CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215431Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	January 30, 2025
From	Heather Fitter, MD Paul R. Lee, MD, PhD, MA
Subject	Summary Review
NDA/BLA # and Supplement#	NDA 215431
Applicant	Axsome Therapeutics Inc.
Date of Submission	July 31, 2024
PDUFA Goal Date	January 31, 2025
Proprietary Name	Symbravo
Established or Proper Name	AXS-07, rizatriptan/meloxicam
Dosage Form(s)	Oral Tablet (10 mg rizatriptan/20 mg meloxicam)
Applicant Proposed Indication(s)/Population(s)	Acute treatment of migraine with or without aura in adults
Applicant Proposed Dosing Regimen(s)	One tablet at the onset of migraine
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Acute treatment of migraine with or without aura in adults
Recommended Dosing Regimen(s) (if applicable)	One tablet at the onset of migraine

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

AXS-07 (Symbravo) is a fixed dose combination product of 20 mg meloxicam and 10 mg rizatriptan for oral administration as a tablet. Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) currently marketed 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-$HT_{1B/1D}$ agonist that is marketed for the acute treatment of migraine with or without aura.

The Applicant is seeking an indication for the acute treatment of migraine with or without aura in adults. The Applicant submitted the original application on June 30, 2021, but that application received a Complete Response (CR) action due to Chemistry, Manufacturing, and Controls (CMC) and nonclinical deficiencies. The CMC deficiencies related to inadequate drug product specification to control potential impurities, inadequate manufacturing controls to ensure consistent product quality, and inadequate data to support the proposed dissolution test method. The nonclinical deficiencies related to the lack of nonclinical data to support chronic oral administration of meloxicam and the lack of data to qualify the proposed limit (b) (4)%) for the impurity, rizatriptan-N-oxide. Additional data was provided in the resubmission to address these deficiencies, including a bioavailability study so that the Applicant could rely on the Listed Drug, Mobic to support chronic administration of Symbravo. The bioavailability study compared pharmacokinetic parameters of Mobic to the meloxicam component of Symbravo, since Mobic is a chronically administered product.

In addition, in this resubmission the Applicant has provided toxicology data to adequately justify the higher than ICH Q3B threshold acceptance criteria for two specified impurities, one is Rizatriptan N-oxide, and the other is a newly identified Meloxicam degradant (b) (4) (b) (4) Based on the validated HPLC methods, the available stability data, the inclusion of the specifications for the (b) (4) and the commitment to monitor the (b) (4) to the end of shelf -life, the risks for the formation of (b) (4) in the drug product manufacturing and storage have been mitigated.

The efficacy data to support this application was reviewed with the original application and will be summarized below: The application included two efficacy trials. One that was required for approval and was considered a pivotal efficacy trial in which subjects treated a migraine attack when the pain was moderate to severe, and a second trial in which subjects were instructed to treat a migraine when the associated pain was mild. The standard for products approved for the acute treatment of migraine is to evaluate the treatment when administered during a migraine attack associated with pain of moderate to severe intensity. During development the Division told the Applicant 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 reviewing data from a single adequate and well controlled efficacy trial to support a marketing application for AXS-07.

Therefore, the Applicant included in the application a single adequate and well-controlled pivotal trial with AXS-07 to support efficacy for the migraine indication, and largely relies on the Maxalt (rizatriptan) and Anjeso (meloxicam) to support efficacy, and relies on Applicant relies on, Maxalt, Anjeso, and Mobic (meloxicam) to support the safety of its product, using a 505(b)(2) approach. In addition, long term safety data were included in this application for AXS-07 that meet ICH guidelines for chronically administered drugs.

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

The efficacy of AXS-07 was demonstrated in a single adequate and well-controlled study (AXS-07-301). The study used well-validated and clinically meaningful co-primary endpoints to establish efficacy; the proportion of patients who were pain-free and the proportion of patients who were most bothersome symptom (MBS)-free at 2 hours after dosing for the acute treatment of a migraine attack. In addition, the study addressed the combination rule regulations (CFR 21 300.50) and demonstrated a contribution of each individual component to the overall effect, demonstrating superiority of the combination over meloxicam and rizatriptan when given individually on the endpoint, sustained pain freedom at 24 hours.

