaks in the 4th decade of life for both males and female. (Lipton & Bigal, 2007)	The burden of migraine is considerable to patients. Attacks can be disabling. Migraine impacts quality of life and can be associated with substantial pain and morbidity.
Current Treatment Options	• Many approved therapies for the acute treatment of migraine exist, and many other therapies are used off-label. • Non-specific therapies (not FDA approved, but used off-label), include Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and acetaminophen • Approved acute migraine treatments include: o Triptans, including oral, oral disintegrating, nasal spray, subcutaneous formulations – however, these treatments are often contraindicated in subjects with cardiovascular or cerebrovascular disease. o Dihydroergotamine (nasal spray, subcutaneous or intramuscular) – however, this is contraindicated in subjects with cardiovascular	There are numerous treatment options for the acute treatment of migraine. Drugs that may act more rapidly, have fewer side effects, or are provided in novel formulations may offer new or more preferable options for patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	disease. o Several calcitonin gene-related peptide (CGRP) antagonists (including rimegepant, ubrogepant and zivegepant) – however, long-term effects are not completely known. o Three FDA approved acute migraine treatments have an NSAID component. These are diclofenac (Cambia), celecoxib oral solution (Elyxyb), and the fixed drug combination of an NSAID (naproxen) with a triptan (sumatriptan), Treximet. • Specifically, the triptans, CGRP antagonists, and several NSAIDs (including diclofenac, celecoxib oral solution, and the naproxen-sumatriptan combination product) have randomized placebo-controlled trial evidence suggesting that they are effective for the acute treatment of migraine. • The therapeutic gain (active drug minus placebo drug effect) for the endpoint of pain freedom at 2 hours, for drugs recently approved for the acute treatment of migraine, ranges from 7%-17% in clinical trials. • The therapeutic gain for the endpoint of most bothersome symptom (MBS) freedom at 2 hours for drugs recently approved for the acute treatment of migraine ranges from 8.3-15.5% in clinical trials.	
Benefit	• The Applicant conducted one adequate and well-controlled trial (AXS-07-301) to evaluate the effect of Symbravo compared to placebo for the treatment of an acute migraine attack of mild headaches. o The study used the agreed-upon trial design of treating a single moderate to severe migraine attack and investigating the co-primary endpoints of pain and MBS freedom at 2 hours. o In AXS-07-301, the therapeutic gain comparing Symbravo to	The Applicant submitted evidence of effectiveness in one adequate and well-controlled clinical trial of Symbravo. A factorial design established the contribution of each individual product (meloxicam and rizatriptan) to the overall efficacy of Symbravo, as required per 21 Code of Federal Regulations (CFR) §

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	placebo was 13.2% on the endpoint of pain freedom at 2 hours, with a p value of <0.001. The therapeutic gain for Symbravo for the endpoint of MBS freedom at 2 hours was 12.5%, with a p value of 0.002. o The Applicant also analyzed the key secondary endpoint of sustained pain freedom from 2-24 hours to demonstrate component contribution using a factorial design, in which subjects were randomized to Symbravo, meloxicam 20 mg, rizatriptan 10 mg or placebo. o Sustained pain freedom with Symbravo was significantly higher than meloxicam (7.3%, p=.001) and rizatriptan (4.9%, p=.038); this information contributes to the establishment of the contribution of each individual product of the fixed-dose combination. o Pain relief at 2 hours and the ability to perform normal daily activities at two hours were also more likely to occur in subjects who took Symbravo compared to placebo (69.2% vs 54.5% and 32% vs 21.1%, respectively). • Rizatriptan is already approved for the acute treatment of migraine. Meloxicam is already approved for the acute treatment of pain. Two additional NSAIDS (diclofenac and celecoxib) are approved for the acute treatment of migraine. A triptan/NSAID combination has previously been approved for acute treatment of migraine. • The Applicant submitted a second randomized, placebo-controlled trial efficacy trial (AXS-07-303) in which subjects treated a mild migraine attack. The therapeutic gain with Symbravo was 16.3% on the endpoint of pain freedom at 2 hours and 17.2% on the endpoint	300.50. The reported treatment effects of Symbravo are consistent with other therapies approved for the acute treatment of migraine and are consistent with the safety and efficacy of the constituent component approved for migraine treatment (rizatriptan). Prior established findings of safety and efficacy for triptans (generally), NSAIDS (generally), and a triptan/NSAID combination in the treatment of acute migraine also support potential for this fixed dose combination of an NSAID and a triptan as a potentially effective treatment for migraines. The Applicant provided evidence of effectiveness in the treatment of a migraine attack in the mild stage. The treatment effects on accepted endpoints were statistically significant and potentially clinically meaningful for patients who do not want to delay treatment until a migraine attack is moderate to severe in intensity. This information may be helpful to patients and providers.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	of MBS freedom at 2 hours. • While Trial AXS-07-303 is not a typical migraine trial that investigated moderate-to-severe attacks, it does provide information on efficacy of early migraine treatment.	
Risk and Risk Management	• The safety profiles for triptans and NSAIDs have been well established. • Relative bioavailability studies provided the necessary bridge to the listed drugs rizatriptan (Maxalt), oral meloxicam (Mobic) and intravenous meloxicam (Anjeso). The dose of meloxicam in Symbravo is capped by the pharmacokinetic profile of Anjeso. • However, the dose of meloxicam in this fixed-dose combination product is 20 mg, and higher than the daily approved dose of the listed drug (Mobic (meloxicam 15 mg)). In addition, Anjeso is not approved for chronic intermittent use. • Since this is a different (higher) dose of Mobic for oral use, a 12-month long term safety trial for this indication was required. • Trials AXS-07-301 and AXS-07-303, as well as one long-term safety trial (AXS-07-302) demonstrated the overall safety of the fixed dose combination of these components within Symbravo. • There were no serious adverse events or significant safety events clearly attributable to Symbravo use in these trials. • The placebo-controlled trials (AXS-07-301 and AXS-07-303) indicated that, in subjects treated with Symbravo, dizziness and somnolence occurred at a ≥ 1% rate and higher than placebo. • In the long-term safety trial (AXS-07-302) nausea, vomiting, dizziness, somnolence, diarrhea, and upper respiratory tract infection was reported at rates of ≥ 2%. The rates of nausea and somnolence	Warnings, precautions, contraindications, and boxed warnings for rizatriptan and meloxicam, the components in Symbravo, should be included in the label for Symbravo. Therefore, the safety information pertaining to Maxalt, Anjeso, and Mobic (the listed drugs for this application) should are included in the label. The safety of more than one dose in a 24-hour period is not known; therefore, the maximum dose in a 24-hour period should be one tablet. The findings from the placebo-controlled trials indicated an increased frequency of dizziness and somnolence in Symbravo-treated subjects that should be described in the approved labeling. No other new substantial safety signals were identified in the clinical trials. Risks of medication overuse headache should be included in the label, as this is a combination of an NSAID and a triptan, and both products individually can lead to

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	were higher than that reported in the controlled clinical trials. • There was no enhanced pharmacovigilance requested for any approved meloxicam or rizatriptan product.	medication overuse headache. There is no obvious need for pharmacovigilance based on the safety data submitted to date.

Source: modified from Dr. Viveca Livezey's clinical review of the original NDA submission

1.3. Patient Experience Data

No new patient experience data were included with this Class 2 resubmission.

2. Therapeutic Context

2.1. Analysis of Condition (modified from Dr. Livezey's review)

Migraine is a well-recognized, common, chronic neurologic disorder, most prevalent in women between the ages of 25 and 55 years (Dodick, 2018). Patients with migraine experience recurrent attacks of moderate to severe head and sometimes neck pain often with other accompanying symptoms that can cause significant disability and impact social and functional abilities.

Diagnostic criteria for migraine with and without aura have been established by the International Headache Society (IHS) and are termed the International Classification for Headache Disorders (ICHD-3). Per the ICHD-3 definition, a migraine is a recurrent headache disorder manifesting in recurrent attacks of head pain that must fulfill the following criteria: last 4-72 hours, have two of the following four characteristics: unilateral location, pulsating quality, moderate or severe pain intensity, aggravation by or causing avoidance of routine physical activity, and must have associated symptoms of either nausea and/or vomiting, or photophobia and/or phonophobia.

2.2. Analysis of Current Treatment Options

Current treatment options for the acute treatment of migraine include FDA-approved drugs (e.g., triptans, ergotamines, NSAIDs, serotonin (5HT1F) agonists, and CGRP antagonists) which span a wide range of therapeutic targets. Many drugs are used off-label, including opiates, over the counter drugs, including NSAIDs (such as ibuprofen), acetaminophen, and drug combinations such as caffeine/acetaminophen/aspirin preparations. Subjects may also use behavioral techniques or approved devices for the treatment of acute migraine (Dodick 2018).

In addition to acute therapies, subjects with episodic and chronic migraine are often prescribed medications for the preventive treatment of migraine that are given on a daily, monthly, or quarterly basis.

There are three FDA-approved NSAIDs for the acute treatment of migraine, diclofenac (Cambia), celecoxib oral solution (Elyxyb), and the NSAID/triptan combination of naproxen and sumatriptan (Treximet). Advil migraine is a nonprescription NSAID indicated for the treatment of migraine. Rofecoxib (Vioxx) is a COX-2 selective NSAID (similar to celecoxib) that was

previously approved for the acute treatment of migraine, prior to being withdrawn from the US market in 2004 due to safety concerns (specifically, increased risk for cardiovascular events).

There is a clear role for triptans and NSAIDs independently in the treatment of acute migraine attacks. One medication, Treximet, combines sumatriptan and naproxen; this received approval in 2008 after the sponsor submitted results of two clinical trials demonstrating efficacy and contributions from each component using a factorial design. Although there were concerns for synergistic effects on the risk of cardiovascular events with a fixed dose combination of a NSAID and a triptan, to the best of our knowledge, this has not been demonstrated in the literature nor in postmarketing data.

Given the existing scientific knowledge about the effectiveness of drugs in the same pharmacologic class as Symbravo for treatment of acute migraine, and the approval of one of the components (rizatriptan) for the treatment of acute migraine, only one adequate and well-controlled trial was assessed, which is consistent with the Guidance for Industry: *"Demonstrating Substantial Evidence of Effectiveness For Human Drug and Biological Products".*[1]

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Symbravo does not have marketing authorization in the United States. The Applicant is using rizatriptan (Maxalt), oral meloxicam (Mobic), and intravenous meloxicam (Anjeso) as LDs, which do have marketing authorization.

Rizatriptan (Maxalt) was initially approved in the U.S. in 1998 at doses of 5 mg or 10 mg tablets (with a maximum daily dose of 30 mg) for the acute treatment of migraine with or without aura in adults. An orally disintegrating tablet (Maxalt-MLT) was approved thereafter. Maxalt subsequently received marketing authorization for the pediatric subjects (ages 6 to 17 years, 5 or 10 mg and weight based) in 2011.

Meloxicam (Anjeso) is an intravenously administered NSAID indicated for use in adults for the management of moderate-to-severe pain, alone or in combination with non-NSAID analgesics. Meloxicam was originally approved as an oral tablet (Mobic), available at doses of 7.5 mg or 15 mg daily, in 2000 for the signs and symptoms of osteoarthritis. The indication was subsequently expanded to include rheumatoid arthritis (2004) and juvenile rheumatoid arthritis (2005). A

[1] https://www.fda.gov/media/133660/download. When final, this guidance will represent the FDA's current thinking on this topic.

subsequent oral solution formulation was marketed but discontinued (not due to reasons of safety).

3.2. Summary of Presubmission/Submission Regulatory Activity

The Regulatory history prior to the issuance of a Complete Response Letter is summarized in the Clinical Review by Dr. Viveca Livezey, dated April 11, 2022.

A Type A End-of-Review meeting occurred on August 29, 2022, and this meeting focused on content of a planned resubmission. Questions were primarily focused on addressing deficiencies in product quality, with the exception of one question related to the Applicant's plan to rely on FDA's findings of safety for the LD Mobic and on the long-term clinical safety trial to support the safety of the meloxicam component for chronic use (which was the substantial review issue identified with the previous reliance on Anjeso.) The Applicant was advised that their plan to (b) (4) was generally not considered a suitable approach to support regulatory decisions. The Division recommended that the Applicant evaluate the relative bioavailability of the meloxicam component between the final product (Symbravo) and the LD (Mobic) to support a PK-based bridge. The Applicant stated they intend to establish a scientific bridge between their product and the LD Mobic using a previously conducted study. On September 2, 2022, the Applicant provided a revised proposal for establishing a scientific bridge.

The Applicant requested and was granted an extension for resubmission of the application until June 30, 2024.

On November 20, 2023, the Applicant requested and was granted a Type D meeting to discuss their resubmission strategy. In the written response, the Division again informed the Applicant that a (b) (4) is generally not suitable, but that the ultimate acceptability of any proposed scientific bridge to support reliance on FDA's previous findings for Mobic will be a matter of review.

On April 22, 2024, the Applicant requested a Type D meeting focused on nonclinical issues. The nonclinical team provided advice to the Applicant that a 13-week toxicity study in a single species would be needed to qualify the recently detected impurity, (b) (4) (b) (4). The acceptability of the proposed limit of (b) (4)% for the impurity (b) (4) would be a matter of review.

The Applicant resubmitted the NDA on June 28, 2024; this submission was not considered a Complete Response due to problematic formatting of the submission, which required extensive searching to determine whether, on face, each deficiency has been addressed. The Applicant resubmitted the NDA with improved formatting on July 31, 2024.

3.3. Foreign Regulatory Actions and Marketing History

No new foreign regulatory actions have occurred since the original review. Symbravo is not authorized for marketing in any country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Please refer to the review conducted by Dr. Cara Alfaro during the original submission cycle, in the Office of Scientific Investigations, for details regarding clinical site inspections for this application. No new inspections from OSI occurred following resubmission.

4.2. Product Quality

Please refer to the Chemistry, Manufacturing, and Controls (CMC) review of the resubmission for further details on how the Applicant addressed quality issues that led to the previous Complete Response.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

During this review cycle, two impurities were identified as potential concerns, rizatriptan anoxide and (b) (4)). Please refer to the nonclinical review for further details regarding nonclinical support for these levels of impurities.

4.5. Clinical Pharmacology

Please refer to the clinical pharmacology review for further details.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

No new clinical trials were included in the resubmission. Please refer to the original review by Dr. Viveca Livezey dated April 11, 2022, for further details and a table describing all the clinical studies included in that review.

5.2. Review Strategy

This application review includes a high-level review of the original submission but focuses on the unresolved issues associated with the resubmission (e.g., labeling and post-marketing requirements). The efficacy and safety determinations were made in the original review authored by Dr. Viveca Livezey dated April 11, 2022.

6. Review of Relevant Individual Trials Used to Support Efficacy

Please refer to the original review by Dr. Viveca Livezey dated April 11, 2022, for a complete review and details of the trials which evaluated Symbravo's efficacy. Additional detail is included here as one secondary endpoints for the pivotal trial, AXS-07-301, was included in labeling but values for components were not described fully in the original review. The portions of the original review reproduced here are in italics.

6.1. *AXS-07-301 (MOMENTUM)*

"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

6.1.1. Study Design

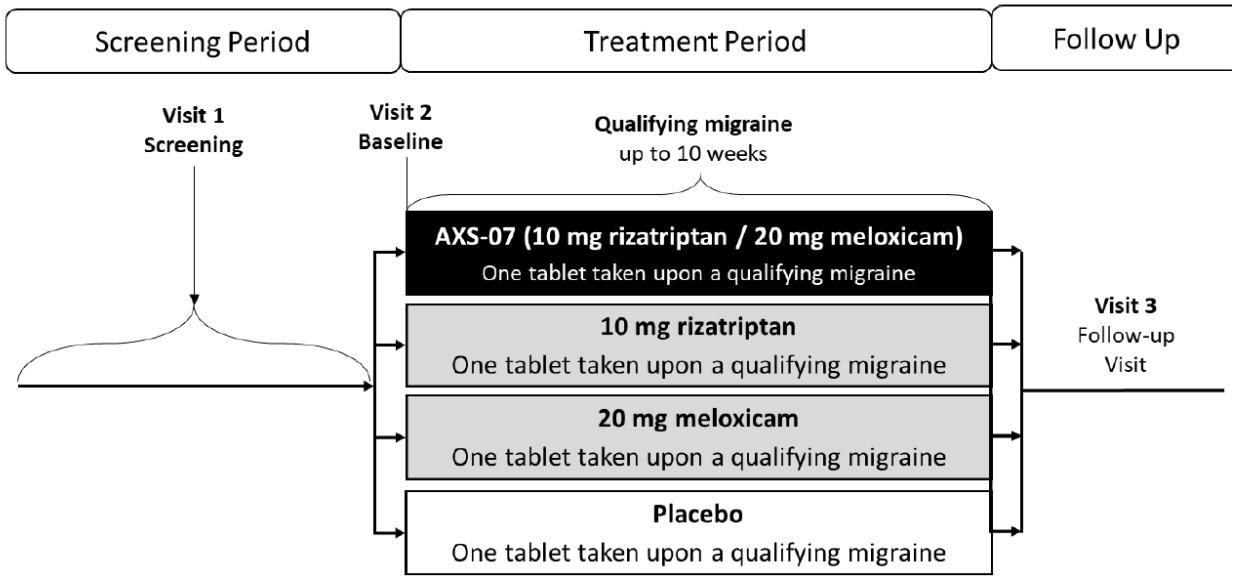
Overview and Objective

The primary objective of Study AXS-07-301 was to evaluate the effect of Symbravo as compared to placebo in the acute treatment of migraine headache in adults as evaluated by the following: pain freedom at 2 hours and MBS freedom at 2 hours. The key secondary objective was to assess the effect of Symbravo on sustained headache pain freedom between hour 2 and hour 24. There were fifteen additional secondary objectives.

Trial Design

Study AXS-07-301 was a phase 3, multicenter, randomized, double-blind, 4-arm, parallel group, single dose, placebo-controlled study to evaluate the safety and efficacy of AXS-07 for the acute treatment of migraine in subjects with migraine with or without aura. Subjects were randomized to one of 4 treatments in a 2:2:2:1 ratio (AXS-07, rizatriptan 10 mg, meloxicam 20 mg or placebo) and instructed to treat one moderate to severe migraine attack within a 12-week period. This study included a 2-week screening period, a 10-week period in which the subjects had to treat a single moderate to severe migraine attack, and a follow-up visit within 1 week (but as soon as possible) of dosing one attack.

Figure 1: Study AXS-07-301: Study Design



Eligibility Criteria
Key Inclusion Criteria

- *18-65 years old*
- *1 year history of migraine with or without aura as defined by the ICHD-3, first diagnosed at < 50 years old*
- *Average of 2 to 8 moderate or severe migraines per month (not more than 10 migraine days per month) over the past 3 months*
- *History of inadequate response to prior acute migraine treatments, 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 prior 4 weeks at screening*

Key Exclusion Criteria

- *8 migraine attacks in 2 months before screening*

- *History of cluster headache or other types of migraine*
- *Chronic daily headache (≥15 days per month in 3 months prior to screening)*
- *Had confirmed or suspected cardiovascular or cerebrovascular disease*
- *Had history, symptoms or risk factors for ischemic heart disease, coronary artery vasospasm, arrhythmia, conduction pathway disorder or cardiovascular disease*
- *If female, taking estrogenic contraceptives and smokes and history of migraine with Aura*
- *Brainstem aura, ophthalmoplegic, or hemiplegic migraine headache or serious neurological condition associated with headache*
- *Uncontrolled hypertension (diastolic blood pressure > 95 mm Hg or systolic blood pressure > 160 mm Hg)*
- *Concurrent chronic use of analgesics, narcotic analgesics, steroidal or NSAIDs, tranquilizers, sedatives, antipsychotic drugs, nitrates*
- *History of significant gastrointestinal disorders*

**=The m-TOQ-4 is a 4-item questionnaire developed to assess treatment efficacy based on 4 aspects of response to acute treatment.* (b) (4) *For additional details, please refer to the separate review in the original submission, conducted by the Division of Clinical Outcome Assessments (COA) reviewer, Dr. Robert Fieo.*

Efficacy Endpoints
Primary endpoint

The co-primary efficacy variables were 1) percentage of subjects with headache pain freedom at 2 hours and 2) percentage of subjects with absence of the MBS (nausea, photophobia, or phonophobia) at 2 hours, and these were used to establish the superiority of AXS-07 over placebo. Pain was rated on a 4-point scale with 0=none, 1=mild, 2=moderate, and 3=severe. MBS freedom was rated with the dichotomous scale (yes/no). To qualify as a responder for headache pain freedom at 2 hours, the pain intensity score at 2 hours must be equal to 0 (none) and to qualify as a responder for absence of the MBS at 2 hours, the MBS scale at 2 hours must be equal to "Absent."

Secondary endpoint
The key secondary efficacy variable was headache pain freedom between 2 and 24 hours (24-hour sustained pain-freedom). This variable was used to establish the superiority of AXS-07 over each of the 2 active components, meloxicam and rizatriptan (i.e., to establish the contribution of the individual components of AXS-07). To be a responder for the key secondary efficacy variable, the subject must have met all the following conditions:

- *All reported pain intensity between 2 and 24 hours must be 0;*
- *Pain intensity at 2 and 24 hours must be 0;*
- *Pain intensity must have been available for at least 12 or 16 hours; and*
- *No rescue medication used through 24 hours.*

Subjects who did not meet these requirements were considered non-responders."

Additional key secondary endpoints, prespecified and tested in order, were:

- 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 freedom at Hour 2 (AXS-07 versus rizatriptan).

The functional disability scale is a four-point rating scale, with the categories of none, mild, moderate, and severe. Ratings on this scale were recorded by subjects in the headache diary. If a subject reported none when reporting on functional disability, the subject was considered able to perform normal daily activity.