The treatment effect size for pain freedom at 2 hours post-dose was 13.2% greater than placebo (AXS-07 responder rate of approximately 19.9%). The treatment effect size for MBS-freedom at 2 hours post-dose was 12.5% greater than placebo (AXS-07 responder rate of 36.9%). Sustained pain freedom in the AXS-07 treatment group was significantly higher than meloxicam (7.3%) and rizatriptan (4.9%) and this information supports the demonstration of a contribution of each individual component to the overall effect of the fixed-dose combination. The efficacy of a second dose was not studied in this development program. These data support the efficacy of AXS-07 for the proposed indication based on the established effect on pain and MBS freedom, and demonstration of a contribution of each individual component of the combination product to the overall effect, with an effect on sustained pain freedom at 24 hours. A second adequate and well-controlled study was submitted (AXS-07-303), although this study was not a required efficacy study for this application. This study evaluated the efficacy of AXS-07 when administered to patients during a migraine associated with mild pain using the standard co-primary endpoints to establish efficacy, the proportion of patients who were pain-free and the proportion of patients who were MBS-free at 2 hours after dosing for the acute treatment of a mild migraine attack.

The safety profile of AXS-07 was supported by pharmacokinetic bridging to the listed drugs (LD), rizatriptan (Maxalt) and meloxicam (Anjeso and Mobic) and data from the two placebo-controlled trials (AXS-07-301 and AXS-07-303), as well as one long-term safety study (AXS-07-302).

Despite the ability of this application to reference safety of the LDs, the long-term extension study was required due to the following limitations to the safety information of the LDs. The Anjeso label supports acute, but not chronic, administration of meloxicam. The Mobic label supports safety of chronic administration of meloxicam, but since the maximum dose of oral meloxicam (Mobic) is lower than the dose of the meloxicam component of Symbravo, the Division required additional clinical long term extension safety data to supplement the safety data provided in the Mobic label. In the original submission of this application, the Applicant did not reference Mobic as a listed drug and therefore there were not adequate data provided in the submission to support chronic intermittent administration of Symbravo from a nonclinical standpoint.

Given that the LD's labels include a Warning and Precaution in the prescribing information (PI) related to cardiovascular risk, an evaluation of long-term safety to determine if this risk is increased when both drugs are used together, was needed. The Warnings and Precautions listed in the LDs Prescribing Information (PIs) should be included in the Symbravo label, and the increased incidence of dizziness and somnolence reported with AXS-07 as compared to placebo, in the controlled clinical trials should also be described in the Symbravo label. The clinical safety data from the long-term extension study support the safety of the use of up to 7 tablets a month, and this information should be relayed in labeling.

Efficacy was demonstrated in the pivotal efficacy trial, and AXS-07 demonstrated an acceptable safety profile for the intended population. The deficiencies from the original submission were addressed with this submission, therefore an Approval action will be taken on this application.