> *Reviewer comment: Pain relief was a common endpoint in medications approved prior to the guidance for acute migraine, and as such including pain relief in approved labeling is acceptable. It is worth noting that analysis of the percentage of subjects with sustained pain relief over time (from Hour 2-24 and Hour 2-48) was not included in the SAP, and thus not considered in this clinical review.*

6.1.2. Study Results

Efficacy Results – Primary Endpoint and Key Secondary endpoint

Please see the clinical review by Dr. Viveca Livezey for a discussion of the findings on the Primary Endpoint and Key Secondary endpoint.

Efficacy Results – Other Key Secondary endpoints

Trial AXS-07-301 demonstrated superiority of Symbravo over placebo in terms of percentage of subjects with pain relief at hour 2; please see Table 8 from the original clinical review. Superiority of Symbravo over placebo in time to pain relief was also demonstrated; this is discussed in the original review and visualized in Figure 4 from that review.

Symbravo demonstrated superiority over placebo on the ability to perform normal daily activities at hour 2, as noted in Table 1 below.

Table 1: Study AXS-07-301: Secondary Endpoints in ITT population, with all arms included

	Symbravo (N=428)	Rizatriptan (N=419)	Meloxicam (N=421))	Placebo (N=209)
Other Secondary Endpoints				
Able to Perform Normal Daily Activities at 2 hours	32.0%	30.3%	24.5%	21.1%
P value		0.594*	0.015*	0.004

*Source: modified from Statistical reviewer, aligns with Table 20 of the clinical study report. *p values for individual components were not part of the SAP and should be viewed as nominal.*

Symbravo did not demonstrate superiority over rizatriptan in percentage of patients with pain freedom at 2 hours (19.9% vs 17.4%, p=0.36).

7. Integrated Review of Effectiveness

Included below is section 7.2 from the original review by Dr. Livezey, which summarizes the efficacy assessment.

7.2 Integrated Assessment of Effectiveness

"The Applicant submitted the results of one adequate and well-controlled clinical trial (AXS-07-301) to support the efficacy of AXS-07 for the acute treatment of migraine. The second trial (AXS-07-303) was submitted to further support efficacy in the treatment of a mild attack. The efficacy of AXS-07 was demonstrated in one adequate and well-controlled study that used the clinically meaningful co-primary endpoints of the proportion of subjects who were pain and MBS free at 2 hours. Study AXS-07-301, evaluated the efficacy of AXS-07 on treatment of a single moderate to severe migraine attack. The study demonstrated statistically significant treatment effects on the prespecified co-primary endpoint. In Study AXS-07-301, the therapeutic gain (active drug minus placebo drug effect) comparing AXS-07 to placebo was 13.2% on the endpoint of pain freedom at 2 hours, with a p value of <.001. The therapeutic gain for AXS-07 for the endpoint of MBS freedom at 2 hours was 12.5%, with a p value of 0.002.

These therapeutic gains reported in these efficacy trials are in line with the results from other clinical trials in drugs recently approved for the acute treatment of migraine, which range from 7%-17% for the endpoint of pain freedom at 2 hours and 8-16% for the endpoint of MBS freedom at 2 hours.

The Applicant also analyzed the key secondary endpoint of sustained pain freedom from 2-24

hours (without using a rescue medication for migraine) to demonstrate component contribution using a factorial design. In Study AXS-07-301, subjects were randomized to AXS-07, meloxicam 20 mg, rizatriptan 10 mg or placebo. The Applicant effectively used Study AXS-07- 301 to establish the contribution of each individual product to the overall efficacy as per 21 CFR § 300.50, by demonstrating a clinically and statistically significant benefit of AXS-07 over meloxicam and rizatriptan on the agreed endpoint of sustained pain freedom at 24 hours.

Study AXS-07-303 was not required to support this application given the adequate scientific bridge and efficacy trial. However, Study AXS-07-303 was reviewed to assess the benefit of treatment of a mild migraine attack and to determine if the study should be described in labeling. With statistically significant and clinically relevant findings for the co-primary endpoints, this study re-demonstrated efficacy for migraine headache, in this instance, in subjects reporting mild symptoms. A finding on the co-primary efficacy outcome measures is sufficient to justify a conclusion of efficacy and the clinical relevance of effective treatment of mild headache symptoms is self-evident.

The Applicant demonstrated efficacy of AXS-07 for the acute treatment of migraine, both in the moderate to severe stage of an attack and during a mild attack. The contributions of both the rizatriptan and meloxicam component of AXS-07 was demonstrated on the pre-specified endpoint of sustained pain freedom at 2-24 hours. This was the same design employed by the sponsor of Treximet that helped this fixed-dose combination product gain approval. The Applicant has submitted adequate evidence of the efficacy of AXS-07 for the proposed indication of the acute treatment of migraine with and without aura.

8. Review of Safety

For a complete review of safety data, please refer to the original review by Dr. Viveca Livezey, dated April 11, 2022. Sections 8.1 and 8.2 include components not described in the original clinical review.

8.1. Use of non-clinical safety and pharmacokinetic data to support safety

Included here is the following summary of how a bridge to the listed drug (Mobic), plus data from a long-term extension study (AXS-302), support safety. This summary was drafted by Beth Goldstein in the Division of Regulatory Policy; I have reviewed this statement and note it to be accurate.

"The application relies on the Agency's finding of non-clinical safety for Mobic (meloxicam) oral tablets, NDA 020938. The applicant conducted a relative bioavailability (BA) study comparing the meloxicam component of Symbravo (20 mg meloxicam/10 mg rizatriptan) to the listed

drug, Mobic oral tablets (15 mg). The BA study (AXS-07-104) was a Phase 1, single-site, open-label, 2 period, 2-way crossover study to evaluate the pharmacokinetics of meloxicam in AXS-07 (the alphanumeric descriptor for Symbravo) compared to meloxicam alone, in healthy subjects. A single dose of AXS-07 was compared with 5 days of Mobic (15 mg meloxicam, QD) dosing.

The overall conclusions of the study were as follows:

- Plasma meloxicam peak and daily exposures (based on Cmax and AUC0-24, respectively) were approximately 106% and 64% higher, respectively, following a single dose of AXS-07 (20 mg meloxicam/10 mg rizatriptan) compared to the first dose of Mobic (15 mg meloxicam).
- Plasma meloxicam peak exposure (based on Cmax or Cmax,ss) was approximately 13% higher following a single dose of AXS-07 (20 mg meloxicam/10 mg rizatriptan) compared to 5 days of Mobic dosing (15 mg meloxicam, QD) at steady state. Plasma meloxicam daily exposure (based on AUC0-24 or AUC0-tau) was approximately 19% lower following a single dose of AXS-07 compared to 5 days of Mobic (15 mg meloxicam, QD) at steady state.
- The median time to peak meloxicam exposure (Tmax or Tmax,ss) was earlier following AXS-07 relative to single or 5 days of Mobic (15 mg meloxicam, QD), at approximately 1 and 2 hours post-dose, respectively.
- A single dose of AXS-07 and 5 days of Mobic (15 mg meloxicam, QD) were safe and well tolerated by the healthy subjects in this study.

Since the strength of the meloxicam component of Symbravo was higher (20 mg) than that of Mobic (15 mg), which explains the differences in the two arms in the results of the BA study above, in addition to this BA study, the applicant supported the safety of Symbravo's higher strength of meloxicam with the clinical safety database from the long-term extension study. Thus, the Applicant has established a scientific bridge to justify reliance on FDA's finding of non-clinical safety for the listed drug Mobic."

8.2. Long-term safety of chronic intermittent use

This section provides additional detail on the open-label study which contributed to the safety database described in Dr. Viveca Livezey's review.

8.2.1. Summary of AXS-07-302

AXS-07-302 was an open-label study which assessed the long-term safety of Symbravo for the acute treatment of migraine. Subjects were eligible if they participated in a prior trial of Symbravo for the acute treatment of migraine, with no significant changes in medical history since participation; although an early version of the protocol allowed for subjects with migraine who did not participate in prior trials of Symbravo, no subjects enrolled in AXS-07-302 who were not previously in a Symbravo trial. Subjects were instructed to treat only one migraine attack in a twenty-four hour period, and to not take more than 10 doses of Symbravo within a

month. Subjects were enrolled for up to twelve months and continued in the trial provided they treated at least two migraines per month (on average).

8.2.2. Overall exposure

A total of 706 subjects were included in the safety population for study AXS-07-302 (Table 2). This study included safety data on at least 300 patients treated for 6 months and 100 patients treated for 1 year, a requirement noted in the Pre-IND meeting minutes dated August 25, 2017, and End of Phase 2 meeting minutes dated June 25, 2019.

Table 2: Study AXS-07-302: Summary of duration of exposure

	Subjects treating ≥ 2 migraines/ month with Symbravo
≥ 1 month intermittent treatment	682
≥ 6 months intermittent treatment	496
≥ 12 months intermittent treatment	132

Source: modified from Table 19 in clinical review by Dr. Livezey

In AXS-07-302, the majority of subjects treated an average of 2-5 attacks, using an average of 2-5 doses of Symbravo, per month. Table 3 shows the distribution of patients who treated a given number of attacks per month with Symbravo over the entire duration of the study.

Table 3: Study AXS-07-302: Average number of treated migraine attacks treated per month

Average number of doses per month	Symbravo N=706 n (%)
>0 and <2	68 (10%)
≥ 2 and <4	332 (47%)
≥ 4 and <6	287 (41%)
≥ 6 and <8	10 (1%)
≥ 8 and <10	0 (0%)
≥ 10	0 (0%)

Source: Information Request response from Applicant, received on January 6, 2025.

The maximum number of migraine attacks treated in AXS-07-302 was higher than the average, with 30% taking 6 or 7 attacks at maximum. Table 4 shows the distribution of patients by maximum number of doses of Symbravo treated within a month.

Table 4: Study AXS-07-302: Maximum number of treated migraine attacks per month

Maximum number of doses per month	Symbravo N = 706 n (%)
>0 and <2	23 (3.3%)
≥ 2 and <4	117 (16.5%)
≥ 4 and <6	309 (43.6%)
≥ 6 and <8	218 (30.8%)
≥ 8 and <10	38 (5.4%)
≥ 10	1 (0.1%)

Source: Information Request response from Applicant, received on January 6, 2025.

Reviewer comment: The number of doses per month (both maximum and average) were verified by the Office of Computational Science using the SDTM EX dataset. These numbers were similar and led to the same conclusion when examining number of treated attacks per month. Taken together, Tables 3 and 4 support the use of Symbravo to treat up to 7 migraines per month (i.e., 7 doses of Symbravo in a 30 day period). This maximum use of up to 7 doses of Symbravo per month should be incorporated into the label. There are too few subjects who treated 8 or 9 migraines per month to make definitive conclusions on safety at these cumulative doses. Treatment of 10 migraines a month (representing at daily use approximately 33% of the average month) with Symbravo may raise concern for medication overuse and development of medication overuse headache so it is reasonable to state that 7 doses per month represents a reasonable treatment course that is supported by the safety database and is below a threshold raising concern for overuse.

8.2.3. Pertinent Safety Findings

The following is a summary from the original clinical review.

No deaths occurred in any of the clinical trials, and eight subjects experienced treatment emergent serious adverse events in trial AXS-07-302. These were captured in the original clinical review (with additional clinical detail) and are reproduced here in Table 5 for reference.

Table 5: Study AXS-07-302: Treatment Emergent Serious Adverse Events

Preferred term	n
Arthralgia	1
Burns third degree	1
Endometrial hyperplasia	1
Hepatitis acute	1

Hiatus hernia	1
Mitral valve incompetence	1
Musculoskeletal procedural complication	1
Skin graft	1
Victim of crime	1

Source: modified from Table 22 in original clinical review by Dr. Livezey.

In trial AXS-07-302, nausea, vomiting, dizziness, somnolence, diarrhea, and upper respiratory tract infection were reported at rates greater than 2% (Table 3). These data have limitations in interpretation as they were collected in an open-label setting.

Table 6: Study AXS-07-302: Adverse Reactions Occurring in Greater than 2%

Preferred term	Symbravo (N=706) n (%)
Nausea	40 (5.7)
Vomiting	33 (4.7)
Dizziness	22 (3.1)
Somnolence	20 (2.8)
Diarrhea	16 (2.3)
Upper respiratory tract infection	14 (2.0)

Source: modified from Table 27 in original clinical review by Dr. Livezey.

8.3. Integrated Assessment of Safety

The Integrated Assessment of Safety, which included a thorough review of the data from the controlled and uncontrolled clinical trials, is reproduced here (in italics) from the original clinical review. These conclusions remain applicable because there were no new data submitted in the resubmission.

"[Symbravo] has a favorable safety profile. In controlled trials, there were no deaths or serious adverse events with a clear association with Symbravo. Common adverse events that occurred at an incidence of at least 1% and greater than placebo were dizziness and somnolence. No other new safety signals were detected. Safety information from the known effects of the individual components of Symbravo should be included in future labeling of this product, in addition to the TEAEs noted in the controlled clinical trials.

All of the warnings, precautions, contraindications and boxed warnings for triptans and NSAIDs should be included in the label for Symbravo. Further, all safety information pertaining to Maxalt and Anjeso (the listed drugs) should also be included in the label. A Warning and Precaution section for medication overuse headache will also be included in the Symbravo PI, as

this risk is associated with overuse of NSAIDs and triptans for the acute treatment of migraine. There is no specific pharmacovigilance that should be requested at this time."

9. Advisory Committee Meeting and Other External Consultations

No advisory committee or external consultations were assessed as necessary.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Because the original application submission received a Complete Response, the Division did not enter labeling negotiations with the Applicant during the initial review cycle. With the expectation of an approval action, the Division will complete labeling negotiations with the Applicant during this review cycle. The following is a summary of the key labeling considerations based on the totality of data presented in the original and resubmission.

10.1.1. Efficacy

Although the relevant migraine guidance could allow for only one clinical trial to support efficacy, both randomized, double-blind, placebo-controlled studies AXS-07-301 and AXS-07-303 should be reported in Section 14 (Clinical Studies) because these adequate and well-controlled trials provide relevant efficacy information that would be informative for patients and prescribers.

Study AXS-07-301 included the typical administration instructions issued to patients in acute migraine trials; that is, subjects took the study drug when their migraine pain was moderate to severe in intensity. Study AXS-07-301 included four arms and demonstrated that each component (rizatriptan and meloxicam) contributed to the overall efficacy of Symbravo. Subjects were more likely to experience relief from pain at two hours and relief from most bothersome symptom at two hours with Symbravo than with placebo. Subjects also were more likely to achieve statistically significant outcomes on these co-primary endpoints with Symbravo than with either component alone. On the key secondary endpoint of 24 hour sustained pain freedom, subjects were statistically more likely to achieve 24 hour sustained pain freedom with Symbravo than with either component. Finally, the other secondary endpoints of pain relief at two hours and ability to perform normal daily activities at two hours were met when comparing Symbravo to placebo, with a greater percentage of subjects meeting these endpoints in the Symbravo arm than in either component. Patients and providers may use data on each component to help in interpreting efficacy and selecting the most appropriate migraine treatment; each arm should be included in tables and text describing co-primary and key

secondary endpoints which were met in the study as they are obviously informative.

In Study AXS-07-303, subjects took the study drug when their migraine pain was mild. Both trials met efficacy on accepted primary endpoints, freedom from pain at 2 hours and freedom from most bothersome symptom at 2 hours. Although the Guidance for Industry: "*Migraine: Developing Drugs for Acute Treatment"*[2] states that "evidence should be obtained that the investigational drug is able to treat a migraine headache of moderate or severe intensity," the guidance also states that "additional trials assessing drug response after treatment of acute migraine at the mild pain stage can be conducted and can be described in labeling." Since trial AXS-07-303 was an adequate and well-designed clinical trial, and its findings appear clinically meaningful for patients with mild headaches, it should be included in the approved labeling. To allow for greater clarity when evaluating results and given the different number of arms and different time to treatment of migraine, data from this study should be separated from the trial data obtained in Study AXS-07-301.

10.1.2. Safety

Within section 6 of labeling (Clinical Trials Experience), the AEs of somnolence and dizziness should be included as they occurred in greater than 1% of subjects who received Symbravo and occurred at a greater frequency than in placebo in both controlled clinical trials. Given the limitations of data collected within safety AXS-07-302 (an open-label uncontrolled study), I would not recommend including additional AEs which solely appeared in that study. To conform with previous labels, safety data from studies AXS-07-301 and AXS-07-303 can be included in a single table, with clear demarcation of data deriving from each study.

An important drug-drug interaction to be addressed in labeling is that between rizatriptan and propranolol. The Maxalt label notes that propranolol can increase the plasma AUC of rizatriptan by 70%, and that the dose of Maxalt should be adjusted in patients on propranolol. Since there is one dose of rizatriptan in the approved formulation of Symbravo (10 mg rizatriptan), the dose of rizatriptan cannot be adjusted. However, the Maxalt label also allows for a maximum of 15 mg rizatriptan within a 24-hour period. Based on this information, I recommend that the

[2] https://www.fda.gov/media/89829/download

Symbravo is a combination product, and, therefore, approved labeling should describe the appropriate safety issues associated with the meloxicam and rizatriptan components that may be applicable to the indicated population.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies

As per the original review of this submission, a Risk Evaluation and Mitigation Strategy (REMS) for Symbravo was not recommended. There are no REMS for the approved components, and no new safety issues were identified that would indicate a need for a REMS for this fixed dose combination.

12. Postmarketing Requirements and Commitments

Pediatric post marketing requirements (PMRs) and a pregnancy registry and database PMR are required for Symbravo because an approval of Symbravo triggers Pediatric Research Equity Act (PREA) requirements and because there are concerns with the safety of this combination product in pregnancy, especially given that the indicated population would disproportionately include women of childbearing potential given the well-established demographics of patients with acute migraines.

1. Pediatric PMRs
    a. A randomized, double-blind, placebo-controlled efficacy and safety study under PREA to evaluate Symbravo for the acute treatment of migraine in pediatric patients ages 6 to less than 18 years. This study should include an initial blinded placebo run-in period to identify placebo-nonresponders for enrollment into the efficacy portion of the study. This efficacy study must be designed to show superiority of Symbravo over placebo.
    b. A long-term open-label safety study in pediatric patients ages 6 years to less than 18 years. The long-term safety study must provide a descriptive analysis of safety data in at least 200 pediatric patients treated with Symbravo for a duration of at least 6 months and 75 pediatric patients treated with Symbravo for 12 months, treating on average at least one migraine attack per month, at doses evaluated in the efficacy study.

2. Pregnancy PMRs
    a. A prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with migraine exposed to Symbravo during pregnancy with two unexposed control populations: one consisting of women with migraine who have not been exposed to Symbravo before and during pregnancy and the other consisting of women without migraine. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.
    b. A pregnancy outcomes study using a different study design than provided for in PMR 2a (for example, a retrospective cohort study using claims or electronic medical record data with outcome validation or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to Symbravo during pregnancy compared to an unexposed control population.

13. Appendices

13.1. References

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13.2. Financial Disclosure

No new financial disclosure information was provided with the resubmission. Please refer to the original review by Dr. Viveca Livezey for details on the necessary disclosures for the efficacy trials.

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CLINICAL REVIEW

Application Type	505(b)(2)
Application Number(s)	NDA 215431
Priority or Standard	Standard
Submit Date(s)	June 30, 2021
Received Date(s)	June 30, 2021
PDUFA Goal Date	April 29, 2022
Division/Office	Division of Neurology 2/Office of Neuroscience
Reviewer Name(s)	Viveca Livezey, MD
Review Completion Date	April 11, 2022
Established/Proper Name	AXS-07
(Proposed) Trade Name	Symbravo
Applicant	Axsome
Dosage Form(s)	One tablet for oral use of meloxicam 20 mg and rizatriptan 10 mg
Applicant Proposed Dosing Regimen(s)	One tablet of meloxicam 20 mg and rizatriptan 10 mg, at the onset of migraine.
Applicant Proposed Indication(s)/Population(s)	Acute treatment of migraine with or without aura in adults.
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	Acute treatment of migraine with or without aura in adults.

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	Confidence Intervals
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
GCP	good clinical practice
ICH	International Council for Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation

PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Axsome Therapeutics, Incorporated (hereafter referred to as the Applicant) developed AXS-07 (SYMBRAVO) as a fixed-dose combination product and each tablet contains 20 mg meloxicam and 10 mg rizatriptan (equivalent to 14.5 mg rizatriptan benzoate). Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID), currently approved for the relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis, and for the management of moderate-to-severe pain. Rizatriptan is a 5-$HT1_{B/D}$ agonist (triptan) currently approved for the acute treatment of migraine. The combination product, referred to as AXS-07 in this document, is delivered as an orally-administered tablet for the proposed indication of the acute treatment of migraine with and without aura.

The Applicant is using a 505(b)(2) regulatory pathway, using the listed drugs (LD) meloxicam (Anjeso) and rizatriptan (Maxalt) along with data from several trials to support this marketing application. A single efficacy study was assessed as adequate to demonstrate efficacy based on the approved indication of rizatriptan (Maxalt) for the acute treatment of migraine and the known analgesic effect of meloxicam (Anjeso). One long-term safety study to demonstrate safety of AXS-07 administration for up to 12 months was also required.

The Applicant submitted data from a trial intended to demonstrate efficacy and safety of AXS-07 (Study AXS-07-301), which utilized the established co-primary endpoints of pain and most bothersome symptom (MBS) freedom at 2 hours to demonstrate efficacy. Since AXS-07 is a fixed-dose combination of two products, the approach to the evaluation of efficacy also involved a factorial design to establish the contribution of each individual product to the overall efficacy as per 21 Code of Federal Regulations (CFR) § 300.50. The Applicant utilized Study AXS-07-301 to demonstrate component contribution (of meloxicam and rizatriptan separately, compared to AXS-07) using the endpoint of 24-hour sustained pain freedom. Additionally, the Applicant submitted the results of AXS-07-303 (studying the effect of AXS-07 on the acute treatment of a mild migraine attack) and AXS-07-302 (a long-term safety study), which contribute to the overall understanding of the efficacy and safety profile of this product.

1.2. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

AXS-07 (SYMBRAVO) is a fixed dose combination product and each tablet contains: 20 mg meloxicam (a nonsteroidal anti-inflammatory drug (NSAID)), and 10 mg rizatriptan (a 5-$HT1_{B/D}$ agonist (triptan)). The Applicant is seeking an indication for the acute treatment of migraine with or without aura in adults. The Applicant is relying on the listed drugs (LD), meloxicam (Anjeso) and rizatriptan (Maxalt). Anjeso is an intravenous formulation of meloxicam indicated for moderate to severe pain. Of note, an oral form of meloxicam (Mobic) is a tablet approved for the signs and symptoms associated with various types of arthritis, at doses up to 15 mg daily. Maxalt is indicated for the acute treatment of migraine in subjects 6 years of age and older.

There are many FDA-approved drugs for the acute treatment of migraine with and without aura in adults, including triptans (5-$HT_{1B/1D}$ receptor agonists), lasmiditan (a 5-HT_{1F} receptor agonist), ubrogepant and rimegepant (CGRP antagonists), dihydroergotamine (DHE), and NSAIDs; the latter of which can be used alone (diclofenac or celecoxib) or in combination with a triptan (e.g., Treximet). In addition, there are over-the-counter products, including NSAIDs, approved for the acute treatment of migraine.

The efficacy of AXS-07 in the treatment of an acute migraine attack was demonstrated in one adequate and well-controlled study. The study used the well-validated and clinically meaningful co-primary endpoints of the proportion of subjects who were pain and most bothersome symptom (MBS) free at 2 hours to establish efficacy. Study AXS-07-301 evaluated the efficacy of AXS-07 on treatment of a single moderate to severe migraine attack. The study demonstrated statistically significant treatment effects on the prespecified co-primary endpoints. In Study AXS-07-301, the therapeutic gain (active drug minus placebo drug effect) comparing AXS-07 to placebo was 13.2% on the endpoint of pain freedom at 2 hours, with a p-value of <.001. The therapeutic gain for AXS-07 for the endpoint of MBS freedom at 2 hours was 12.5%, with a p-value of 0.002. These results are similar to other clinical trials in drugs recently approved for the acute treatment of migraine, with therapeutic gains ranging from 7%-17% for the endpoint of pain freedom at 2 hours and therapeutic gains of 8-16% for the endpoint of MBS freedom at 2 hours.

The Applicant also analyzed the key secondary endpoint of sustained pain freedom from 2-24 hours (without using a rescue medication for migraine) to demonstrate component contribution of both meloxicam and rizatriptan, using a factorial design. In Study AXS-07-301, subjects were randomized to AXS-07, meloxicam 20 mg, rizatriptan 10 mg or placebo. The Applicant effectively used Study AXS-07-301 to establish the contribution of each individual product (meloxicam and rizatriptan) to the overall efficacy of AXS-07 as per 21 Code of Federal Regulations (CFR)

§ 300.50 CFR, by demonstrating a clinically and statistically significant benefit of AXS-07 over meloxicam and rizatriptan on the endpoint of sustained pain freedom at 24 hours.

The Applicant submitted one adequately designed trial with endpoints generally agreed upon by the Division that provides substantial evidence of efficacy for the acute treatment of migraine. One adequate and well-controlled clinical investigation of AXS-07 was assessed as acceptable since rizatriptan is already approved for the acute treatment of migraine, and meloxicam is already approved for a pain indication. Further, the component contribution of the products that comprise AXS-07 (meloxicam and rizatriptan) were established by use of a factorial design.

The Applicant submitted a second trial, Study AXS-07-303, randomized, double-blind, placebo-controlled trial that demonstrated efficacy of AXS-07 in the treatment of a mild migraine attack. This trial also contributes to the short-term safety of AXS-07.

The Applicant submitted data from the two placebo-controlled trials, Studies AXS-07-301 and AXS-07-303, and one long-term safety study, Study AXS-07-302, to support safety of AXS-07 for the acute treatment of migraine. A long-term safety study was required since the dose of meloxicam in this product is 20 mg and higher than the daily recommended dose of oral meloxicam (15 mg daily). The safety data included in this application demonstrate that AXS-07 is safe for its intended use in this population.

The findings from the placebo-controlled trials indicated an increased frequency of dizziness and somnolence in AXS-07 treated subjects. No other new safety signals were detected. Nausea, vomiting, dizziness, somnolence, diarrhea and upper respiratory tract infection were observed in the long-term safety study. All of the warnings, precautions, contraindications and boxed warnings that already exist for triptans and NSAIDs should be included in the label for AXS-07. Further, all safety information pertaining to Anjeso and Maxalt (the LDs) should also be included in the label. The risks that can occur with this product can be mitigated through labeling. There is no specific pharmacovigilance that should be requested at this time.

From the clinical perspective, the risk/benefit profile of AXS-07 is acceptable and supports approval for the acute treatment of migraine with and without aura in adults. The evidence does not suggest that AXS-07 is more effective than other FDA-approved drugs for the acute treatment of migraine; however, AXS-07 offers another treatment option.

Future labeling should clearly convey the safety profile demonstrated with extensive experience with both triptans and NSAIDs and should also describe the increase in the incidence of dizziness and somnolence with the use of AXS-07 as compared with placebo. The overall benefit-risk profile of AXS-07 is favorable from the clinical perspective, as described in the Benefit-Risk Framework.

The NDA was reviewed by the multidisciplinary review team. The drug product, manufacturing, and biopharmaceutics disciplines have unresolved quality issues. Specifically, the proposed drug product specification is inadequate to control potential impurities, including potential (b) (4) degradants, manufacturing controls are inadequate to ensure consistent product quality, and the applicant has not provided adequate data to support the proposed dissolution test method. Although this product demonstrated evidence of safety and effectiveness from the clinical perspective, from the quality perspective it is not approvable and therefore, the recommendation is for a Complete Response.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Migraine is a primary headache disorder characterized by recurrent headaches that are moderate to severe, accompanied by associated symptoms of nausea, vomiting, and light and/or sound sensitivity. The typical headache of migraine is throbbing, unilateral, and aggravated by movement. • Migraine attacks typically last 4 to 72 hours when untreated. About one third of people with migraine experience transient neurological symptoms before and/or during an attack, referred to as migraine aura. • Migraine can be very disabling and contribute to loss of productivity and diminished quality of life. • Migraine can occur on an episodic or chronic basis. • Migraine is more frequent in females than in males. (Lipton, Stewart, et al. 2001). • Migraine prevalence peaks in the 4th decade of life for both males	The burden of migraine is large to subjects who have this condition. Migraine affects quality of life and contributes to significant pain and morbidity.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	and females (Lipton, Bigal, et al. 2007).	
Current Treatment Options	• There are currently many approved therapies for the acute treatment of migraine, as well as many other therapies that are used off-label. • Non-specific therapies (not FDA approved, but used off-label), include Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and acetaminophen • Currently used acute migraine treatments include: o Triptans, including oral, oral disintegrating, nasal spray, subcutaneous formulations – however, these treatments are often contraindicated in subjects with cardiovascular or cerebrovascular disease. o Dihydroergotamine (nasal spray, subcutaneous or intramuscular) – however, this is contraindicated in subjects with cardiovascular disease. o Several calcitonin gene-related peptide (CGRP) antagonists have recently been approved for the acute treatment of migraine (including ubrogepant and rimegepant); long-term effects are not completely known. o At the time of this application, there are three FDA approved acute migraine treatments that have an NSAID component. These are diclofenac (Cambia) and celecoxib oral solution (Elyxyb) used alone, and the fixed drug combination of the NSAID (naproxen) with the triptan (sumatriptan), Treximet. o Specifically, the triptans and several NSAIDs (including	There are numerous treatment options for the acute treatment of migraine. Drugs that may act more rapidly, have fewer side effects or are provided in novel formulations, may be advantageous for some subjects.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	diclofenac, celecoxib oral solution, and the naproxen-sumatriptan combination product) have randomized placebo-controlled trial evidence suggesting that they are effective for the acute treatment of migraine. o The therapeutic gain (active drug minus placebo drug effect) for the endpoint of pain freedom at 2 hours, for drugs recently approved for the acute treatment of migraine, ranges from 7%-17% in clinical trials. o The therapeutic gain for the endpoint of most bothersome symptom (MBS) freedom at 2 hours for drugs recently approved for the acute treatment of migraine ranges from 8.3-15.5% in clinical trials.	
Benefit	• The Applicant conducted one adequate and well-controlled confirmatory trial (Study AXS-07-301) to evaluate the effect of AXS-07 compared to placebo for the treatment of an acute migraine attack. • The study used the agreed-upon trial design of treating a single moderate to severe migraine attack and investigating the co-primary endpoints of pain and MBS freedom at 2 hours. • In AXS-07-301, the therapeutic gain comparing AXS-07 to placebo was 13.2% on the endpoint of pain freedom at 2 hours, with a p value of <.001. The therapeutic gain for AXS-07 for the endpoint of MBS freedom at 2 hours was 12.5%, with a p value of 0.002. • The Applicant also analyzed the key secondary endpoint of sustained pain freedom from 2-24 hours to demonstrate component contribution using a factorial design, in which subjects were randomized to AXS-07, meloxicam 20 mg, rizatriptan 10 mg or	The Applicant submitted evidence of effectiveness in one adequate and well-controlled clinical investigation of AXS-07 supported by scientific knowledge about the effectiveness of other drugs in the same pharmacological class (i.e., including the approvals of triptans and NSAIDs and one triptan/NSAID combination for the acute treatment of migraine). The therapeutic gains with AXS-07 are in line with drugs recently approved for the acute treatment of migraine. The Applicant effectively used a factorial design to establish the contribution of each

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	placebo. • Sustained pain freedom in the AXS-07 was significantly higher than meloxicam (7.3%, p=.001) and rizatriptan (4.9%, p=.038) and this information contributes to the establishment of the contribution of each individual product of the fixed-dose combination. • Rizatriptan is already approved for the acute treatment of migraine, and this is supported by positive efficacy data from Study AXS-07-301. • There are two NSAIDs approved for the acute treatment of migraine (diclofenac and celecoxib oral solution). • There is one fixed dose combination product of a triptan/NSAID (sumatriptan/naproxen) indicated for the acute treatment of migraine. • The Applicant did submit a second randomized, placebo-controlled trial efficacy trial (Study AXS-07-303) in which subjects treated a mild migraine attack. The therapeutic gain with AXS-07 was 16.3% on the endpoint of pain freedom at 2 hours and 17.2% on the endpoint of MBS freedom at 2 hours. • While Study AXS-07-303 has a study design that is not reflective of the trial design required for approval of AXS-07 (i.e., treatment of a moderate to severe attack), it does provide information on efficacy of early migraine attack treatment.	individual product (meloxicam and rizatriptan) to the overall efficacy of AXS-07 as per 21 Code of Federal Regulations (CFR) § 300.50 CFR. The second trial provided evidence of effectiveness in the treatment of a migraine attack in the mild stage. These gains were statistically significant and likely clinically meaningful to subjects who do not want to delay treatment until a migraine attack is moderate to severe in intensity. This information may be helpful to subjects and providers.
Risk and Risk Management	• The Applicant used both pharmacokinetic bridging to the listed drugs, rizatriptan (Maxalt) and meloxicam (Anjeso) and data from the safety portion of AXS-07-301 and AXS-07-303, as well as one long-term safety study (AXS-07-302) to demonstrate safety of AXS-07. • The safety profiles for both triptans and NSAIDs have been well-	All of the warnings, precautions, contraindications and boxed warnings for triptans and NSAIDs should be included in the label for AXS-07. Further, all safety information pertaining to Maxalt and Anjeso (the listed

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	established. However, the dose of meloxicam in this fixed-dose combination product is 20 mg, and higher than the daily approved dose of the listed drug (Mobic (meloxicam 15 mg)). Also, though the dosage of meloxicam in AXS-07 is capped by the pharmacokinetic profile of Anjeso, it is not intravenous and not typically prescribed for chronic intermittent use. Since this is a new indication with a different route of administration than Anjeso, a 12-month long-term safety study for this indication was required. • The placebo-controlled trials indicated that in subjects treated with AXS-07, dizziness and somnolence occurred at a ≥ 1% rate and higher than placebo. • There were no serious adverse events or significant safety events in the placebo-controlled trials. • Only one dose in a 24-hour period was allowed with a maximum of 10 doses per month in the long-term safety study. • In the long-term safety, Study AXS-07-302, nausea, vomiting, dizziness, somnolence, diarrhea and upper respiratory tract infection was reported at rates of ≥ 2%. The rates of nausea and somnolence were higher than that reported in the controlled clinical trials. • There were no serious adverse events or significant safety signals clearly attributable to AXS-07 use in the long-term safety study.	drugs) should also be included in the label. The safety of more than one dose in a 24-hour period is not known; therefore, the maximum dose in a 24-hour period should be one tablet. The findings from the placebo-controlled trials of an increased frequency of dizziness and somnolence in AXS-07 treated subjects should be included in a table in the label. No other new safety signals were detected. Risks of medication overuse headache should be included in the label, as this is a combination of an NSAID and a triptan, and both products individually can lead to medication overuse headache. There is no specific pharmacovigilance that should be requested at this time.

1.3. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		x	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

The proposed indication for AXS-07 is for the acute treatment of migraine with and without aura in adults. Migraine is a common, chronic, neurological disorder that is most prevalent in women and between the ages of 25 and 55 years (Dodick 2018). Subjects with migraine experience recurrent attacks of moderate to severe head pain that can cause significant disability and cause an impact on social and functional abilities.

Diagnostic criteria for migraine with and without aura have been established by the International Headache Society (IHS) and are termed the International Classification for Headache Disorders (ICHD-3). Per the ICHD-3 definition, a migraine is a recurrent headache disorder manifesting in recurrent attacks of head pain that must fulfill the following criteria: last 4-72 hours, have two of the following four characteristics: unilateral location, pulsating quality, moderate or severe pain intensity, aggravation by or causing avoidance of routine physical activity, and must have associated symptoms of either nausea and/or vomiting, or photophobia and/or phonophobia.

2.2. Analysis of Current Treatment Options

Current treatment options for the acute treatment of migraine include FDA-approved drugs (e.g., triptans, ergotamines, NSAIDs, serotonin ($5HT_{1F}$) agonists, and CGRP antagonists). There are three FDA-approved NSAIDs for the acute treatment of migraine, diclofenac (Cambia), celecoxib oral solution (Elyxyb), and the NSAID/triptan combination of naproxen and sumatriptan (Treximet). Many drugs are used off-label, including opiates, over the counter drugs, including NSAIDs (such as ibuprofen), acetaminophen, and drug combinations such as caffeine/acetaminophen/aspirin preparations. Subjects may also use behavioral techniques or approved devices for the treatment of acute migraine (Dodick 2018).

In addition to these acute therapies, subjects with episodic and chronic migraine are often prescribed medications for the preventive treatment of migraine that are given on a daily, monthly, or quarterly basis.

Table 1. Summary of Acute Treatment Options for Migraine

Product (s) Name	Year of Approval	Route	Important Safety and Tolerability Issues	Other Comments (for example, subgroups addressed)
FDA Approved Treatments				
ERGOTS				
Dihydroergotamine (DHE) Nasal Spray 2 mg	1997	Nasal spray	CYP3A4 inhibitor interaction; contraindicated with cardiovascular disease; fibrotic complications	

DHE 1 mg injection	1946	Sub-cutaneous	CYP3A4 inhibitor interaction; contraindicated with cardiovascular disease; fibrotic complications	
TRIPTANS				
Almotriptan 12.5 mg	2001	Tablet	Contraindicated in subjects with coronary artery disease, coronary artery vasospasm, conduction pathway disorders, cerebrovascular disease, hemiplegic or basilar migraine, peripheral vascular disease, ischemic bowel disease or uncontrolled hypertension; Warnings/precautions in subjects with history of myocardial ischemia, arrhythmias, cerebral hemorrhage, subarachnoid hemorrhage or stroke	Indicated for subjects ages 12 to 17 years old
Eletriptan 20, 40 mg	2002	Tablet		Interacts with CYP3A4 inhibitors
Frovatriptan 2.5 mg	2001	Tablet		
Naratriptan 1, 2.5 mg	1998	Tablet		
Rizatriptan 5, 10 mg	1998	Tablet		Indicated for subjects ages 6 to 17 years old
Sumatriptan Oral 25, 50, 100mg	1992	Tablet		
Sumatriptan Nasal Spray 10, 20 mg		Nasal Spray		
Sumatriptan Nasal Powder 22 mg	2016	Nasal Powder		
Sumatriptan SC 4, 6 mg	2009	Sub-cutaneous		
Zolmitriptan NS 2.5, 5 mg	2015	Nasal Spray		Indicated for subjects 12 years of age or older
Zolmitriptan Oral 2.5, 5 mg	1997	Tablet		
Sumatriptan/naproxen 85/500 mg	2008	Tablet		NSAID included; Indicated for subjects 12 years and older; Cardiovascular risk, increased risk of bleeding due to naproxen component
NSAIDS				
Diclofenac (Cambia) 50 mg	2009	Oral (Packet)	Cardiovascular risk for thrombotic events, myocardial infarction and stroke; gastrointestinal adverse events, especially in elderly	
Celecoxib oral solution (Elyxyb) 120 mg	2020	Oral solution	Cardiovascular risk for thrombotic events, myocardial infarction and stroke; gastrointestinal adverse events, especially in elderly	
5-HT1F receptor agonists				
Lasmiditan	2019	Oral	Driving impairment for up to 8 hours; May	

			lower heart rate; Adverse events include dizziness, fatigue, paresthesia, sedation, nausea and/or vomiting, muscle weakness;	
CGRP antagonist				
Ubrogepant 50 mg, 100 mg	2019	Oral	Nausea, somnolence, dry mouth	Interacts with CYP3A4 Inhibitors/inducers; substrate of BCRP and P-gp efflux transporters
Rimegepant 75 mg	2020	Oral	Nausea	Interacts with CYP3A4 Inhibitors/inducers; inhibitors of BCRP and P-gp efflux transporters
Devices				
GammaCore device	2017	Device		
Cerena device	2013	Device	Contraindicated in subjects with magnetic metals in head, neck or upper body, or pacemakers, or other implanted devices	
Cefaly ACUTE device	2017	Device	Contraindicated with recent trauma to skull/face or with skin conditions/rashes	
Nonprescription, FDA approved				
NSAIDs (ibuprofen,)	2000 (Advil Migraine)	Tablet, capsule	Gastrointestinal toxicity, bleeding complications	Advil Migraine is a nonprescription drug indicated for the treatment of migraine.
Acetaminophen/aspirin /caffeine	1998 (Excedrin Migraine)	Tablet	Overuse, see effects for individual categories	Excedrin Migraine is a nonprescription drug indicated for the temporary relief of mild to moderate pain associated with migraine headache.

*I created this table using the Drugs@FDA website, and reviewing the approvals, labels, and dates for drugs and devices indicated for the acute treatment of migraine.

The current treatment options span a wide range of therapeutic targets. While NSAIDs are often used by providers for the acute treatment of migraine, as noted previously and in the table, only three NSAIDs (diclofenac, celecoxib, and naproxen (the latter given as a sumatriptan/naproxen combination product)) are FDA approved as prescription drugs for this indication. Advil migraine is a nonprescription NSAID indicated for the treatment of migraine. Rofecoxib (Vioxx) is a COX-2 selective NSAID (similar to celecoxib) that was previously approved for the acute treatment of migraine, prior to being withdrawn from the US market in 2004 due to safety concerns (specifically, increasing the risk for cardiovascular events).

This overview suggests there is already a clear role for triptans and NSAIDs, independently, in the treatment of acute migraine attacks. There is also one prior approval for a triptan/NSAID combination (sumatriptan/naproxen, Treximet) which received approval in 2008 after the sponsor submitted results of two clinical trials demonstrating efficacy and component contribution using a factorial design. There were concerns during the review of a synergistic effect with increased risk of cardiovascular events, such as hypertension, given that each drug individually increases risk of cardiovascular events per the warnings and precautions. A review of the literature and postmarketing data has not suggested an increase documented cardiovascular risk in subjects taking this fixed-dose combination product.

In the setting of scientific knowledge about the effectiveness of other drugs for acute migraine in the same pharmacological class as AXS-07, only one adequate and well-controlled clinical trial of AXS-07 was assessed as necessary by the Agency (Guidance for Industry: "*Demonstrating Substantial Evidence of Effectiveness For Human Drug and Biological Products*").[1]

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

AXS-07 does not have marketing authorization in any country and this is the first submission for this product in the United States (U.S.), or any country. The Applicant is using two LDs as part of this application, rizatriptan (Maxalt) and meloxicam (Anjeso).

Rizatriptan (Maxalt) was initially approved in the U.S. in 1998 at doses of 5 mg or 10 mg tablets (with a maximum daily dose of 30 mg) for the acute treatment of migraine with or without aura in adults. It subsequently received marketing authorization for the pediatric subjects (ages 6 to 17 years, 5 or 10 mg and weight based) in 2011. An orally disintegrating tablet (Maxalt-MLT) became available subsequently.

Meloxicam (Anjeso) is an intravenously administered NSAID indicated for use in adults for the management of moderate-to-severe pain, alone or in combination with non-NSAID analgesics. Meloxicam was originally approved as an oral tablet, available at doses of 7.5 mg or 15 mg daily, in 2000 for the signs and symptoms of osteoarthritis. The indication was subsequently expanded to include rheumatoid arthritis (2004) and juvenile rheumatoid arthritis (2005). A

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

subsequent oral solution formulation was marketed but discontinued (not due to reasons of safety).

There are no currently available meloxicam/rizatriptan fixed dose combination products on the U.S. market.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant opened the Investigational New Drug (IND) application 135972 for this product with the pre-IND submission in July 2017. Pre-IND Written Responses were submitted on August 25, 2017, to discuss the Applicant's development plan for AXS-07. The Applicant completed its first Phase 1 trial of AXS-07 (Study AXS-07-101) in 6 subjects with a history of migraine (b) (4) and then submitted the opening IND for a second Phase 1 trial (Study AXS-07-102) in the US on August 31, 2018. The IND was allowed to proceed. The Applicant was told that because the product being studied is a combination product for which one component is already approved for the treatment of migraine and the second component is an analgesic, the Division was open to considering an argument that a single adequate and well controlled efficacy trial might be sufficient to support a marketing application.