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 various associated symptoms. The typical headache of migraine is throbbing, unilateral, and aggravated by motion, but bilateral and/or non-throbbing headaches are also commonly reported. Typical migraine-associated symptoms include nausea, vomiting, photophobia, and phonophobia, but a myriad of other neurological symptoms may occur, and various degrees of cognitive impairment are often present.	Migraine is a serious and frequently disabling condition that can impact the quality of patients' lives.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Migraine attacks typically last from 4 to 72 hours in adults. About one-third of people with migraine experience transient neurological symptoms before and/or during an attack, referred to as a migraine aura. • Migraine was found to be the second highest cause of disability in the Global Burden of Disease Study in 2016. The prevalence of migraine is approximately 9% in males and 20% in females in the U.S., thus resulting in a major impact to public health.	
Current Treatment Options	• There are many FDA-approved therapies for acute migraine such as triptans, dihydroergotamine (DHE), lasmiditan, CGRP receptor antagonists and certain non-steroidal anti-inflammatory drugs (NSAIDs), the latter which can be used alone or in combination with a triptan. In addition, there are several over-the-counter drugs marketed for migraine.	Several classes of drugs are indicated for the acute treatment of migraine with or without aura in adults. However, many patients still do not respond adequately to these therapies. AXS-07, which combines a NSAID and a triptan into a single tablet, offers another treatment option for migraine patients.
Benefit	• The efficacy of AXS-07 was demonstrated in an adequate and well-controlled clinical study (Study AXS-07-301). The study used well-validated and clinically meaningful endpoints to evaluate efficacy, the proportion of patients that are pain-free (PF) at 2 hours post-dose, and most bothersome symptom (MBS)-free at 2 hours post-dose. In addition, to demonstrate a contribution of the individual components of the combination product to the overall effect, a higher treatment effect was seen on sustained pain freedom from 2 to 24 hours in the comparison of the AXS-07 group to the rizatriptan group, as well as in the comparison of the AXS-07 group to the meloxicam group. There was a statistically significant increase ($p \leq 0.001$) in the rate of pain freedom at 2 hours in the AXS-07 group (19.9%) as compared to the placebo group (6.7%). There was also a statistically significant	AXS-07 is effective for the acute treatment of a migraine with or without aura in adults. These data support the efficacy of AXS-07 for the proposed indication based on the established effect on pain freedom and MBS freedom at 2 hours, in one trial in the context of the known efficacy of rizatriptan indicated for the same indication and of meloxicam with an acute pain indication.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	increase (p=0.002) in the rate of MBS freedom at 2 hours in the AXS-07 group (36.9%) as compared to the placebo group (24.4%). • A second dose to treat a single migraine attack was not evaluated in the clinical efficacy study. • Rizatriptan has demonstrated efficacy for the acute treatment of migraine, such as Maxalt and Maxalt MLT. • Meloxicam is an NSAID with an acute pain indication. • The efficacy of AXS-07 was also demonstrated in one adequate and well controlled clinical study (Study AXS-07-303) that evaluated treatment during a mild migraine attack, rather than a moderate-severe migraine attack. Pain freedom at 2 hours was 32.6% in the AXS-07 treated group, compared to 16.3% in placebo (p=0.002). MBS freedom at 2 hours was 43.9% in the AXS-07 treated group, compared to 26.7% in the placebo group (p=0.003)	AXS-07 is a combination product of 20 mg meloxicam and 10 mg rizatriptan. The efficacy and safety of a second dose for a single migraine attack was not evaluated.
Risk and Risk Management	• Supportive safety data for AXS-07 is provided by the listed drugs, Anjeso, Mobic, and Maxalt. • The Anjeso and Mobic labels includes a boxed warning for serious cardiovascular and gastrointestinal events, as well as Warnings and Precautions sections pertaining to hepatoxicity, hypertension, heart failure and edema, renal toxicity, anaphylactic reactions, exacerbation of asthma related to aspirin sensitivity, serious skin reactions, drug reaction with eosinophilia and systemic symptoms (DRESS), fetal toxicity, and hematologic toxicity. • The Maxalt label includes Warning and Precautions sections pertaining to myocardial ischemia, arrhythmias, Chest/throat/neck and/or jaw pain/pressure, cerebrovascular events, other vasospasm reactions, medication overuse headache, serotonin syndrome, and increase in blood pressure. • Safety of chronic intermittent use of Symbravo was supported based on reliance on the Mobic label (based on review of a BA study	There were no significant new safety findings in the clinical studies that would preclude approval of AXS-07. The resubmission resolved the CMC quality issues identified in the first review cycle related to drug product, manufacturing, and biopharmaceutics disciplines. Nonclinical chronic toxicity data was provided for meloxicam based on reliance on the Mobic label. Clinical safety data for chronic administration was also provided based on the results of the long-term extension trial. Adequate

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	evaluating the meloxicam component of Symbravo to Mobic) and supplemented by the safety database in the clinical long term extension trial. • There were no serious safety issues identified in the controlled clinical trials conducted with AXS-07. • The incidence of dizziness (1.6% vs 0.9%) and somnolence (1.4% vs 0.5%) in the controlled clinical trials was increased in subjects that received AXS-07 compared to placebo, respectively. • The safety data supports the use of up to 7 tablets a month, and no more than 1 tablet in a 24-hour period. • The Applicant has provided toxicology data to adequately justify the higher than ICH Q3B threshold acceptance criteria for two specified impurities, one is Rizatriptan N-oxide, and the other is a newly identified Meloxicam degradant (b) (4) (b) (4) • Based on the validated HPLC methods, the available stability data, the inclusion of the specifications for the (b) (4) and the commitment to monitor the (b) (4) to the end of shelf -life, the risks for the formation of (b) (4) in the drug product manufacturing and storage have been mitigated. Other uncertainties • Safety and efficacy in pediatric migraine patients and in pregnant patients has not been established.	safety data was provided to support chronic intermittent administration of Symbravo. The impurities, rizatriptan-N-oxide and (b) (4) were adequately qualified. The risks for the formation of (b) (4) in the drug product have been adequately mitigated. The data provided support granting a 6-month shelf life. PMRs will be issued to evaluate safety and efficacy in pediatric subjects and safety in pregnant subjects.