The Applicant submitted a request for a Special Protocol Assessment (SPA) for its Phase 3 clinical trial protocol for Study AXS-07-301 on October 26, 2018. The Phase 3 trial used a full factorial design, and the intent was to use this single study as the basis for the 505(b)(2) NDA submission. The Applicant was issued a SPA No Agreement letter in December 2018, due to the request for an indication for (b) (4) The proposed study design did not include an acceptable enrichment strategy to support such an indication. The Applicant re-submitted the SPA removing the portion of the indication that included the language (b) (4) (b) (4) and was subsequently issued a SPA Agreement letter in January 2019. The co-primary endpoint of pain freedom and MBS freedom at 2 hours compared to placebo was assessed as adequate to demonstrate efficacy of the combination product. The key secondary endpoint of 2-24 hours of sustained pain freedom compared to each individual component (rizatriptan and meloxicam separately) was assessed as adequate to demonstrate each component contribution. Of note, 2 to 24 hour pain freedom as the key secondary endpoint to demonstrate component contribution of a fixed dose combination product was utilized by the Applicant (Pozen) to obtain approval of the fixed drug combination product (sumatriptan/naproxen (Treximet)) as part of NDA 021926.

The Applicant requested an End-of-Phase 2 meeting to the IND application 135972 and this was granted, including an in-person meeting May 30, 2019. The Applicant was advised there may not be an adequate pharmacokinetic bridge of AXS-07 to Mobic (orally administered

meloxicam) due to a dose of meloxicam (20 mg) that is higher than the daily approved dose of Mobic (15 mg). Furthermore, the intravenous formulation is not typically administered in a chronic, intermittent dosage pattern when administered as the intravenous Anjeso. The Applicant was advised that a long-term safety study would be required.

3.3. Foreign Regulatory Actions and Marketing History

Not applicable.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Please refer to the review conducted by Dr. Cara Alfaro, in the Office of Scientific Investigations, for details regarding clinical site inspections for this application. To summarize, three sites were inspected in support of this NDA, covering Studies AXS-07-301 and AXS-07-303. Despite some protocol deviations, the studies were assessed as having been conducted adequately. The data generated from these three sites appeared acceptable to support the indication in this population.

4.2. Product Quality

The Chemistry, Manufacturing, and Controls (CMC) review determined that this application is not approvable due to concerns with manufacturing and the need for new registration batches and new stability testing.

Per the review:

> The Office of Pharmaceutical Quality Review (OPQ) team has evaluated NDA 215431 with respect to drug substance and facilities and has determined that it meets all of those applicable standards to support the identity, strength, quality, and purity that it purports. However, the drug product, manufacturing, and biopharmaceutics disciplines have unresolved quality issues. Specifically, the proposed drug product specification is inadequate to control potential impurities, including potential (b) (4) degradants, manufacturing controls are inadequate to ensure consistent product quality, and the applicant has not provided adequate data to support the proposed dissolution test method. Therefore, from an OPQ perspective, this NDA is not deemed ready for approval in its present form until the above-mentioned issues are satisfactorily resolved. As such, OPQ recommends a Complete Response (CR) action from a product quality perspective.

Please refer to the Integrated Quality Review by the Office of Product Quality for further details on these specific deficiencies.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

Please refer to the review written by Dr. Edmund Nesti for details on the nonclinical review of this product.

4.5. Clinical Pharmacology

Please refer to the review written by Dr. Gopichand Gottipati for details on the clinical pharmacology review.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

Table of Clinical Studies

The studies submitted to this application to support the efficacy and safety of AXS-07 for the acute treatment of migraine are described in Table 2 below.

Table 2. Summary of Clinical Trials Contributing to Safety & Efficacy Evaluation

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of subjects enrolled	Study Population	No. of Investigators, Centers and Countries
Controlled Studies to Support Efficacy and Safety								
AXS-07-301 MOMENTUM	03896009	Phase 3, randomized, multicenter, double-blind, active comparator, placebo-controlled, single-dose study treating one *moderate to severe* single migraine attack	AXS-07 (20 mg meloxicam, 10 mg rizatriptan), rizatriptan 10 mg, meloxicam 20 mg, placebo orally once	Primary: pain and most bothersome symptom (MBS) freedom at 2 hours; Safety including: treatment emergent adverse events (TEAEs), vital signs (VS), physical exam (PE)	1 migraine attack, follow up within 1 week	AXS-07 N=441, rizatriptan N=434, meloxicam N=433, placebo N=218	18-65 year old adults with a history of migraine with or without aura and a history of inadequate treatment response. Conducted under a SPA.	87 investigators, 85 clinical sites in US
AXS-07-303 INTERCEPT	04163185	Phase 3, randomized, double-blind, placebo-controlled, single-dose study treating one *mild* single migraine attack.	AXS-07, Placebo orally once	Primary: pain and most bothersome symptom (MBS) freedom at 2 hours; Safety including: treatment emergent adverse events (TEAEs), vital signs (VS), physical exam (PE)	1 migraine attack, follow up within 1 week	AXS-07 N=132, Placebo N=135	18-65 year old adults with a history of migraine with or without aura.	41 investigators in US
Studies to Support Safety								
AXS-07-302	04068051	Open-label, multicenter, long-term safety study	AXS-07 orally, treat all migraine attacks, up to 12 months	Safety, including TEAEs, VS, PE, laboratory and electrocardiogram (EKG)		AXS-07 N=706	18-65 year old adults who participated in a prior AXS-07 study	54 investigators in US
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)								
AXS-07-101	n/a	Phase 1, single center, single-dose, open-label study	AXS-07 orally once	Safety, including TEAEs, VS, PE, laboratory and EKG		AXS-07 N=6	Subjects with a history of migraine	1 site in Canada

5.1. Review Strategy

This is a 505(b)(2) application in which the Applicant submitted data from the listed drugs Anjeso (meloxicam – NDA 219583) and Maxalt (rizatriptan – NDA 020864), two efficacy trials (one in subjects with migraine with moderate to severe pain and one in subjects with migraine with mild pain) and one long-term safety study. A scientific bridge was provided to the LDs allowing for the Applicant to rely on the LDs for the following sections of the label: Drug Interactions, Special Populations, Clinical Pharmacology and Nonclinical Toxicology. The Applicant provided a single study supporting efficacy in subjects with migraine to evaluate the effect of AXS-07 in the treatment of a moderate to severe acute migraine attack. The Applicant relied on the listed drugs to support some safety, as indicated below in Section 8, however the data obtained from the two randomized controlled studies (Studies AXS-07-301 and AXS-07-303) and the open-label long-term safety study (Study AXS-07-302) was used to further inform Section 6 of the proposed label, as pertains to AXS-07 specifically in the acute treatment of migraine.

Study AXS-07-301 was considered the pivotal trial for this application since it utilized the standard study design recommended to support an acute migraine indication (including treatment of a moderate to severe migraine attack and the co-primary endpoints of pain and MBS freedom at 2 hours), as described in the Guidance for Industry: *Developing Drugs for the Acute Treatment of Migraine*. The Study AXS-07-303 was also submitted to this application and this study was designed to demonstrate the efficacy of AXS-07 compared to placebo for the treatment of a migraine attack of mild severity.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. AXS-07-301 (MOMENTUM)

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

6.1.1. Study Design

Overview and Objective

The primary objective of Study AXS-07-301 was 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: pain freedom at 2 hours and MBS freedom at 2 hours. In order to demonstrate a contribution of each component of the combination product to the overall effect, the key secondary

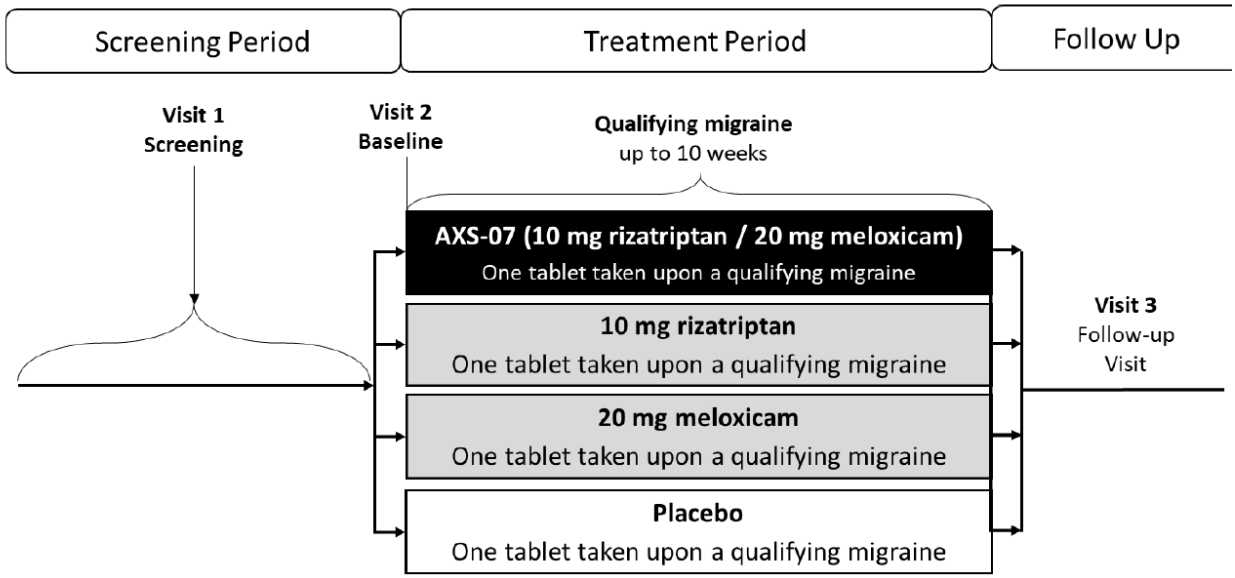
endpoint measured the effect of AXS-07 on sustained headache pain freedom from 2 to 24 hours as compared to each individual component.

Trial Design

Study AXS-07-301 was a phase 3, multicenter, randomized, double-blind, 4-arm, parallel group, single dose, placebo-controlled study to evaluate the safety and efficacy of AXS-07 for the acute treatment of migraine in subjects with migraine with or without aura. Subjects were randomized to one of 4 treatments in a 2:2:2:1 ratio (AXS-07, rizatriptan 10 mg, meloxicam 20 mg or placebo) and instructed to treat one moderate to severe migraine attack within a 12-week period. This study included a 2-week screening period, a 10-week period in which the subjects had to treat a single moderate to severe migraine attack, and a follow-up visit within 1 week (but as soon as possible) of dosing one attack.

This study was conducted under a SPA.

Figure 1. Study AXS-07-301: Study Design



Source: Sponsor's Clinical Study Protocol for Study AXS-07-301, Figure 6.1

Eligibility Criteria

Key Inclusion Criteria

- 18-65 years old
- 1 year history of migraine with or without aura as defined by the ICHD-3, first diagnosed at < 50 years old

- Average of 2 to 8 moderate or severe migraines per month (not more than 10 migraine days per month) over the past 3 months
- History of inadequate response to prior acute migraine treatments, 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 prior 4 weeks at screening

Key Exclusion Criteria

- > 8 migraine attacks in 2 months before screening
- History of cluster headache or other types of migraine
- Chronic daily headache (≥15 days per month in 3 months prior to screening)
- Had confirmed or suspected cardiovascular or cerebrovascular disease
- Had history, symptoms or risk factors for ischemic heart disease, coronary artery vasospasm, arrhythmia, conduction pathway disorder or cardiovascular disease
- If female, taking estrogenic contraceptives and smokes and history of migraine with aura
- Brainstem aura, ophthalmoplegic, or hemiplegic migraine headache or serious neurological condition associated with headache
- Uncontrolled hypertension (diastolic blood pressure > 95 mm Hg or systolic blood pressure > 160 mm Hg)
- Concurrent chronic use of analgesics, narcotic analgesics, steroidal or NSAIDs, tranquilizers, sedatives, antipsychotic drugs, nitrates
- History of significant gastrointestinal disorders

**=The m-TOQ-4 is a 4-item questionnaire developed to assess treatment efficacy based on 4 aspects of response to acute treatment. For additional details, please refer to the separate review in this application, conducted by the Division of Clinical Outcome Assessments (COA) reviewer, Dr. Robert Fieo.*

Reviewer comments: (b) (4) *the Applicant was advised that this is not an acceptable enrichment strategy. An acceptable enrichment strategy would have involved enrolling subjects into a trial with an active comparator arm of an approved therapy, demonstrating lack of an effect of the acute migraine therapy, and then randomizing into a second portion of the study with active study drug and placebo. This study design conducted by this Applicant does not support that this subject population truly does have a lack of inadequate response to prior therapies from documentation of this on the m-TOQ-4 alone.* (b) (4) *per the review by Dr. Fieo, the m-TOQ-4, as used in this trial, had an arbitrary cut-point with no real evidence to support it, was modified from a larger instrument to 4-item instrument (and it is unclear if measurements are still meaningful to subjects), and was originally developed for use in primary care setting, not for the clinical trial space.* (b) (4)

(b) (4)

lease refer to the separate COA review by Dr. Fieo for a complete review of the m-TOQ-4.

It is notable that subjects with uncontrolled hypertension and brainstem aura, ophthalmoplegic and hemiplegic migraine were excluded from this study. This would be a population of concern given the potential for additive cardiovascular risks when combining triptans and NSAIDs.

Statistical Analysis Plan

For Study AXS-07-301, enrolling approximately 250 subjects in each of the active groups and 125 subjects in the placebo group provided 90% power to detect a treatment difference at a 2-sided significance level of 0.05, assuming that the responder rate for pain freedom at Hour 2 was ≤ 15% for placebo and ≥ 29% for AXS-07.

Efficacy Endpoints

Primary endpoint

The co-primary efficacy variables were 1) percentage of subjects with headache pain freedom at 2 hours and 2) percentage of subjects with absence of the MBS (nausea, photophobia, or phonophobia) at 2 hours, and these were used to establish the superiority of AXS-07 over placebo. Pain was rated on a 4-point scale with 0=none, 1=mild, 2=moderate, and 3=severe. MBS freedom was rated with the dichotomous scale (yes/no). To qualify as a responder for headache pain freedom at 2 hours, the pain intensity score at 2 hours must be equal to 0 (none) and to qualify as a responder for absence of the MBS at 2 hours, the MBS scale at 2 hours must be equal to "Absent."

Percentage of responders for each of the co-primary efficacy variables are presented. Between treatment group comparisons were performed via chi-square tests. The differences and the 2-sided 95% Confidence Intervals (CI) of the differences as well as the p-values of the differences are presented. The primary comparison was AXS-07 versus placebo. For completeness, results for all 6 pairs of comparisons are presented.

In the primary analysis, subjects who took rescue medication before 2 hours, or who did not have a 2-hour value were treated as non-responders.

Secondary endpoint

The key secondary efficacy variable was headache pain freedom between 2 and 24 hours (24-hour sustained pain-freedom). This variable was used to establish the superiority of AXS-07 over each of the 2 active components, meloxicam and rizatriptan (i.e., to establish the

contribution of the individual components of AXS-07). To be a responder for the key secondary efficacy variable, the subject must have met all the following conditions:

- All reported pain intensity between 2 and 24 hours must be 0;
- Pain intensity at 2 and 24 hours must be 0;
- Pain intensity must have been available for at least 12 or 16 hours; and
- No rescue medication used through 24 hours.

Subjects who did not meet these requirements were considered non-responders.

Efficacy Analysis Population

There were 1594 subjects randomized in Study AXS-07-301. Efficacy analysis populations were based on the intent to treat (ITT) populations and were determined prior to unblinding. The ITT population (total = 1477 subjects) was defined as all randomized subjects who had a qualifying migraine.

Table 3. Study AXS-07-301: Analysis Populations

	Placebo (n)	Meloxicam 20 mg (n)	Rizatriptan 10 mg (n)	AXS-07 10/20 mg (n)	Total (n)
Randomized	227	455	456	456	1594
Safety	218	433	434	441	1526
Intention to treat	209	421	419	428	1477
Per Protocol	209	419	417	425	1470

Analysis Methods

For detailed analysis methods, please refer to the biostatistics review written by Dr. Jinnan Liu, FDA biostatistician.

All hypothesis testing was conducted at a two-sided significance level of 0.05. Continuous data was summarized using descriptive statistics. Unless otherwise stated, CIs were constructed at the two-sided 95% level. Missing values were not to be imputed.

Sensitivity analyses were performed for the primary analysis and the key secondary endpoint.

Subjects were given headache diaries to record the severity of the headache, presence or absence of associated symptoms, functional disability, and Patient-Global Impression of Change (PGI-C) scores. Subjects were instructed to complete the diary for 48 hours after treating the first migraine that occurred after randomization that involved study drug dosing.

Multiplicity Adjustment

There were three main objectives for this study – to establish superiority of AXS-07 over placebo on the co-primary efficacy variables, to establish superiority of AXS-07 over meloxicam as the key secondary efficacy variable, and to establish the superiority of AXS-07 over rizatriptan on the key secondary efficacy variable.

To control for the above at a two-sided significance level of 0.05, the null hypothesis for the four objectives (including the two co-primary endpoints for the first objective) was tested at the stated step-down hierarchical fashion.

If the first 4 objectives were met, then the study also had the following pre-specified key secondary claims (in order):

1) Superiority of AXS-07 over placebo based on percentage of subjects with pain relief at 2 hours

2) Superiority of AXS-07 over placebo based on time to pain relief

3) Superiority of AXS-07 over placebo based on percentage of subjects able to perform normal daily activities at 2 hours (defined as a reduction to none on the functional disability scale, for those who reported greater than none at baseline)

4) Superiority of AXS-07 over rizatriptan based on percentage of subjects with pain relief at 2 hours

Protocol Amendments

This study was conducted under an agreed SPA with no protocol amendments submitted to the IND.

6.1.2. Study Results

Compliance with Good Clinical Practices

Per the Applicant, the study was designed and monitored in accordance with Axsome's procedures, which comply with the ethical principles of Good Clinical Practice (GCP) as required

by regulatory authorities, and in accordance with the Declaration of Helsinki.

Financial Disclosure

The Applicant stated that there were no Principal Investigators with reportable financial disclosures. Please see Section 13.2 for financial disclosures.

Subject Disposition

Subject disposition is summarized in the table below. Reasons for discontinuation were balanced across groups.

Table 4. Study AXS-07-301: Summary of Study Discontinuation and Reasons for Discontinuation (Randomized Population)

End of Study Status	Placebo (N=227)	Rizatriptan (N=456)	Meloxicam (N=455)	AXS-07 (N=456)
Completed	218 (96.0%)	434 (95.2%)	433 (95.2%)	441 (96.7%)
Discontinued	9 (4.0%)	22 (4.8%)	22 (4.8%)	15 (3.3%)
Reason for Discontinuation				
Screen Failure	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)
Failure to meet continuation criteria	3 (1.3%)	5 (1.1%)	7 (1.5%)	7 (1.5%)
Withdrawal by subject	0 (0.0%)	3 (0.7%)	1 (0.2%)	0 (0.0%)
Lost to Follow-up	1 (0.4%)	3 (0.7%)	3 (0.7%)	1 (0.2%)
Other	5 (2.2%)	11 (2.4%)	10 (2.2%)	6 (1.3%)

Source: Applicant provided table from CSR for Study AXS-07-301 (Table 14.1.4.1.)

Protocol Violations/Deviations

Protocol deviations were reviewed and were generally balanced across arms (refer to Table 5 below for details) with <1% of subjects in any group taking a rescue medication prior to 2 hours.

Table 5. Study AXS-07-301: Summary of Major Deviations by Category (Randomized Population)

Deviation Category	Placebo (N=227)	Rizatriptan (N=456)	Meloxicam (N=455)	AXS-07 (N=456)
Exclusion Criteria	0	3 (0.7%)	2 (0.4%)	2 (0.4%)
Inclusion Criteria	0	0	1 (0.2%)	2 (0.4%)

Missing Endpoint Assessment	9 (4.0%)	21 (4.6%)	25 (5.5%)	15 (3.3%)
Rescue medication	2 (0.9%)	1 (0.2%)	2 (0.4%)	2 (0.4%)
Study Treatment Administration	9 (4.0%)	14 (3.1%)	11 (2.4%)	12 (2.6%)

Source: Applicant provided table (reformatted) from CSR for Study AXS-07-301 (Table 14.5.1.)

Demographic Characteristics

Demographic characteristics were balanced across groups and representative of the mostly White and female population with an average age of 41. This is the common demographic in clinical trials for migraine (Robbins and Bernat, 2017). There were few subjects over 60 and no subjects over 65.

Table 6. Study AXS-07-301: Demographic characteristics of the primary efficacy analysis (Safety population)

Subgroup	**Placebo (N = 218) n (%)**	**Meloxicam 20 mg (N = 433) n (%)**	**Rizatriptan 10 mg (N = 434) n (%)**	**AXS07 10/20 mg (N = 441) n (%)**
Sex				
Female	185 (84.9)	363 (83.8)	366 (84.3)	357 (81.0)
Male	33 (15.1)	70 (16.2)	68 (15.7)	84 (19.0)
Age				
Mean	41.0	41.06	41.59	41.2
Standard Deviation	11.71	12.14	10.74	11.64
Minimum	18	18	18	18
Median	42	41	42	41
Maximum	65	67	64	65
Age Group				
Age < 20	4 (1.8)	7 (1.6)	3 (0.7)	9 (2.0)
Age 20 ≤ and < 40	95 (43.6)	192 (44.3)	185 (42.6)	191 (43.3)
Age 40 ≤ and < 60	107 (49.1)	198 (45.7)	229 (52.8)	220 (49.9)
60 +	12 (5.5)	36 (8.3)	17 (3.9)	21 (4.8)
Race				
American Indian or Alaska Native	1 (0.5)	2 (0.5)	2 (0.5)	4 (0.9)
Asian	4 (1.8)	9 (2.1)	6 (1.4)	9 (2.0)
Black or African American	47 (21.6)	88 (20.3)	84 (19.4)	75 (17.0)
Other	6 (2.8)	4 (0.9)	7 (1.6)	8 (1.8)
White	160 (73.4)	330 (76.2)	335 (77.2)	345 (78.2)

Subgroup	Placebo (N = 218) n (%)	Meloxicam 20 mg (N = 433) n (%)	Rizatriptan 10 mg (N = 434) n (%)	AXS07 10/20 mg (N = 441) n (%)
Ethnicity				
Hispanic or Latino	61 (28.0)	108 (24.9)	114 (26.3)	113 (25.6)
Missing	0 (0.0)	3 (0.7)	1 (0.2)	3 (0.7)
Not Hispanic or Latino	157 (72.0)	322 (74.4)	319 (73.5)	325 (73.7)
Region				
United States	218 (100.0)	433 (100.0)	434 (100.0)	441 (100.0)

Source: Reviewer analyses, confirming Applicant's analyses.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

In AXS-07-301, all subjects reported a history of migraine. Migraine characteristics included the following: the most bothersome symptom as light sensitivity (59%), nausea (19%) and sound sensitivity (19%), and 6.9% reported using a migraine preventive medication and 7.5% reported menstrual migraines. These data were similar across all treatment arms. Allodynia was reported in 75.4% of subjects.

Medical history included a history of seasonal allergies in 27.4% of subjects, followed by anxiety in 16% and gastroesophageal reflux disease, depression and headache in 13% each. Twelve percent of subjects reported hypertension, 3% reported hypercholesterolemia and 3% reported diabetes mellitus (type 2). The percent of subjects with cardiovascular risk factors is overall low.

The Applicant collected the m-TOQ-4 scores at baseline and the mean score was 3.6 points. Greater than 70% of subjects reported allodynia on the 12-item Allodynia Symptom Checklist (ASC-12) (score ≥3) at baseline, with scores of 3-5 indicated mild allodynia, scores of 6-8 indicating moderate allodynia and scores greater than 9 indicating severe allodynia.

Concomitant Medications

In AXS-07-301, many subjects in the safety population reported taking concomitant medications. The following were the most reported or pertinent concomitant medications:

- 7% reported taking rizatriptan for migraines
- ~1% reported taking meloxicam for migraines
- 42% of subjects reported taking ibuprofen for migraine and 43.1% for a concomitant medical condition
- 36% of subjects reported taking a combination of aspirin, caffeine and acetaminophen for migraines
- 25% reported taking sumatriptan for migraines
- 3% reported taking a combination of butalbital, caffeine and acetaminophen for

migraine
- ~6% reported taking topiramate for migraine, and ~1% reported amitriptyline for migraine

Data Quality and Integrity

There were no significant issues with data quality or integrity that arose during the review of this application.

Efficacy Results – Primary Endpoint

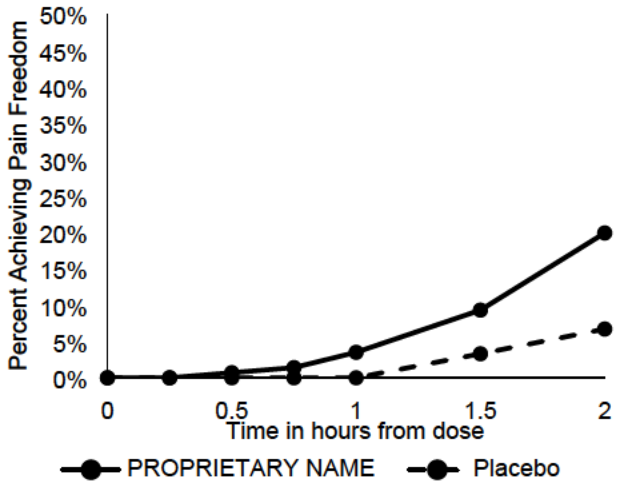
The following table presents the primary efficacy data. The study drug, AXS-07, demonstrated statistically significant treatment differences compared to placebo on the prespecified co-primary endpoints of pain freedom at 2 hours and MBS freedom at 2 hours. Numerically, the proportion of responders in the AXS-07 arm were similar to the rizatriptan arm for both of these co-primary endpoints.

Table 7. Study AXS-07-301: Co-Primary Efficacy Endpoint

Co-Primary Endpoint	Placebo (N=209)	Meloxicam 20 mg (N=421)	Rizatriptan 10 mg (N=419)	AXS-07 (N=428)
2-hour Pain Freedom	14 (6.7%)	49 (11.6%)	73 (17.4%)	85 (19.9%)
Difference from placebo	-	4.9%	10.7%	13.2%
P value vs placebo	-	.0516	<.001	<.001
2-hour MBS Freedom	51 (24.4%)	137 (32.5%)	150 (35.8%)	158 (36.9%)
Difference from placebo	-	8.1%	11.4%	12.5%
P value vs placebo	-	.0355	0.0039	0.002

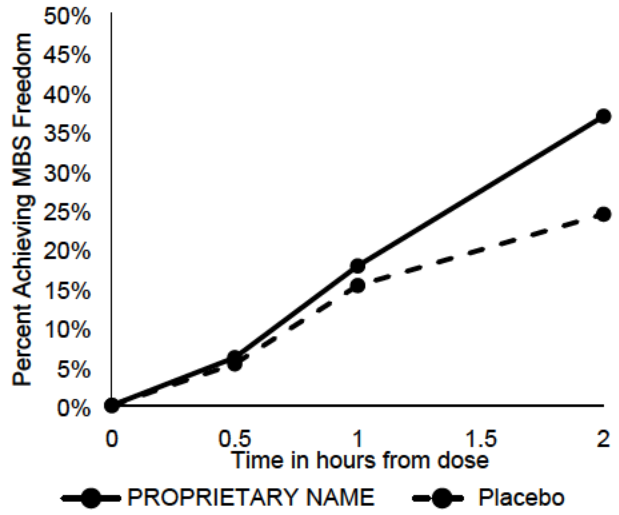
p value from Chi-square test.
Source: Analysis conducted by statistical reviewer, Dr. Liu.

Figure 2. Study AXS-07-301: Percentage of Subjects Achieving Pain Freedom Over Time



Source: Applicant provided figure in proposed label.

Figure 3. Study AXS-07-301: Percentage of Subjects Achieving MBS Freedom Over Time



Source: Applicant provided figure in proposed label.

Reviewer comments: The Applicant met the prespecified primary endpoint of pain and MBS freedom at 2 hours comparing AXS-07 to placebo. There was no apparent difference on this endpoint when comparing AXS-07 to rizatriptan (p=0.363, not in table), though there was a numerical and statistical difference when comparing AXS-07 to meloxicam (p=.001, not in table). The figures above can also be included in proposed labeling.

To demonstrate the benefit of the fixed-dose combination over either component alone, the Applicant also had to demonstrate component contributions of these two products to the fixed

dose to-be-marketed product. This was examined using the key secondary endpoint of sustained pain freedom from 2-24 hours after product administration (see below) comparing AXS-07 to each component (meloxicam and rizatriptan separately).

Missing Data and Sensitivity Analyses

The overall missing data for the primary endpoints was relatively low for each arm of this study, and relatively balanced across arms. Missing data rate was <5% for each arm in the study with 3.3% missing in the AXS-07 and placebo arms. In the primary analysis, missing data was treated as a treatment failure.

The Applicant performed sensitivity analyses, including a Multiple Imputation analysis, and a more conservation imputation assuming the "worst case" scenario, and this produced similar efficacy results as the primary analysis. For details on the sensitivity analyses, please refer to the review by Dr. Liu.

Efficacy Results – Secondary and other relevant endpoints

The trial met the key secondary outcome measure of 24 hours sustained pain relief of AXS-07 compared to each component of AXS-07 (meloxicam and rizatriptan). Though, the difference in treatment effect was smaller when AXS-07 was compared to rizatriptan, it was statistically significant (p=0.038, 5.1% difference between AXS-07 and rizatriptan) and likely clinically meaningful.

Table 8. Study AXS-07-301: Key Secondary Endpoint (ITT Population)

Secondary Endpoints	Placebo (N=209) (n, %)	Meloxicam 20 mg (N=421) (n, %)	Rizatriptan 10 mg (N=419) (n, %)	AXS-07 (N=428) (n, %)
24-hour Sustained Pain Freedom (Key secondary)	11 (5.3%)	37 (8.8%)	47 (11.2%)	69 (16.1%)
P value vs AXS-07	<.001	0.001	0.038	-
Pain relief at 2 hours	114 (54.5%)	261 (62.0%)	275 (65.6%)	296 (69.2%)
P value vs placebo	-	0.028	0.274	<.001

Since both co-primary endpoints and the key secondary endpoint was met, the next set of endpoints in the hierarchy were analyzed. The first endpoint in the hierarchy was time to pain relief comparing AXS-07 to placebo. Median time to pain relief was reported by the Applicant to be 1.5 hours for AXS-07 and 4 hours for both the meloxicam and rizatriptan arms (data not shown), compared to 12 hours for placebo.

Reviewer comments: The data as presented in the table below (as median time to pain relief) is misleading. Intervals varied from 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 12, 16, and 24 hours, and 75.2% in the AXS-07 group had pain relief at one or more of the 10 timepoints compared to the placebo group (53.1%.) Presenting this data as the median (as below) is misleading and a Kaplan-Meier plot of time to pain relief is more informative (Figure 4).

The pre-specified second endpoint in the hierarchy was pain relief at 2 hours comparing AXS-07 to placebo only. This endpoint showed AXS-07 was superior to placebo and this difference was statistically significant. Including this information may be helpful in labeling, to help with cross drug comparisons since prior approvals did use pain relief (and not pain freedom) as the primary endpoint.

The fourth pre-specified endpoint of "able to perform normal daily activities" based on a 4-point disability scale was a comparison of AXS-07 to placebo. The endpoint did demonstrate superiority over placebo.

Table 9. Study AXS-07-301: Secondary Endpoints (ITT Population), Selected Arms

Secondary Endpoints	Placebo (N=209) (n, %)	AXS-07 (N=428) (n, %)
Time to pain relief (median)	12 hours	1.5 hours
P value vs placebo	-	<.001
Able to perform normal daily activities based on scale at 2 hours	21.1%	32.0%
P value vs placebo	-	.004
48-hour Sustained Pain Freedom*	11 (5.3%)	66 (15.4%)
P value vs placebo	-	<.001

*Not controlled for multiple comparisons.

Reviewer comments: Pain relief is a lower bar to reach than pain freedom and the treatment effect in this trial is still in line with older approvals (e.g., triptan products like rizatriptan) which used pain relief as the primary endpoint. This could be included in the label. While many of the secondary endpoints were statistically significant compared to placebo, it is likely more important to subjects to be completely free of pain (pain freedom) than just relieved of pain, so a more clinically relevant endpoint is time to pain freedom.

The benefit of the fixed-dose combination product is primarily due to the benefit on 24-hour

sustained pain freedom as per the key secondary endpoint results noted above.

Of note, though sustained 24-hour pain freedom was prespecified to be the endpoint to demonstrate component contribution, the fixed dose combination would also be expected to not worsen MBS symptoms through the 24-hour timepoint. This analysis was conducted and presented in the table below. Though differences between AXS-07 and individual components were not statistically significant (nor were they powered to be), AXS-07 did not worsen MBS symptoms compared to individual components up to 4 hours post dose.

Table 10. Study AXS-07-301: Other Endpoints

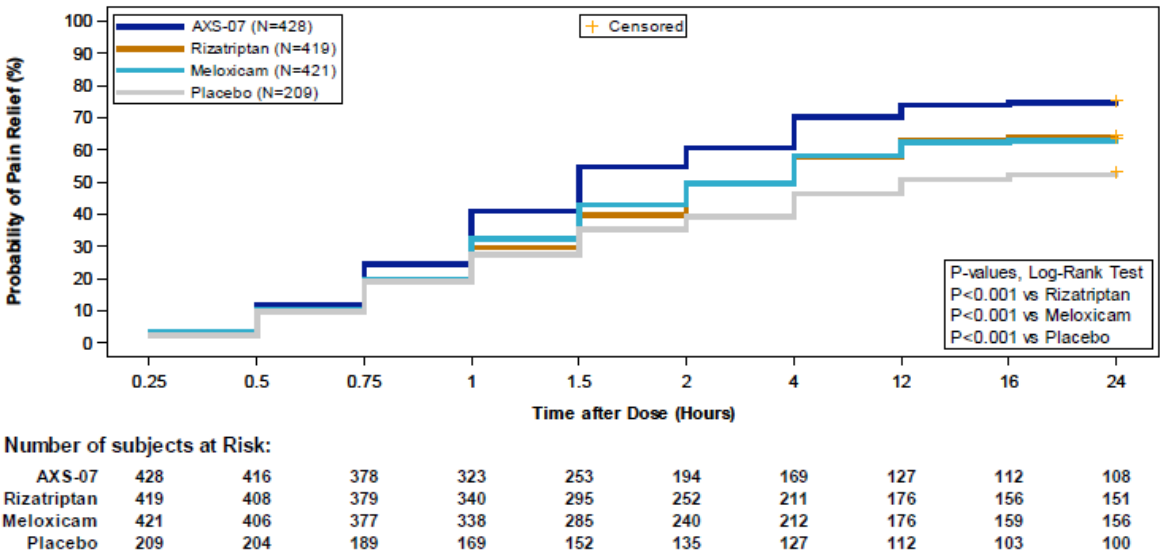
Endpoint	Placebo (N=209) (n, %)	Meloxicam 20 mg (N=421) (n, %)	Rizatriptan 10 mg (N=419) (n, %)	AXS-07 (N=428) (n, %)
MBS Freedom @ 2 hours	24.4%	32.5%	35.8%	36.9%
P value vs AXS-07	<.001	0.123	0.290	-
MBS Freedom @ 4 hours	35.9%	47.7%	49.4%	53.0%
P value vs AXS-07	<.001	0.123	0.290	-

*Not controlled for multiple comparisons.

The Kaplan-Meier plot provided by the Applicant (Figure 4) demonstrates the time to pain relief for the four treatment arms. There is a clear separation between AXS-07 and other treatment arms. However, this endpoint is measuring pain relief and a lower bar to reach than pain freedom. If the Applicant is including a graph in the label of the co-primary endpoint of pain

freedom at 2 hours, this plot would not offer much additional information. From a clinical standpoint, it is not informative and duplicative of the primary endpoint.

Figure 4. Study AXS-07-301: Kaplan Meier - Plot Time to Pain Relief



Number of subjects at Risk:

AXS-07	428	416	378	323	253	194	169	127	112	108
Rizatriptan	419	408	379	340	295	252	211	176	156	151
Meloxicam	421	406	377	338	285	240	212	176	159	156
Placebo	209	204	189	169	152	135	127	112	103	100

Source: Figure 4 in CSR, verified by statistical reviewer, Dr. Liu.

Dose/Dose Response

A dose response was not evaluated. The dose selection is discussed in detail below in Section 7.1, summarizing that the rationale for pursuing the 20 mg dose of meloxicam was not clearly supported by data from a post-surgical population. The dose for rizatriptan 10 mg is the highest approved dose and has a clear justification. The higher dose of meloxicam did demonstrate efficacy for this indication as the endpoints above indicated. The long-term safety of chronic, intermittent administration of meloxicam at this higher dose was evaluated in a required long-term safety study (Results in Section 8).

Durability of Response

The durability of the response was measured by sustained pain freedom at 24 hours and 48 hours as demonstrated in Table 8. Both measures demonstrated that the pain freedom that was achieved at 24 hours was maintained out to at least 48 hours in most subjects, with differences that demonstrated superiority of AXS-07 compared to other treatment groups. The persistence of the effect was also measured by the exploratory endpoint of headache pain recurrence or relapse as measured at 48 hours. Per the Applicant's analyses, in the AXS-07 arm, 21.2% of subjects who were pain free at 2 hours had relapse of headache pain within 48 hours, compared to 26.5% in the meloxicam group (p=0.001) and 45.2% in the rizatriptan arm

(p=0.037).

Rescue medication use, which would signify incomplete response to acute migraine treatment, was assessed by the Applicant as an exploratory endpoint. Rescue medication use (within 24 hours of study drug administration) was reported in 23.0% of subjects in the AXS-07 arm, 43.5% of subjects in the placebo arm, 35.1% in the meloxicam arm and 34.7% in the rizatriptan arm.

Reviewer comments: There was a higher responder rate of subjects with pain freedom at 24 and 48 hours in the AXS-07 arms compared to the meloxicam and rizatriptan arms and this was also reflected in a decreased relapse rate at 48 hours in the AXS-07 treated subjects. Though pain freedom and MBS freedom rates were similar in the AXS-07 and rizatriptan arms, pain relapse at 48 hours occurred at almost twice the rate in the rizatriptan arm compared to AXS-07. Though this is an exploratory endpoint, it does suggest that the initial effects of achieving pain freedom with AXS-07 may be more durable than those of rizatriptan alone.

Rescue medication use as an indicator of incomplete response and lack of durability of the response, demonstrated a higher numerical percentage in the placebo, meloxicam and rizatriptan arms, compared to AXS-07. Though this was an exploratory endpoint, these differences are likely clinically meaningful and could be described in the label (without including p values).

6.2 AXS-07-303 (INTERCEPT)

The INTERCEPT (Initiating Early Control of Migraine Pain and Associated Symptoms) Study: 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.

6.2.1. Study Design

Overview and Objective

The primary objective of Study AXS-07-303 was to evaluate the effect of AXS-07 as compared to placebo in the acute treatment of migraine headache in adults in the treatment of a migraine attack (at first onset of migraine pain and at the mild pain stage), as evaluated by the following: pain freedom at 2 hours and MBS freedom at 2 hours.

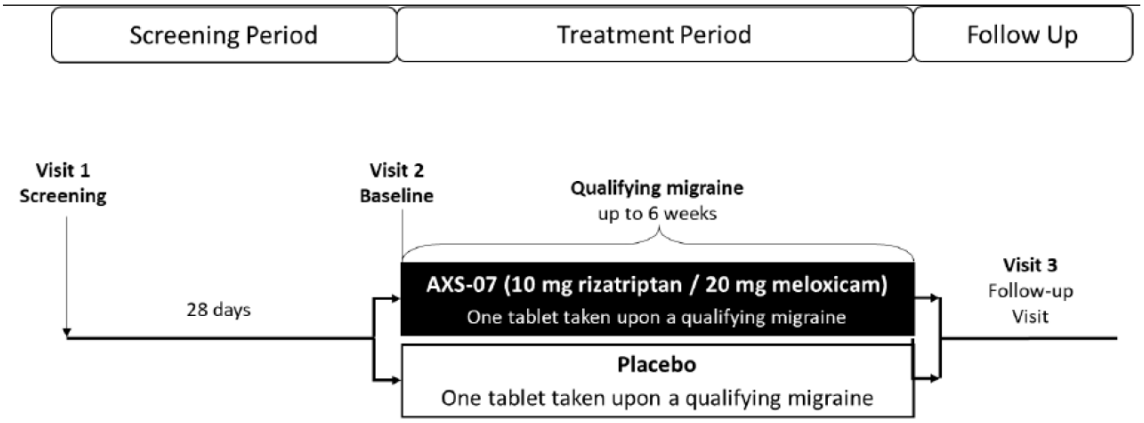
Trial Design

Study AXS-07-303 was a phase 3, multicenter, randomized, double-blind, 2-arm, parallel group, single dose and placebo-controlled study to evaluate the safety and efficacy of AXS-07 for the acute treatment of mild migraine in subjects with episodic migraine with or without aura (≤ 8 migraines per month). Subjects were randomized in a 1:1 ratio (AXS-07 or placebo) and

instructed to treat one mild migraine attack within a 6-week period. This study included a 4-week screening period, a 6-week period in which the subjects had to treat a single mild migraine attack, and a follow-up visit within 1 week of dosing one attack (but as soon as possible). Subjects were instructed to treat early in the migraine attack (at the mild stage).

Reviewer comments: Unlike Study AXS-07-301, this study was not conducted under a SPA and subjects were instructed to treat a mild migraine attack, which is not typical of trials to investigate the acute treatment of migraine (in which a moderate to severe migraine attack is treated). However, early treatment of migraine is often recommended, so the data from this trial was evaluated to determine if early treatment during a migraine attack would be beneficial to subjects (Lipton, Stewart, Stone et al, 2000). Data from this trial was also evaluated as part of the safety review (Section 8).

Figure 5. Study AXS-07-303: Study Design



Source: Sponsor's Clinical Study Protocol for Study AXS-07-303, Figure

Eligibility Criteria

Key Inclusion Criteria

- Same as Study AXS-07-301 (see Section 6.1.1. above) except a history of inadequate response to prior acute migraine treatments was not required

Key Exclusion Criteria

- Similar to Study AXS-07-301

Statistical Analysis Plan

For Study AXS-07-303, the Applicant asserted that enrolling approximately 150 subjects per

group would provide 90% power to detect a treatment difference at a 2-sided significance level of 0.05, assuming that the responder rate for pain freedom at Hour 2 was ≤15% for placebo and ≥29% for AXS-07.

Efficacy Endpoints

Primary endpoint

The co-primary efficacy endpoints were 1) percentage of subjects with headache pain freedom at 2 hours and 2) percentage of subjects with absence of the MBS (nausea, photophobia, or phonophobia) at 2 hours, and these were used to establish the superiority of AXS-07 over placebo. Pain was rated on a 4-point scale with 0=none, 1=mild, 2=moderate, and 3=severe. MBS freedom was rated with the dichotomous scale (Present/Absent). To qualify as a responder for headache pain freedom at 2 hours, the pain intensity score at 2 hours had to be equal to 0 (none) and to qualify as a responder for absence of the MBS at 2 hours, the MBS scale at 2 hours must be equal to "Absent." In the primary analysis, subjects who took rescue medication before 2 hours or who did not have a 2-hour value were treated as non-responders.

The results are presented as the percentage of responders for each of the co-primary efficacy endpoints. Between treatment group comparisons were performed via chi-square tests. The differences and the 2-sided 95% CI of the differences as well as the p-values of the differences are presented. The primary comparison was AXS-07 versus placebo.