2. Background

Axsome Therapeutics Inc. (the Applicant) provided this resubmission in support of a 505(b)(2) new drug application (NDA) for AXS-07 (Symbravo), a fixed dose combination product of an oral tablet of meloxicam 20 mg and rizatriptan 10 mg, for the acute treatment of migraine with or without aura in adults. This review discusses the data presented in this resubmission received July 31, 2024, following the original submission of June 30, 2021, that received a Complete Response action on April 29, 2022, due to CMC and nonclinical issues. Specifically, the drug product, manufacturing, and biopharmaceutics disciplines cited unresolved quality issues that precluded an approval action. In addition, the proposed drug product specification was inadequate to control potential impurities, including (b) (4) degradants, and manufacturing controls were inadequate to ensure consistent product quality. The Applicant also did not provide adequate data to support the proposed dissolution test method. From a nonclinical standpoint, there was inadequate support for chronic administration of meloxicam, and inadequate support for the proposed level of (b) (4)% for the rizatriptan impurity, (b) (4) (b) (4)

In this resubmission, the Applicant added a bioavailability (BA) study to allow reliance on the listed drug (LD), Mobic for this application as well. Overall, this Applicant now relies on the LDs Mobic (meloxicam [NDA 20938]), Anjeso (meloxicam injection [NDA 210583]), and Maxalt (rizatriptan [NDA 20864]), to support the safety of its product, in addition to data from a 12-month long-term safety study using AXS-07.

Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) marketed for the management of moderate to severe pain as Anjeso and as Mobic, in tablet form applications with indications for the relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis treatment. Rizatriptan is a 5-$HT_{1B/1D}$ agonist marketed for the proposed indication for this application and marketed as Maxalt (tablets) and Maxalt MLT (orally disintegrating tablets, NDA 20865). During development the Division told the Applicant 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 reviewing data from a single adequate and well controlled efficacy trial to support a marketing application for AXS-07.

Migraine is a primary headache disorder characterized by recurrent headaches that are moderate to severe, accompanied by various associated symptoms. The typical headache of migraine is throbbing, unilateral, and aggravated by motion, but bilateral and/or non-throbbing headache is also commonly reported. Typical migraine-associated symptoms include nausea, vomiting, photophobia, and phonophobia, but a range of other neurological symptoms may occur, with various degrees of cognitive impairment often present. Migraine attacks typically last between 4 to 72 hours in adults. About one-third of individuals with migraine experience transient neurological symptoms before and/or during a migraine attack, referred to as migraine aura. Generally accepted diagnostic criteria for migraine are presented in the International Classification of Headache Disorders-3 (ICHD-3).

Many products are FDA-approved for the acute treatment of migraine in adults. These products include a number of different triptans, dihydroergotamine, NSAIDs used alone or in combination with a triptan, a 5-HT_{1F} agonist (lasmiditan), and CGRP receptor antagonists (ubrogepant, rimegepant, and zavegepant). There are also many over-the-counter medications that are labeled for the acute treatment of migraine. Despite the availability of numerous products, not all migraineurs respond well to the available therapies, the use of which can also be limited by safety concerns (e.g., restrictions for the use of triptans, ergotamines, and NSAIDs in patients with cardiovascular (CV) disease and driving restrictions for lasmiditan).

During the original submission, the Division reviewed the data from the single placebo-controlled efficacy trial, Study AXS-07-301 (referred to as Study 301 in this review) in adult patients with migraine with or without aura to support the efficacy of AXS-07 for the proposed indication. In addition, a second placebo-controlled efficacy trial, Study AXS-07-303 (referred to as Study 303 in this review) was submitted that evaluates the efficacy of AXS-07 for the acute treatment of migraine in patients that experienced a mild attack. The current submission includes a BA study to allow for reliance on the LD, Mobic, to provide the needed chronic toxicity nonclinical safety support for this application.

3. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Martha Heimann (refer to her review for the entire OPQ list of participants in the review of this application).

The Applicant has developed a fixed dose combination tablet for oral administration composed of 20 mg meloxicam and 10 mg rizatriptan (as rizatriptan benzoate). This is the second review cycle for this NDA. During the first review cycle, the review team identified significant deficiencies related to tablet manufacturing process, control of drug product impurities including potential (b) (4) degradants, and biopharmaceutics (dissolution). During the initial review cycle Dr. Heimann concluded that the drug substance and facilities met all applicable standards. Therefore, this resubmission will not include a drug substance discussion since, from an OPQ standpoint, the information submitted during the first review cycle was adequate.

Drug Product

Dr. Heimann reports that the (b) (4) issue was adequately addressed in this resubmission.