Secondary endpoints

The secondary endpoints were examined in hierarchical order to adjust for multiplicity and included the following:

- The key secondary efficacy variable was the ability to perform normal activity (functional disability was "none") at 2 hours and the time to headache pain freedom. Functional disability was measured by a 4-point rating scale; none, mild, moderate, or severe and was recorded by the subject in the headache diary
- Percentage of subjects with headache pain freedom over time
- Average pain intensity over time
- Percentage of subjects with headache pain freedom between 2 and 24 hours (24 hour sustained pain freedom)
- Percentage of subjects with headache pain freedom between 2 and 48 hours (48 hour sustained pain freedom)
- Other endpoints, including sustained pain relief, variations on the time points to pain freedom, pain relapse, time to pain freedom, time to pain worsening and functional disability, MBS freedom, rescue medication use, and PGI-C scores measured at various time points

Efficacy Analysis Population

Efficacy analysis populations were based on the intent to treat (ITT) populations and were determined prior to unblinding. The ITT population in both controlled studies was defined as all randomized subjects who had a qualifying migraine, which was rated with a pain intensity of 1 (mild) on a 4-point scale (0-none, 1-mild, 2-moderate, 3-severe).

The Safety Population included all subjects who received study drug. Analyses based on this population grouped subjects according to the treatment they actually received regardless of the treatment they were randomized to receive. All safety analyses used the Safety Population.

Analysis Methods

For detailed analysis methods, please refer to the biostatistical review written by Dr. Liu.

Protocol Amendments

This study had one protocol amendment submitted December 13, 2019, in which the following changes were made: the name of the trial was changed to reflect treating a migraine attack of mild intensity, a baseline assessment of migraine disability was included using the Migraine Disability Assessment (MIDAS), and it was clarified that study drug was to be taken at first onset of migraine pain (not at the onset of moderate to severe pain).

6.2.2. Study Results

Compliance with Good Clinical Practices

Per the Applicant, the study was designed and monitored in accordance with Axsome's procedures, which comply with the ethical principles of Good Clinical Practice (GCP) as required by regulatory authorities, and in accordance with the Declaration of Helsinki.

Financial Disclosure

The Applicant stated that there were no Principal Investigators with reportable financial disclosures. Please see Section 13.2 for financial disclosures.

Subject Disposition

Table 11. Study AXS-07-303: Subject Disposition

End of Study Status	Placebo (N=150)	AXS-07 (N=152)
Completed	143 (95.3%)	140 (92.1%)
Discontinued	7 (4.7%)	12 (7.9%)
Reason for Discontinuation		
Lost to Follow-up	0 (0%)	1 (0.7%)
No qualified migraine	6 (4.0%)	7 (4.6%)
Protocol Deviation	0 (0%)	2 (1.3%)
Withdrawal by subject	1 (0.7%)	2 (1.3%)

Source: Applicant provided analysis from CSR for Study AXS-07-303 (Table 14.1.5.)

Protocol Violations/Deviations

Major protocol deviations were classified and documented by the Applicant before database lock. In Study AXS-07-303, major protocol deviations from entry criteria and treatment compliance were summarized as far as they could be extracted from numeric or coded study data. A total of 23 subjects had a major protocol deviation, 12 (7.9%) subjects in the AXS-07 group and 11 (7.3%) subjects in the placebo group. The deviations resulted from missing endpoint assessments or with subjects taking study treatment without being prompted to do so by the electronic diary.

Demographic Characteristics

The demographic characteristics of Study AXS-07-303 are summarized below. The characteristics are similar to Study AXS-07-301 and balanced across treatment arms.

Table 12. Study AXS-07-303: Demographic Characteristics (Safety Population)

Subgroup	AXS-7 10/20 mg (N = 140) n (%)	Placebo (N = 143) n (%)	Total (N = 283) n (%)
Sex			
Female	119 (85.0)	122 (85.3)	241 (85.2)
Male	21 (15.0)	21 (14.7)	42 (14.8)
Age			
Mean	41.73	41.42	41.57
Standard Deviation	11.58	10.67	11.11
Minimum	19	19	19
Median	43	41	42
Maximum	63	65	65
Age Group			
Age < 20	1 (0.7)	1 (0.7)	2 (0.7)
Age 20 ≤ and < 40	56 (40.0)	63 (44.1)	119 (42.0)
Age 40 ≤ and < 60	75 (53.6)	73 (51.0)	148 (52.3)
Age 60 +	8 (5.7)	6 (4.2)	14 (4.9)
Race			
American Indian or Alaska Native	2 (1.4)	0 (0.0)	2 (0.7)
Asian	1 (0.7)	7 (4.9)	8 (2.8)
Black or African American	18 (12.9)	17 (11.9)	35 (12.4)
Other	1 (0.7)	3 (2.1)	4 (1.4)
White	118 (84.3)	116 (81.1)	234 (82.7)
Ethnicity			
Hispanic or Latino	48 (34.3)	35 (24.5)	83 (29.3)
Missing	0 (0.0)	1 (0.7)	1 (0.4)
Not Hispanic or Latino	92 (65.7)	107 (74.8)	199 (70.3)
Region			
United States	140 (100.0)	143 (100.0)	283 (100.0)

Source: Reviewer analysis using MAED software.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Among subjects who selected a MBS, the most common selected symptom was photophobia, followed by nausea and phonophobia. Disease characteristics included a mean monthly migraine frequency of 4.6 (SD 1.67) migraines per month, and a mean baseline Migraine Disability Assessment (MIDAS) score of 21.9 in the placebo group and 25.8 in the AXS-07 group. This suggests that migraine associated disability might have been slightly higher in the AXS-07-treated group compared to placebo.

Data Quality and Integrity

There were no significant issues with data quality or integrity that arose during the review of this application.

Analysis Sets

The analysis sets included 302 subjects randomized, 283 subjects in the safety set and 267 subjects in the ITT population.

Efficacy Results – Primary Endpoint

The co-primary endpoints of pain and MBS freedom at 2 hours demonstrated that AXS-07 was superior to placebo.

Table 13. Study AXS-07-303: Primary Endpoint Analysis

Co-Primary Endpoint	Placebo (N=135)	AXS-07 (N=132)
2-hour Pain Freedom	16.3%	32.6%
Difference from placebo	-	16.3%
P value vs placebo	-	0.002
2-hour MBS Freedom	26.7%	43.9%
Difference from placebo	-	17.2%
P value vs placebo	-	0.003

Source: FDA statistician.

Efficacy Results – Sensitivity Analyses and Secondary Endpoints

Sensitivity analyses (in which placebo subjects with missing 2-hour values were treated as responder and AXS-07 treated subjects were missing 2-hour values were treated as non-responders) demonstrated similar results. Overall, missing data rates were low and similar across groups. Please see Dr. Liu's review for additional details.

The key secondary endpoints for this study, in hierarchical order, were the ability to perform normal activity (functional disability = none) at 2 hours and time to headache pain freedom. The percentage of subjects reporting they were able to perform normal activity at 2 hours (ITT) was 38.6% in the AXS-07 treated group compared to 31.1% in the placebo treated group (p = 0.197). Since this test (for the first of the two prespecified key secondary endpoints) was not significant, the testing stopped.

The results of key secondary efficacy endpoints were not clinically meaningful or statistically significant. There were numerous other secondary endpoints, but these were not evaluated in detail due to the tests not being significant for the first of the two key secondary endpoints (i.e. testing stopped).

Reviewer comments: The first key secondary endpoint tested was not significant, so other endpoints were not examined. The Applicant could have designed the trial to prespecify other endpoints, such as the proportion of subjects with headache pain freedom at 24 hours or at 48 hours or the proportion of subjects requiring a rescue medication in the first 24 hours, in the hierarchy.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

To demonstrate efficacy, AXS-07 had to demonstrate superiority of AXS-07 to placebo in the treatment of an acute migraine attack of moderate to severe intensity. To demonstrate efficacy, the agreed endpoints were pain and MBS freedom at 2 hours. To satisfy the requirements of 21 CFR § 300.50 Fixed-combination prescription drugs for humans, AXS-07 had to demonstrate superiority versus its individual components, rizatriptan and meloxicam. To demonstrate component contribution, the agreed efficacy endpoint was "sustained pain freedom 2-24 hours" defined as no pain at 2 hours, no relapse of pain (to mild, moderate, or severe) and no use of rescue medication during the 24-hour period after dosing.

7.1.1. Primary Endpoints

Study AXS-07-301 examined the effect of one dose of AXS-07 compared to placebo on the rates of pain freedom and MBS freedom at 2 hours after treatment of a moderate to severe migraine attack. Study AXS-07-303 had the same primary endpoints, but subjects were instructed to treat a mild migraine attack. Both studies demonstrated a benefit of AXS-07 compared to placebo on these co-primary endpoints.

7.1.2. Secondary and Other Endpoints

In Study AXS-07-301, the key secondary endpoint of sustained pain freedom 2-24 hours after study drug administration demonstrated superiority of AXS-07 over meloxicam and rizatriptan and is further evidence of the therapeutic benefit of this fixed dose combination product compared to its individual components. Several prespecified secondary endpoints were also met in this pivotal study to support the efficacy of AXS-07, including pain relief at 2 hours, and percentage of subjects reporting normal function at 2 hours. In Study AXS-07-303, the secondary endpoints were the ability to perform normal activity (functional disability = none) at 2 hours and time to headache pain freedom and neither of these were met.

7.1.3. Subpopulations

Subgroup analyses on the primary and key secondary endpoints were assessed. The analyses of the co-primary endpoints by sex demonstrate that the differences from placebo remained statistically significant for females, with less of a difference (numerically) between groups for Study AXS-07-303. The results for Study AXS-07-301 remain numerically different for both co-primary endpoints in male subjects.

Table 14. Pooled Controlled Studies: Subgroup Analyses – Primary Endpoint of Pain Freedom at 2 Hours, by Sex

Sex	Study ID	Result	AXS-07 (N=560)	Placebo (N=344)	Proportion Difference (%) (95% CI) (AXS-07-Placebo)	p-value
Female	AXS-07-301	Responder	62 (17.9)	12 (6.8)	11.1 (5.7, 16.6)	<0.001
		Total	346	177		
	AXS-07-303	Responder	41 (36.3)	20 (17.4)	18.9 (7.6, 30.1)	0.001
		Total	113	115		
	Pooled	Responder	103 (22.4)	32 (11.0)	13.7 (8.5, 18.9)	<0.001
		Total	459	292		
Male	AXS-07-301	Responder	23 (28.0)	2 (6.3)	21.8 (9.0, 34.6)	0.012
		Total	82	32		
	AXS-07-303	Responder	2 (10.5)	2 (10.0)	0.5 (-18.5, 19.6)	0.957
		Total	19	20		
	Pooled	Responder	25 (24.8)	4 (7.7)	15.5 (4.2, 26.7)	0.022
		Total	101	52		

CI=confidence interval; ITT=intent-to-treat; N=total number.
Source: Applicant provided table (Table 39 of Summary of Clinical Efficacy), confirmed by Dr. Liu.

Reviewer comments: AXS-07-303 was a smaller study with fewer male subjects enrolled overall and this may be driving the inability to detect a difference between groups in many of the above subgroup analyses.

Table 15. Pooled Controlled Studies: Analysis of MBS Freedom at 2 Hours, by Sex

Sex	Study ID	Result	AXS-07 (N=560)	Placebo (N=344)	Proportion Difference (%) (95% CI) (AXS-07-Placebo)	p-value
Female	AXS-07-301	Responder	125 (36.1)	45 (25.4)	10.7 (7.2, 18.8)	0.013
		Total	346	177		
	AXS-07-303	Responder	54 (47.8)	31 (27.0)	20.8 (8.6, 33.1)	0.001
		Total	113	115		
	Pooled	Responder	179 (39.0)	76 (26.0)	14.0 (7.2, 20.8)	<0.001
		Total	459	292		
Male	AXS-07-301	Responder	33 (40.2)	6 (18.2)	21.5 (4.3, 38.7)	0.030
		Total	82	32		
	AXS-07-303	Responder	4 (21.1)	5 (25.0)	-3.9 (-30.3, 22.4)	0.773
		Total	19	20		
	Pooled	Responder	37 (36.3)	11 (20.8)	13.9 (-1.0, 28.8)	0.085
		Total	101	52		

CI=confidence interval; ITT=intent-to-treat; N=total number.
Source: Applicant provided table (Table 40 of Summary of Clinical Efficacy), confirmed by Dr. Liu.

The Applicant analyzed the co-primary endpoints by race and the results of the analysis on pain freedom is presented below. The analysis of MBS freedom at 2 hours is not included, as results are similar. The analyses of the co-primary endpoints by race only demonstrate a numerical difference in the White population. These analyses were not powered to demonstrate a statistically significant difference. There were too few subjects of other races to determine how AXS-07 works in populations other than White subjects.

Table 16. Pooled Controlled Studies: Analysis of Pain Freedom at 2 Hours, by Race

Sex	Study ID	Result	AXS-07 (N=560)	Placebo (N=344)	Proportion Difference (%) (95% CI) (AXS-07-Placebo)	p-value
White	AXS-07-301	Responder	76 (22.6)	9 (5.8)	16.7 (10.9, 22.5)	<0.001
		Total	337	154		
	AXS-07-303	Responder	37 (32.7)	18 (16.5)	16.2 (5.1, 27.3)	0.005
		Total	113	109		
	Pooled	Responder	113 (25.1)	27 (10.3)	16.5 (11.1, 21.9)	<0.001
		Total	450	263		
Black	AXS-07-301	Responder	5 (6.9)	4 (8.9)	-1.9 (-12.1, 8.2)	0.702
		Total	72	45		
	AXS-07-303	Responder	4 (25.0)	2 (13.3)	12.5 (-14.2, 39.2)	0.373
		Total	16	16		
	Pooled	Responder	9 (10.2)	6 (9.8)	1.3 (-8.6, 11.2)	0.798
		Total	88	61		
Asian	AXS-07-301	Responder	3 (37.5)	1 (25.0)	12.5 (41.6, 66.6)	0.678
		Total	8	4		
	AXS-07-303	Responder	1 (100.0)	2 (28.6)	71.4 (38.0, 100.0)	0.197
		Total	1	7		
	Pooled	Responder	4 (44.4)	3 (27.3)	27.1 (-19.1, 73.2)	0.307
		Total	9	11		

CI=confidence interval; ITT=intent-to-treat; N=total number.
Source: Applicant provided table (Table 41 of Summary of Clinical Efficacy), confirmed by Dr. Lin.

Reviewer comments: Since the majority of subjects enrolled in these trials were White, it is expected that the table above demonstrates that the benefits of AXS-07 compared to placebo were driven by the White subjects.

An analysis of the primary endpoints by age was conducted by the Applicant. No subjects over the age of 65 were enrolled in any study. The Applicant used a median age of 41 years to analyze categories of subjects. The analysis of MBS freedom at 2 hours is not included as a table, as results are similar. The analyses of the co-primary endpoints by age did not reveal differences by age and AXS-07 appeared to work similarly in subjects younger and older than 41 years of age. There were no subjects over the age of 65 so it is not possible to determine if efficacy is the same in this population as in subjects younger than 65.

Table 17. Pooled Controlled Studies: Analysis of Pain Freedom at 2 Hours, by Age

Age	Study ID	Result	AXS-07 (N=560)	Placebo (N=344)	Proportion Difference (%) (95% CI) (AXS-07-Placebo)	p-value
< Median Age	AXS-07-301	Responder	32 (15.6)	7 (7.0)	8.6 (1.6, 15.7)	0.035
		Total	205	100		
	AXS-07-303	Responder	21 (35.0)	9 (13.6)	21.4 (6.7, 36.0)	0.005
		Total	60	66		
	Pooled	Responder	53 (20.0)	16 (9.6)	12.7 (6.0, 19.3)	<0.001
		Total	265	166		
≥ Median Age	AXS-07-301	Responder	53 (23.8)	7 (6.4)	17.3 (10.1, 24.6)	<0.001
		Total	223	109		
	AXS-07-303	Responder	22 (30.6)	13 (18.8)	11.7 (-2.4, 25.8)	0.109
		Total	72	69		
	Pooled	Responder	75 (25.4)	20 (11.2)	15.5 (8.8, 22.3)	<0.001
		Total	295	178		

CI=confidence interval; ITT=intent-to-treat; N=total number.
Median age = 41 years
Source: Applicant provided table (Table 43 of Summary of Clinical Efficacy), confirmed by Dr. Lin.

Dose and Dose-Response

The Applicant stated it selected the dose of rizatriptan 10 mg because it is the currently approved dose for the acute treatment of migraine, and this dose has been demonstrated to be effective in several large, well-controlled clinical trials (Maxalt label). It stated it chose the meloxicam dose of 20 mg based on an analysis of the dose-dependent effect of intravenously (IV) administered meloxicam in the treatment of acute pain in a 460-subject, placebo and active-controlled trial (Mack, et al, 2016). This trial was conducted in female subjects undergoing open abdominal hysterectomy and involved doses of 5, 7.5, 15, 30 or 60 mg of meloxicam IV compared to morphine 10-15 mg or placebo, with the primary endpoints of the summed pain intensity difference and total pain relief over the first 24 hours post dose. Results of this trial indicated that statistically significant differences on endpoints only occurred at doses above 15 mg IV compared to the morphine arm. The Applicant stated that the 15 mg IV dose is approximately equivalent to the selected oral dose of 20 mg based on the oral bioavailability of meloxicam (89%) reported in the FDA product label for Mobic. (Mobic PI)

Reviewer comments: The rationale for the dose selected for rizatriptan is adequate since this is

the approved dose. However, the dose selected for the meloxicam component of this fixed-dose product is based on a study in only female subjects post open abdominal hysterectomy. This population is not entirely reflective of either the population that will use this drug (which will include males) or the type of pain or pain intensity and severity that is experienced with migraine. Although the doses were comparable to a morphine dose, the treatment of acute migraine is not truly comparable to treatment of post-surgical pain and a drug like morphine is not typically required for migraine treatment. The rationale for the selection of the meloxicam dose is inadequate for a population with migraine.

No dose-finding studies were conducted and only one dose was studied in this pivotal trial. The lowest effective dose should have been assessed to help mitigate the potential cardiovascular risk of AXS-07, given that both components individually do carry an increased cardiovascular risk as per the respective labels. The rationale provided does not justify using doses that are higher than the approved daily meloxicam dose, however long-term safety data at this dose was provided by the Applicant to support the safety of this dose for this indication.

7.1.4. Onset, Duration, and Durability of Efficacy Effects

Time to pain freedom (onset) was analyzed by the Applicant (see Table above) for Study AXS-07-301. The time to pain relief (mild to no pain) was faster in the AXS-07 arms compared to placebo. The Applicant stated this was statistically significant (1.5 hours in AXS-07 compared to 12 hours in placebo, p <.001) and an endpoint controlled for multiplicity. However, as described in Section 6.1, this endpoint is misleading as presented. The graph (Figure 4) demonstrates that more subjects in the AXS-07-07 treated arm did achieve pain relief faster than other arms. Duration of pain freedom (defined as no pain) at 24 hours was higher in the AXS-07 treated arm compared to placebo (16.1% compared to 5.3%, p<.001). Pain freedom at 48 hours was also reached in more subjects in the AXS-07 arm than placebo, although this was not a prespecified endpoint.

7.2. Integrated Assessment of Effectiveness

The Applicant submitted the results of one adequate and well-controlled clinical trial (AXS-07-301) to support the efficacy of AXS-07 for the acute treatment of migraine. The second trial (AXS-07-303) was submitted to further support efficacy in the treatment of a mild attack.
The efficacy of AXS-07 was demonstrated in one adequate and well-controlled study that used the well-validated and clinically meaningful co-primary endpoints of the proportion of subjects who were pain and MBS free at 2 hours. Study AXS-07-301, evaluated the efficacy of AXS-07 on treatment of a single moderate to severe migraine attack. The study demonstrated statistically significant treatment effects on the prespecified co-primary endpoint. In Study AXS-07-301, the therapeutic gain (active drug minus placebo drug effect) comparing AXS-07 to placebo was 13.2% on the endpoint of pain freedom at 2 hours, with a p value of <.001. The therapeutic gain for AXS-07 for the endpoint of MBS freedom at 2 hours was 12.5%, with a p value of 0.002.

These therapeutic gains are in line with the results from other clinical trials in drugs recently approved for the acute treatment of migraine, which range from 7%-17% for the endpoint of pain freedom at 2 hours and 8-16% for the endpoint of MBS freedom at 2 hours.

The Applicant also analyzed the key secondary endpoint of sustained pain freedom from 2-24 hours (without using a rescue medication for migraine) to demonstrate component contribution using a factorial design. In Study AXS-07-301, subjects were randomized to AXS-07, meloxicam 20 mg, rizatriptan 10 mg or placebo. The Applicant effectively used Study AXS-07-301 to establish the contribution of each individual product to the overall efficacy as per 21 CFR § 300.50, by demonstrating a clinically and statistically significant benefit of AXS-07 over meloxicam and rizatriptan on the agreed endpoint of sustained pain freedom at 24 hours.

Study AXS-07-303 was not required to support this application. However, Study AXS-07-303 was reviewed to assess the benefit of treatment of a mild migraine attack and to determine if the study should be described in labeling, since the co-primary endpoints were met, and efficacy was demonstrated in this study. Of note, the key secondary endpoints for this study (time to headache pain freedom and ability to perform normal activity, based on a 4-point functional rating scale), were not demonstrated to be statistically significant, compared to placebo.

The Applicant demonstrated efficacy of AXS-07 for the acute treatment of migraine, both in the moderate to severe stage of an attack and during a mild attack. The contributions of both the rizatriptan and meloxicam component of AXS-07 was demonstrated on the pre-specified endpoint of sustained pain freedom at 2-24 hours. This was the same design employed by the sponsor of Treximet that helped this fixed-dose combination product gain approval. The Applicant has submitted adequate evidence of the efficacy of AXS-07 for the proposed indication of the acute treatment of migraine with and without aura.

8. Review of Safety

8.1. Safety Review Approach

The safety review focused on the safety of AXS-07 for the acute treatment of migraine, when taken on a chronic intermittent basis. The data sources included reviewing the results of the controlled clinical trials (Study AXS-07-301 and Study AXS-07-303) and the open-label long-term safety study (Study AXS-07-302). The safety population in the placebo-controlled studies was defined as any subject who received one or more doses of AXS-07 in any of these studies. In order to be included in the long-term safety database, subjects had to treat at least 2 migraines per month on average for up to 6 or 12 months. The data is presented in the following groups:

- Pivotal Trial – Study AXS-07-301 only

- ISS Group 1: Controlled clinical efficacy and safety studies (Studies AXS-07-301 and AXS-07-303).
- ISS Group 2: Open-label long-term safety study (Study AXS-07-302). Of note, some of this data is open-label data and may be subject to bias (due to confounding since subjects and providers know they are receiving active drug), so the data is presented separately. Only 3 subjects in this study were *de novo* subjects (and had not previously participated in either AXS-07-301 or AXS-07-303). The protocol had been updated in amendment to only include subjects who had participated in AXS-07-301 or AXS-07-303.

Of note, combining controlled and open-label safety study for longest exposure was not analyzed separately since this dataset is the same as ISS Group 2, and since all but 3 subjects in the open-label safety study were rollovers from the controlled studies.

In this review, summaries of the Applicant's findings with confirmatory analyses by the Clinical Reviewer are presented. Adverse Event (AE) tables in this review refer to treatment-emergent adverse events (TEAEs) by dose treatment group (the dose the subject received). Tables were created by the Clinical Reviewer.

AXS-07-302 Study Design

This trial was a multicenter, open-label trial to evaluate the long-term safety of intermittent chronic dosing with AXS-07 in subjects with migraine attacks. Eligible subjects were advised to take a dose of AXS-07 following the onset of a moderate-to-severe migraine. Subjects were enrolled for up to 12 months and encouraged to treat all migraine attacks with AXS-07. Subjects were eligible if they participated in Study AXS-07-301 or Study AXS-07-303 protocols only. Subjects also had to meet the following criteria: 18 to 65 years of age, had 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, and experienced an average of 2 to 8 moderate or severe migraine attacks per month. Subjects who met all eligibility criteria were enrolled at visit 1 and dispensed AXS-07 for at-home treatment of migraine attacks. Subjects were instructed to treat each qualifying migraine attack with AXS-07 and return for clinic visits at Months 1, 3, 6, 9, and 12 (5 return visits). Subjects were instructed to only treat one attack with AXS-07 in a 24-hour period and not take more than 10 doses of AXS-07 in a month. In this study, 485 subjects received their first dose of AXS-07, as they had received either meloxicam, rizatriptan or placebo in AXS-07-301 or AXS-07-303.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Table 18. Overall Exposure to AXS-07[1]

Clinical Trial Groups	AXS-07 (n= 1098)
Healthy volunteers, AXS-07-102 and AXS-07-103 (single dose PK and single dose food-effects study)	26
Controlled trials conducted for this indication[2]	581
Open-label trials for this indication[3]	485
All other trials conducted for this indication[4]	6

[1] All doses of AXS-07 included meloxicam 20 mg and rizatriptan 10 mg.
[2] Controlled trials included ASX-07-301 and AXS-07-303.
[3] Open-label trials included AXS-07-302. 706 subjects were dosed in Study AXS-07-302, 485 had their first exposure to AXS-07 in this study, as these subjects received either meloxicam, rizatriptan or placebo in AXS-07-301 or AXS-07-303.
[4] One Phase 1, PK study in subjects with a history of migraine.

In AXS-07-302, subjects who took AXS-07 for ≤ 6 months took a mean of 3.9 (SD 1.40) doses per month with a range of 2.0-9.0 doses per month, and subjects who took AXS-07 for ≤ 12 months took a mean of 4.3 (SD 1.28) doses per month with a range of 1.8-9.0 doses per month. The protocol did stipulate (in a protocol amendment) that subjects were not to take more than 1 dose of AXS-07 in a 24-hour period and no more than 10 doses per month.

Table 19. ISS Group 3: Summary of Duration of Exposure

	Number of subjects treating ≥ 2 migraines with AXS-07 by months			
Dosage	≥ 1 dose	≥ 1 month	≥ 6 months	≥ 12 months
AXS-07 [1]	N=1066	N=682	N=496	N=132

[1] All doses of AXS-07 included a fixed dose of meloxicam 20 mg and rizatriptan 10 mg.

Table 20. ISS Group 3: Total Exposure of AXS-07 (Months and Total Tablets)

Exposure	AXS-07 (n= 1066)
Months of Exposure	
Mean (SD)	4.9 (4.4)
Median	5.7
Min - Max	0.0-13.0
Total Drug Exposure (Tablets)	
Mean (SD)	23.6 (21.6)
Median	22
Min - Max	1 -108

SD=Standard Deviation

8.2.2. Relevant characteristics of the safety population:

The following table includes the demographic characteristics of the safety population for ISS Group 1 (both placebo-controlled trials). The demographic characteristics of AXS-07-301 (the pivotal trial used to support both safety and efficacy of AXS-07) included 83.3% females, a mean age of 41.3 years old with 5.6% of subjects ≥ 60 years old with an average BMI of 29.3. The majority of subjects were White (76.7%), followed by Black or African American (19.3%). These characteristics were similar to the data in the table for the pooled placebo-controlled trials.

The demographic characteristics of Study AXS-07-302, the long-term safety study, included 82.2% females, a mean age of 42 (age range 19-65), with the majority of subjects White (77.1%) or Black or African American (18.7%).

Table 21. ISS Group 1: Demographics of Safety Population (Controlled Trials*)

Subgroup	Placebo (N = 361) n (%)	Meloxicam 20 mg (N = 433) n (%)	Rizatriptan 10 mg (N = 434) n (%)	AXS07 10/20 mg (N = 581) n (%)	Total (N = 1809) n (%)
Sex					
Female	307 (85.0)	363 (83.8)	366 (84.3)	476 (81.9)	1512 (83.6)
Male	54 (15.0)	70 (16.2)	68 (15.7)	105 (18.1)	297 (16.4)
Age (years)					
Mean	41.25	41.06	41.59	41.35	41.32
SD	11.31	12.14	10.74	11.62	11.47
Minimum	18	18	18	18	18
Median	42	41	42	41	42
Maximum	65	67	64	65	67
Age group (years)					
< 20	5 (1.4)	7 (1.6)	3 (0.7)	10 (1.7)	25 (1.4)
20 to ≤ 40	157 (43.5)	192 (44.3)	185 (42.6)	247 (42.5)	781 (43.2)
40 to ≤ 60	180 (49.9)	198 (45.7)	229 (52.8)	295 (50.8)	902 (49.9)
60+	19 (5.3)	36 (8.3)	17 (3.9)	29 (5.0)	101 (5.6)
Race					
American Indian or Alaska Native	2 (0.6)	2 (0.5)	2 (0.5)	6 (1.0)	12 (0.7)
Asian	10 (2.8)	9 (2.1)	6 (1.4)	10 (1.7)	35 (1.9)
Black or African American	63 (17.5)	88 (20.3)	84 (19.4)	94 (16.2)	329 (18.2)
Other	11 (3.0)	4 (0.9)	7 (1.6)	8 (1.4)	30 (1.7)
White	275 (76.2)	330 (76.2)	335 (77.2)	463 (79.7)	1403 (77.6)
Ethnicity					
Hispanic or Latino	97 (26.9)	108 (24.9)	114 (26.3)	161 (27.7)	480 (26.5)
Missing	0 (0.0)	3 (0.7)	1 (0.2)	3 (0.5)	7 (0.4)
Not Hispanic or Latino	264 (73.1)	322 (74.4)	319 (73.5)	417 (71.8)	1322 (73.1)
Region					
United States	361 (100.0)	433 (100.0)	434 (100.0)	581 (100.0)	1809 (100.0)

*Includes Studies AXS-07-301 and AXS-07-303.

SD=Standard Deviation

8.2.3. Adequacy of the safety database:

The safety database is adequate to allow for a comprehensive safety assessment of AXS-07 for the proposed indication, subject population, dosage regimen, and duration of therapy. The overall exposure to AXS-07 exceeds the minimum number of subjects recommended by the International Council for Harmonisation E1 Guideline for chronically administered medication.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There were no submission specific issues regarding data integrity and/or quality.

8.3.2. Categorization of Adverse Events

TEAEs were defined as AEs that developed or worsened during the on-treatment period and not more than 5 days after the last dose of study drug. Post-treatment AEs were defined as AEs that developed or worsened up to 10 days after the last dose of study drug. All AEs were coded using the Medical Dictionary for Regulatory Activities (Version 22).

All TEAEs are summarized by the following:

- System organ class (SOC) and Preferred Term (PT);
- Severity categories (e.g., mild, moderate, severe);
- Relationship to the study drug (e.g., unrelated or related [defined as at least probably related]).

The severity of each AE was classified into the 3 categories of mild, moderate, and severe. If a subject had multiple occurrences of the same SOC or PT, then only the most severe event was summarized in the tables for that SOC and PT within each phase of the trial. If severity was missing, the severity was considered as severe.

8.3.3. Routine Clinical Tests

Routine clinical tests included serum chemistry and blood count, urinalysis and toxicology screen were conducted at baseline. No follow up laboratory tests were conducted in Study AXS-07-301.

8.4. Safety Results

8.4.1. Deaths

No deaths were reported in any of the AXS-07 clinical trials.

8.4.2. Serious Adverse Events

Serious Adverse Events (SAEs) were defined as occurring from the time of first dose of study drug up to 30 days after the last dose of study drug.
An SAE was any untoward medical occurrence that at any dose and:

- Resulted in death.
- Was life-threatening.
- Required in-patient hospitalization or prolongation of existing hospitalization.
- Resulted in persistent or significant disability or incapacity.
- Was a congenital anomaly.
- Was an important medical event.

There were 9 subjects in the safety population (treated with AXS-07) who experienced a treatment emergent SAE, including 1 subject in the controlled clinical trials and 8 in the long-term safety study.

The narratives of the select SAEs, which may have had a relationship to study drug, follow:

> Subject AXS-07-301 (b) (6) was a subject in Study AXS-07-301 who experienced a spontaneous abortion on day 13 of the study. The subject was a 34 year old White female with a history of migraines and on no medications, who experienced a spontaneous abortion on day 13 of Study AXS-07-301. This subject was randomized on (b) (6) and had a negative urine pregnancy test. She took a dose of study drug (AXS-07) on (b) (6) On her follow up visit on (b) (6) she had a positive urine pregnancy test with last menstrual period (b) (6) On (b) (6) she had a spontaneous abortion.
>
> *Reviewer comments: It is difficult to assess causality of this SAE since the spontaneous abortion occurred 12 days after dosing with study drug. However, this spontaneous abortion was at approximately 5 weeks of gestation, at which time it is not uncommon to have a spontaneous abortion (Everett C, 1997). Also of note, there were 4 additional pregnancies in this study, during active treatment with AXS-07, which resulted in deliveries of healthy infants per Applicant report.*

Table 22. ISS Group 3: Summary of Serious TEAEs

Summary of Serious TEAEs								
Preferred Term	Placebo		Meloxicam 20 mg		Rizatriptan 10 mg		AXS07 10/20mg	
	(N=361)		(N=433)		(N=434)		(N=581)	
	n	(%)	n	(%)	n	(%)	n	(%)
Phase 3 Placebo-Controlled Trials								
Abortion spontaneous	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)
Open-label long-term safety study (original arm of randomization)								
Arthralgia	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Burns third degree	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)
Endometrial hyperplasia	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Hepatitis acute	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Hiatus hernia	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Mitral valve incompetence	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Musculoskeletal procedural complication	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Skin graft	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)
Victim of crime	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)

The subject who experienced the SAE of burns (third degree) on day 172 of treatment also experienced the SAE of skin graft on day 190. This was a 49-year-old white female with a history of migraine who received her first dose of AXS-07 on (b) (6) On (b) (6) she spilled boiling water on her left leg and right foot and was noted to have third degree burns requiring skin grafting. She continued to treat migraines with AXS-07 after this event. This event is assessed as not related to AXS-07.

The other SAEs reported in the long-term safety study are not reviewed here as they were assessed as not related to AXS-07 by this reviewer. Notably, there were no cardiovascular and/or gastrointestinal events that were SAEs.

Table 23. ISS Group 1: Serious Adverse Events

Subject ID	Sex/Race/Age (years)	Preferred Term	Study Day of Event Start / End	Relationship to Study Drug	Outcome	Action Taken with Study Drug
Phase 3 Controlled Trials						
AXS-07-301-(b) (6)	Female/White/34	Abortion spontaneous	13 / 13	Not related	Recovered/Resolved	Not applicable
Long-Term Trial						
AXS-07-301-(b) (6)	Female/White/47	Arthralgia	142 / 153	Not related	Recovered/Resolved	Dose not changed
AXS-07-301-(b) (6)	Female/White/52	Mitral valve incompetence	54 / 165	Unlikely	Recovered/Resolved	Dose not changed
AXS-07-301-(b) (6)	Female/White/50	Endometrial hyperplasia	74 / 90	Not related	Recovered/Resolved	Dose not changed
AXS-07-301-(b) (6)	Female/White/49	Hiatus hernia	175 / 175	Not related	Recovered/Resolved	Dose not changed
AXS-07-301-(b) (6)	Female/Black or African American/47	Musculoskeletal procedural complication	111 / 114	Not related	Recovered/Resolved	Dose not changed
AXS-07-301-(b) (6)	Female/White/42	Victim of crime	264 / 264	Not related	Recovered/Resolved with Sequelae	Drug withdrawn
AXS-07-303-(b) (6)	Male/White/49	Burns third degree	172 / ongoing	Not related	Not Recovered/Not Resolved	Dose not changed
		Skin graft	190 / 197	Not related	Not Recovered/Not Resolved	Dose not changed
AXS-07-303-(b) (6)	Female/Black or African American/27	Hepatitis acute	143 / 168	Not related	Recovered/Resolved	Dose not changed

Source: Applicant provided table from Summary of Clinical Safety (Table 18)

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

There were no TEAEs leading to discontinuations in either placebo controlled study (Study AXS-07-301 or Study AXS-07-303).

In the long-term safety study, 5 subjects discontinued due to nausea or vomiting, of which nausea was also a commonly reported TEAE (see Section 8.4.5.). In the controlled clinical trials, dizziness and somnolence were also the most common AEs, however in the long-term safety study, only one subject discontinued due to sedation and no subjects discontinued due to dizziness.

8.4.4. Significant Adverse Events

"Other significant adverse events" were any AEs (other than those reported as SAEs) that led to an intervention, including withdrawal of drug/investigational product treatment or significant additional concomitant therapy.

There were no hospitalizations due to AEs report in either placebo controlled study. In the long-term safety study, there were 7 (1.0%) subjects hospitalized due to an AE. These were assessed as not related to study drug, as described in above.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Analyses were conducted using SOC (not shown here), however no trends were noted except for an increase in gastrointestinal disorders, driven by the higher rates of nausea, and for neurological disorders, driven by the higher rates of somnolence, as presented below.

TEAEs are presented for Study AXS-07-301, the pooled controlled trials (ISS Group 1) and the long-term safety study (ISS Group 2).

Table 24. Study AXS-07-301: Adverse Reactions Occurring at Greater Than 1% and Greater than Placebo

	Placebo (N=218)	Meloxicam 20 mg (N=433)	Rizatriptan 10 mg (N=434)	AXS07 10/20mg (N=441)
Dizziness	2 (0.9)	5 (1.2)	9 (2.1)	7 (1.6)
Somnolence	1 (0.5)	10 (2.3)	9 (2.1)	6 (1.4)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRT01A = "Meloxicam 20 mg" and SAFFL = "Y" (Meloxicam 20 mg); TRT01A = "Rizatriptan 10 mg" and SAFFL = "Y" (Rizatriptan 10 mg); TRT01A = "AXS07 10/20mg" and SAFFL = "Y" (AXS07 10/20 mg); TRTEMFL = "Y" (Adverse Events).
Percent Threshold: Any Column ≥ 1%.

Table 25. ISS Group 1: Adverse Reactions Occurring at Greater Than 1% and Greater than Placebo

Preferred Term	Placebo (N=361) n (%)	Meloxicam 20 mg (N=433) n (%)	Rizatriptan 10 mg (N=434) n (%)	AXS07 10/20 mg (N=581) n (%)
Dizziness	4 (1.1)	5 (1.2)	9 (2.1)	11 (1.9)
Somnolence	4 (1.1)	10 (2.3)	9 (2.1)	12 (2.1)

*Includes Studies AXS-07-301 and AXS-07-303.
Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRT01A = "Meloxicam 20 mg" and SAFFL = "Y" (Meloxicam 20 mg); TRT01A = "Rizatriptan 10 mg" and SAFFL = "Y" (Rizatriptan 10 mg); TRT01A = "AXS07 10/20mg" and SAFFL = "Y" (AXS07 10/20 mg); TRTEMFL = "Y" (Adverse Events).

In the placebo-controlled trials, rates of nausea in the AXS-07-treated arm were 2.4%, and similar to placebo (2.5%) (data not shown). Rates of dizziness and somnolence were higher in the AXS-07 treated group compared to the placebo arm. However, rates of dizziness and somnolence were similar to those in each component arm (meloxicam and rizatriptan) of AXS-07. Preferred terms similar to somnolence, including fatigue and lethargy were reviewed, but were less frequently reported and so these terms were not included in the analysis of somnolence presented above. Generally, maximum severity of the most common TEAEs was mild or moderate in severity. Rates of dizziness and somnolence were mild in the AXS-07 treated arms.

Table 26. ISS Group 1: Summary of TEAEs by Maximum Severity

Preferred Term	Placebo (N=361)			Meloxicam 20 mg (N=433)			Rizatriptan 10 mg (N=434)			AXS07 10/20 mg (N=581)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Dizziness	4 (1.1)	0 (0.0)	0 (0.0)	5 (1.2)	0 (0.0)	0 (0.0)	8 (1.8)	1 (0.2)	0 (0.0)	11 (1.9)	0 (0.0)	0 (0.0)
Nausea	4 (1.1)	3 (1.4)	1 (0.5)	12 (2.8)	1 (0.2)	1 (0.2)	15 (3.5)	5 (1.2)	1 (0.2)	15 (2.6)	0 (0.0)	0 (0.0)
Somnolence	3 (0.8)	1 (0.5)	0 (0.0)	8 (1.8)	2 (0.5)	0 (0.0)	8 (1.8)	1 (0.2)	0 (0.0)	12 (2.1)	0 (0.0)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer, Studies AXS-07-301 and AXS-07-303.

In the open-label trial, Study AXS-07-302, nausea, vomiting, dizziness, somnolence, diarrhea and upper respiratory tract infection was reported at rates of ≥ 2%. The rates of nausea and somnolence were higher than that reported in the controlled clinical trials. The severity of most TEAEs in the open-label trial were mild. These data are limited in interpretation due to the open-label nature of this clinical trial.

Table 27. ISS Group 2: Adverse Reactions Occurring at Greater than 1% in the Long-term Safety Study

Preferred Term	AXS-07 (N=706) n (%)
Nausea	40 (5.7)
Vomiting	33 (4.7)
Dizziness	22 (3.1)
Somnolence	20 (2.8)
Diarrhea	16 (2.3)
Upper respiratory tract infection	14 (2.0)
Urinary tract infection	13 (1.8)
Nasopharyngitis	10 (1.4)
Fatigue	9 (1.3)
Bronchitis	8 (1.1)
Sinusitis	8 (1.1)
Weight increased	7 (1.0)

Source: OCS Analysis Studio, Safety Explorer, AXS-07-302
Filters: ACTARM = "AXS07 10/20mg" and SAFFL = "Y" (AXS-07); TRTEMFL = "Y" (Adverse Events).
Percent Threshold: Any Column ≥ 1%.

Table 28. ISS Group 2: TEAEs by Maximum Severity in Long-Term Safety Study

Preferred Term	AXS-07 (N=706)		
	Mild n (%)	Moderate n (%)	Severe n (%)
Diarrhea	14 (2.0)	2 (0.3)	0 (0.0)
Dizziness	21 (3.0)	1 (0.1)	0 (0.0)

Fatigue	7 (1.0)	2 (0.3)	0 (0.0)
Nausea	29 (4.1)	10 (1.4)	1 (0.1)
Somnolence	16 (2.3)	3 (0.4)	1 (0.1)
Upper respiratory tract infection	9 (1.3)	5 (0.7)	0 (0.0)
Urinary tract infection	7 (1.0)	6 (0.8)	0 (0.0)

8.4.6. Laboratory Findings

Laboratory data, including hematology, serum chemistry, urinalysis, pregnancy test (for women of childbearing potential) and urine drug screens were evaluated at baseline only for Study AXS-07-301 and at baseline and follow up for Study AXS-07-303. Per the Applicant, no clinical laboratory abnormality led to an intervention, such as significant additional concomitant therapy. This was a single attack study with follow up visits up to 1 week post study drug administration. The association of any single laboratory abnormality with AXS-07 use would be difficult to assess.

8.4.7. Vital Signs

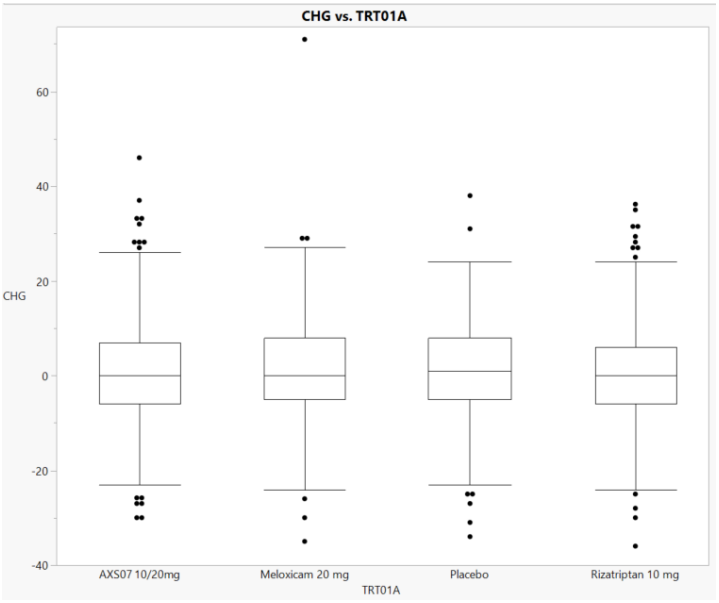
Vital signs analyses were conducted. Vital sign changes after treatment were examined for the placebo-controlled trials and the long-term safety study.

Study AXS-07-301

In Study AXS-07-301, there were 74 subjects who had at least a 20 -millimeters of mercury (mmHg) increase in their systolic blood pressure reading from the baseline visit to the visit 3 or early termination visit. There were 45 subjects with a 20-40 mm Hg decrease in systolic blood pressure, as well. An outlier analysis did not reveal significant differences between groups with those in the rizatriptan and AXS-07 arms having slightly more subjects with increases in systolic blood pressure compared to placebo. However, this analysis also demonstrated similar decreases in systolic blood pressure in both groups (see Figure below).

The subjects with larger changes were examined and no clear trends were demonstrated between groups and no adverse events related to cardiovascular events were reported in these subjects.

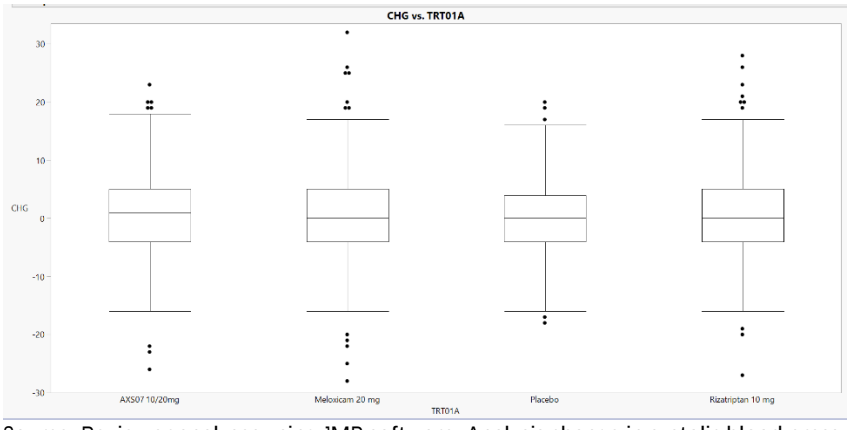
Figure 6. Study AXS-07-301: Systolic Blood Pressure Change Outlier Analysis



Source: Reviewer analyses using JMP software. Analysis change in systolic blood pressure from final visit compared to baseline visit per each treatment arm.

Similar outlier analyses were conducted for diastolic blood pressure (shown below) and changes in pulse rate (figure not included). Outlier analyses for systolic blood pressure, diastolic blood pressure and pulse rate at the final visit were fairly balanced between groups. There were no clear differences between treatment groups for any vital sign analyses.

Figure 7. Study AXS-07-301: Diastolic Blood Pressure Change Outlier Analysis



Source: Reviewer analyses using JMP software. Analysis change in systolic blood pressure from final visit compared to baseline visit per each treatment arm.

The subjects' baseline vital signs and the changes were examined individually, and the following subjects were noted:

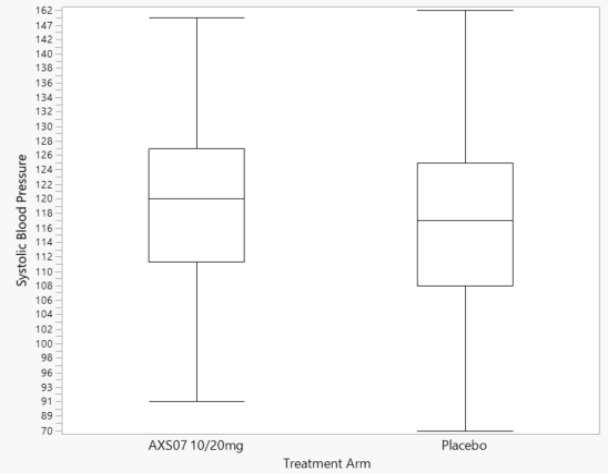
- Subject 301 (b) (6) had a 46 mm Hg rise in systolic blood pressure 6 days after treating with AXS-07.
- Subject 301 (b) (6) had a 37 point increase 2 days after treating with AXS-07.
- Subject 301- (b) (6) had a baseline systolic blood pressure of 147 which increased to 180 mm Hg at the final visit 3 days after treatment with meloxicam 20 mg.

It is difficult to assign causality of AXS-07 to the elevations in blood pressure treatment since this also occurred in one subject in the meloxicam treated arm.

Study AXS-07-303

Vital signs for this study were also examined. At screening, systolic blood pressure was balanced between groups. However, at the follow up (final) visit, more subjects had higher systolic blood pressure readings in the AXS-07 treated arms compared to placebo. In the figure below, the average systolic blood pressure in the AXS-07 treated arm appears to be ~120 mm Hg compared to 116 in the placebo arm. However, the confidence interval suggests that though elevated compared to baseline, these readings were still in the span of a "normal" blood pressure reading (<120 mm Hg) or "elevated" (120 -129 mm Hg) in adults, but not meeting the definition of hypertension using systolic blood pressure measurements (Whelton et al, 2017). Changes in blood pressure (outlier analyses) did not reveal significant differences between groups. The change in diastolic blood pressure was greater for the AXS-07 treated group, but the average change was 2.5 mmHg increase in diastolic blood pressure compared to no change in the placebo group (not shown).

Figure 8. Study AXS-07-303: Final Visit Systolic Blood Pressure

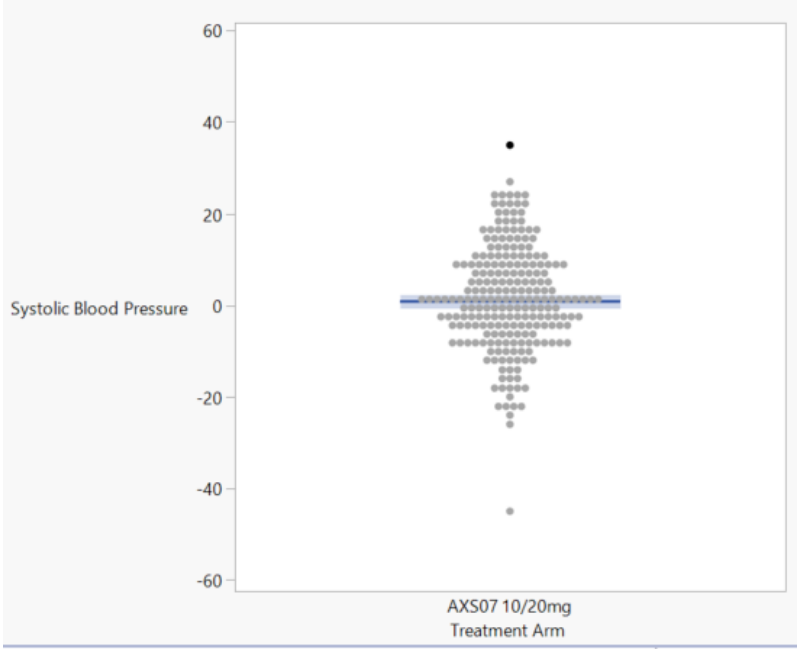


Source: Reviewer analyses using JMP software. Analysis change in systolic blood pressure from final visit compared to baseline visit per each treatment arm.

Study AXS-07-302

In the long-term safety study, most subjects did not experience a major change from their baseline systolic blood pressure reading at the final study visit as per the graph below. However, many subjects did have an up to 10-point increase in systolic blood pressure and similar numbers had a decrease in systolic blood pressure. There were two outliers – Subject AXS-07-301 (b) (6) a 52-year-old white man with a 35-point increase in systolic blood pressure (112 at baseline and 147 at the final visit 12 months later) and Subject AXS-07-301- (b) (6) a 58-year-old while female who experienced a 16 mm Hg decrease in her systolic blood pressure (from 116 at baseline to 100 at final visit 12 months later). On examination of each systolic blood pressure change in subjects who experienced a greater than 10-point elevation, only 48 subjects had systolic blood pressure readings that were greater than 130 mm Hg and would have met the criteria for a new diagnosis of hypertension and of those 19 had a greater than 10 mm Hg increase from baseline. Most of these subjects who experienced increases in blood pressure were between the ages of 40-60. Graphs for diastolic blood pressure changes at the final study visit compared to baseline were similar to values for systolic blood pressure changes (not shown).

Figure 9. Study AXS-07-302: Final Visit Change in Systolic Blood Pressure



Source: Reviewer analyses using JMP software. Analysis change in systolic blood pressure from final visit compared to baseline visit per each treatment arm.

Reviewer comments: The totality of the vital sign data on blood pressure changes suggests there may be a slight increase in systolic blood pressure in subjects treated with AXS-07. The long-term safety study suggests a slight increase in systolic blood pressure in some subjects, however interpretation is limited by the single arm (lack of placebo), the up to one week interval between dosing and follow up visit for the final blood pressure check, and the natural history of blood pressure changes in subjects in this age group.

8.4.8. Electrocardiograms (ECGs)

ECG data was examined for the placebo controlled and open label safety studies as a pooled dataset, since subjects from each study were rolled into the open label safety study. At day 1, 39% of subjects had "abnormal, not clinically significant" ECG findings and one subject had an abnormal clinically significant ECG at day 1. Month 12 data was similar per the Applicant's analysis. The following was the total number of abnormal clinically significant ECGs over time in the safety population (ISS Group 2):

- Month 3 - 1 subject, ECG interpreted as prolonged QT, possibly due to artifact
- Month 6 - 2 subjects, ECG in one subject of sinus bradycardia, possible left atrial enlargement, same as month 3 ECG; ECG in other subject of marked sinus arrhythmia, normal at follow up and at early termination visit.
- Months 9 and 12 - 0 subjects
- Early termination - 1 subject with ECG finding of sinus bradycardia, present at month 1 and other visits and not clinically significant.

Reviewer comments: The review of ECG data did not reveal any significant concerns that would affect safety of this product.

8.4.9. QT

A dedicated QT study was not performed by this Applicant due to this product being the combination of two approved products that have had QT analyses conducted (see Prescribing Information). The Applicant evaluated the QT intervals (corrected by Fridericia's correction formula) over time, and the average values remained consistent over time. An outlier analysis conducted by the Applicant did not reveal any trends in increasing QT interval over time after chronic, intermittent dosing.

8.4.10. Immunogenicity

Immunogenicity is not a concern with this product, as it is not a biologic.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Evaluation of increased risk of cardiovascular events

There is a known cardiovascular safety class effect of NSAIDs and triptans, individually. AXS-07 contains both meloxicam and rizatriptan, which are both known to increase blood pressure.

In Study AXS-07-301, there were 2 subjects in the AXS-07 treated group that reported chest discomfort, 1 report of dyspnea, and no reports of chest pain, tachycardia or palpitations.

In Study AXS-07-303, there was one subject with palpitations in the AXS-07 treated group. There were several subjects reporting dizziness (5 (3.6%) including one reporting postural dizziness) compared to 2 (1.4%) in the placebo group. There were no additional cardiovascular related events.

In the long-term safety study, Study AXS-07-302, there were 2 reports of chest pain, 2 reports of chest discomfort, and 1 subject each with peripheral swelling or edema. Cardiac disorders were reported as a TEAE in 1.4% of subjects, and these included palpitations (0.7%), first degree atrioventricular block, and 1 subject each reporting angina pectoris, atrial fibrillation, right bundle branch block and mitral valve incompetence. Of the 706 subjects in this long-term safety study, with 496 subjects using AXS-07 for an average of two times monthly for 6 months and 132 subjects for one year, there were no serious cardiovascular events reported.

Per the Applicant's report, two subjects in the AXS-07 overall group reported vascular or cardiac AESIs – peripheral edema and peripheral swelling in 1 subject each during the long-term safety study. The times to event were 260 and 253 days, respectively and the duration was 75 and 162 days, respectively. One subject in the rizatriptan group reported peripheral edema on day 1 that resolved on day 4. No subjects in the placebo or meloxicam group reported a vascular or cardiac AESI. There were no other reported vascular or cardiac AESI.

Reviewer comments: The data do not indicate an increased risk of cardiovascular events within 24 hours after a first dose of AXS-07 (Studies AXS-07-301 and AXS-07-303) or with chronic intermittent use (Study AXS-07-302). However, in the absence of demonstration of efficacy or safety of a second dose, it cannot be determined if an increased cardiovascular risk would exist if a second dose is administered or if the product was used more frequently than an average of 4x/month (as in Study AXS-07-302). Therefore, the label should include a statement that the safety and efficacy of a second dose of AXS-07 has not been established.

I recommend that the dosage and administration section state to "Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals," as in labels for other NSAIDs. This language may help mitigate the risk of a higher dose of meloxicam than the lowest oral dose that is currently approved, and that the choice of meloxicam dose should be made on an individual basis, weighing the possible benefit of a higher dose with the potential for a greater risk of adverse events.

8.5.2. Evaluation of increased risk of gastrointestinal events

There are known gastrointestinal (GI) risks associated with NSAIDs. There are no known GI risks with triptans as a class. There were no SAEs in any of the reviewed trials related to GI events.

In Study AXS-07-301, there were single reports of abdominal pain, abdominal discomfort, diarrhea, dyspepsia in the AXS-07 treated group. There were multiple reports of nausea as reported previously.

In Study AXS-07-303, there were several reports of nausea (as noted previously), one subject with abdominal discomfort, but no other GI related TEAEs reported.

In the long-term safety study, Study AXS-07-302, 13.6% of subjects experienced a GI-related TEAE, including nausea (5.7%), vomiting (4.7%), diarrhea (2.3%), gastroesophageal reflux disease (GERD) (0.6%), dyspepsia (0.3%) and gastritis (0.3%). There were no serious GI-related TEAEs.

Reviewer comments: The data do not indicate an increased risk of gastrointestinal adverse events with the use of AXS-07. Nausea and vomiting, though reported with AXS-07 use, are symptoms often associated with migraines. With use of this product limited to < 10 times per month (as should be advised in the PI (see Section 8.8.4. to avoid the risk of medication overuse headache), GI-related risks should be mitigated slightly. This approach is consistent with that taken for all of approved drugs in the NSAID and triptan classes to date.

8.6. Safety Analyses by Demographic Subgroups

Safety analyses were evaluated by the following subgroups: sex, race and age for the following pools: Group 1 (AXS-07-301); Group 2 (AXS-07-301 and AXS-07-303) and Group 3 (AXS-07-302). Only the results from Group 1 are included below, as the results for the other groups did not differ significantly.

Table 29. Study AXS-07-301: Common TEAEs by Sex

Preferred Term	AXS07 10/20mg		Meloxicam 20 mg		Placebo		Rizatriptan 10 mg	
	F (N=357)	M (N=84)	F (N=363)	M (N=70)	F (N=185)	M (N=33)	F (N=366)	M (N=68)
Dizziness	6 (1.7)	1 (1.2)	5 (1.4)	0	1 (0.5)	1 (3.0)	7 (1.9)	2 (2.9)
Nausea	8 (2.2)	4 (4.8)	13 (3.6)	1 (1.4)	7 (3.8)	1 (3.0)	16 (4.4)	5 (7.4)
Somnolence	4 (1.1)	2 (2.4)	9 (2.5)	1 (1.4)	1 (0.5)	0	9 (2.5)	0

F=Female, M=Male

Source: Reviewer conducted analyses using MAED software.

Table 30. Study AXS-07-301: Common TEAEs by Race

Preferred Term	AXS07 10/20mg		Meloxicam 20 mg		Placebo		Rizatriptan 10 mg	
	White[1] (N=345)	Black (N=76)	White (N=330)	Black (N=88)	White (N=160)	Black (N=48)	White (N=332)	Black (N=84)
Dizziness	7 (2.0)	0 (0)	4 (1.2)	1(1.1)	2 (1.2)	0 (0)	6 (1.8)	3 (3.6)
Nausea	11 (3.2)	1 (1.3)	9 (2.7)	5 (5.7)	5 (3.1)	2 (4.2)	16 (4.8)	3 (3.6)
Somnolence	6 (1.7)	0 (0)	8 (2.4)	2 (2.3)	0 (0)	1 (2.1)	7 (2.1)	2 (2.4)

[1]Other Races (Asian, American Indian or Alaska Native, Multiple and Other) are not included since there were very limited number of subjects in each subgroup and 0 or 1 subject who experienced a given TEAE.

Source: Reviewer conducted analyses using MAED software.

Table 31. Study AXS-07-301: Common TEAEs by Age

Preferred Term Age group (years)	Placebo (N =) n (%)	Meloxicam 20 mg (N =) n (%)	Rizatriptan 10 mg (N = 434) n (%)	AXS07 10/20 mg (N =) n (%)
Dizziness				
< 20	0	0	0	0
20 to ≤ 40	0	2	6	4
40 to ≤ 60	2	1	3	3
60+	0	2	0	0
Nausea				
< 20	0	0	0	0
20 to ≤ 40	5	7	9	7
40 to ≤ 60	2	7	11	5
60+	1	0	1	0
Somnolence				
< 20	0	1	0	0
20 to ≤ 40	1	4	5	2
40 to ≤ 60	0	4	4	4
60+	0	1	0	0

Source: Reviewer conducted analyses using MAED software.

8.7. Specific Safety Studies/Clinical Trials

There were no additional specific safety studies conducted as part of this application, aside from those noted above.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Not applicable.

8.8.2. Human Reproduction and Pregnancy

The prescribing information (PI) regarding risks on human reproduction and pregnancy from the Anjeso and Maxalt labels should be included in the label for AXS-07.

8.8.3. Pediatrics and Assessment of Effects on Growth

A pediatric study plan has been submitted and this plan includes these assessments.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is no information on drug abuse potential or withdrawal in the labels for any of the listed drugs. No information on overdose, drug abuse potential or withdrawal was included in this application. In the long-term safety study, Study AXS-07-302, subjects were instructed to only take 1 dose of AXS-07 in a 24-hour period and to take no more than 10 doses per month. Therefore, the safety of taking more than 1 dose of AXS-07 in a 24-hour period and taking more than 10 doses per month is not known.

The PI for rizatriptan (Maxalt) does include information (Section 5.6) on Medication Overuse Headache. The PI for sumatriptan/naproxen (Treximet) includes the following language (Section 5.10) regarding medication overuse headache:

> Overuse of acute migraine drugs (e.g., ergotamine, triptans, opioids, or a combination of these drugs for 10 or more days per month) may lead to exacerbation of headache (medication overuse headache). Medication overuse headache may present as migraine-like daily headaches, or as a marked increase in frequency of migraine attacks. Detoxification of subjects, including withdrawal of the overused drugs, and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

Reviewer comments: The PIs for triptans and NSAID containing products indicated for the acute treatment of migraine include language regarding medication overuse headache. This language should be included in the AXS-07 PI, especially given that each component of AXS-07 can independently lead to medication overuse headaches or rebound headache. The statement should also include that NSAIDs can lead to medication overuse headache. The safety of taking more than 1 dose of AXS-07 in a 24-hour period and taking more than 10 doses per month is not known.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

There are no pending safety concerns with either product known to this reviewer, that have not already been incorporated into labeling of each of the individual products in this fixed-dose combination product.

8.9.2. Expectations on Safety in the Postmarket Setting

8.10. Integrated Assessment of Safety

AXS-07 has a favorable safety profile. In controlled trials, there were no deaths or serious adverse events with a clear association with AXS-07. Common adverse events that occurred at an incidence of at least 1% and greater than placebo were dizziness and somnolence. No other new safety signals were detected. Safety information from the known effects of the individual components of AXS-07 should be included in future labeling of this product, in addition to the TEAEs noted in the controlled clinical trials.

All of the warnings, precautions, contraindications and boxed warnings for triptans and NSAIDs should be included in the label for AXS-07. Further, all safety information pertaining to Maxalt and Anjeso (the listed drugs) should also be included in the label. A Warning and Precaution section for medication overuse headache will also be included in the AXS-07 PI, as this risk is associated with overuse of NSAIDs and triptans for the acute treatment of migraine.
There is no specific pharmacovigilance that should be requested at this time

9. Advisory Committee Meeting and Other External Consultations

No advisory committee or external consultations were assessed as necessary.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Review of prescription drug labeling is ongoing at the time of this review.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

Based on the review of this package, a REMS for AXS-07 is not recommended.

12. Postmarketing Requirements and Commitments

Pediatric PMRs and a pregnancy registry and database are required for NDA 215431.

1. Pediatric PMRs

(b) (6)

   b) A randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy and safety of AXS-07 versus placebo during a single migraine attack in pediatric subjects, 6 to less than 18 years of age. This study must be designed to show superiority of AXS-07 over placebo.
   c) A long-term, open-label, safety study of AXS-07 in migraine subjects, 6 to less than 18 years of age, for up to one year.
2. Pregnancy Registry
3. Pregnancy Database Study

13. Appendices

13.1. References

1. Everett C. Incidence and outcome of bleeding before the 20th week of pregnancy: prospective study from general practice. BMJ. 1997;315:32–4.

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29;284(20):2599-605.

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6. Robbins NM, Bernat JL. Minority Representation in Migraine Treatment Trials. Headache. 2017 Mar;57(3):525-533.

7. Whelton PK, Carey RM, Aronow, WS, Casey DE, Collins KJ, Himmelfarb CD, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018;71(19):e127–e248.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study AXS-07-301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 85		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: n/a Significant payments of other sorts: n/a Proprietary interest in the product tested held by investigator: n/a Significant equity interest held by investigator in study n/a Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant) N/A
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): Study AXS-07-303

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 40		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: n/a Significant payments of other sorts: n/a Proprietary interest in the product tested held by investigator: n/a Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant) N/A
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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