The Applicant has developed and adequately validated high performance liquid chromatography (HPLC) methods to detect, and quantify the potential (b) (4) (b) (4) (b) (4) formed during the API/drug product manufacturing

process and drug product storage. Up to 9-month stability data for the newly manufactured registration batches show that none of the [redacted] were observed above the acceptable intake (AIs). Specifically, the levels of [redacted] are lower than [redacted]% of AIs, and the amount of [redacted] was found to be over [redacted]% of the AI.

Because the amount of [redacted] was found to be over [redacted]% of the AI, and the levels of [redacted] were more than [redacted]% of the AI by the original semi-quantitative method, acceptance criteria for [redacted] and [redacted] have been included in the release and stability specification to ensure the amount of these will not exceed the AI throughout the shelf-life [redacted]. In addition, the Applicant committed to continue to monitor the [redacted] in the registration batches through the end of stability studies. Based on the validated HPLC methods, the available stability data, the inclusion of the specifications for the [redacted] and the commitment to monitor the [redacted] to the end of shelf -life, the risks for the formation of [redacted] in the drug product manufacturing and storage have been mitigated.

In this resubmission, to address the concern that [redacted] for [redacted] during storage of drug product, the Applicant has included a specific acceptance criterion to ensure that the [redacted] The Applicant has demonstrated that presence of [redacted] at [redacted] level of detection, does not adversely impact product performance (i.e., the solubility).

The Applicant has provided toxicology data to adequately justify the higher than ICH Q3B threshold acceptance criteria for two specified impurities, one is rizatriptan N-oxide and the other is a newly identified meloxicam degradant [redacted] The Applicant has provided 6-month long term and accelerated stability data for 6 registration batches (2 for each presentation, 3 tablets/bottle and 9 tablets/bottle) manufactured by the revised manufacturing process to address the failed [redacted]. All the data met the specification. As mentioned in the Complete Response Letter, and as discussed in the August 29, 2022, Type A meeting, the Applicant's original registration batches failed in [redacted], and therefore they cannot simulate a viable commercial process. The proposed [redacted] shelf-life derived from such registration batches is not acceptable. A 6-month shelf-life can only be warranted based on the no trending 6-month long term data from 6 new registration batches. Because the Applicant has adequately addressed the issues for [redacted], and primary stability studies, the OPQ team recommends approving this NDA from a drug product perspective.

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer for this application was Dr. Elizabeth Khoury, with Dr. David Carbone performing the secondary review.

Dr. Khoury reports that the nonclinical deficiencies that precluded approval of the original submission consisted of inadequate support for chronic administration of meloxicam, and

inadequate support for the proposed level of (b) (4)% for the rizatriptan impurity, (b) (4) (b) (4) Additional review issues that were not identified in the initial submission but required nonclinical assessment in the resubmission consisted of a proposed specification limit of (b) (4)% for the impurity (b) (4) which, due to a change in the manufacturing process prior to the resubmission, was identified at levels above the qualification threshold in subsequent marketing batches. Additionally, based on information provided by the CMC team, (b) (4) (b) (4) were identified as potential (b) (4) impurities.

The nonclinical deficiencies described in the Complete Response, as well as concerns regarding the impurity (b) (4) and the potential (b) (4) impurities were adequately addressed in the resubmission. To support chronic administration of meloxicam, the Applicant is now also relying on the approved product Mobic, which is approved for the indications of osteoarthritis and juvenile rheumatoid arthritis. The proposed levels of rizatriptan n-oxide and (b) (4) are also supported by data indicating that rizatriptan n-oxide is formed by (b) (4) and would, therefore, have been assessed in the genetic toxicity studies submitted to support the approval of rizatriptan. For (b) (4) the Applicant conducted a quantitative structure-activity relationship (QSAR) assessment which did not indicate any alerting structures. To address general toxicity, the sponsor provided data to demonstrate that both impurities were present at sufficient levels in a GLP, 13-week study in minipig study of AXS-07, (b) (4) to support the proposed specification limits. For the potential (b) (4) impurities, (b) (4) the Applicant provided analytical methods that support the proposed specification limits. Thus, there are no nonclinical concerns regarding these potential (b) (4) impurities.

5. Clinical Pharmacology

The primary reviewer from the Office of Clinical Pharmacology (OCP) was Dr. Ping Du and Dr. Anantha Ram Nookala was the Team Leader. Dr. Du states that the current submission includes a detailed study report for the relative bioavailability study (AXS-07-104) to support bridging to the LD, Mobic. Dr Du reports that Study AXS-07-104 is a randomized, open label, two-way crossover study to evaluate the pharmacokinetics (PK) of meloxicam in AXS-07 compared to Mobic tablets. The LD, Mobic tablets, was originally approved in the US in 2000 for chronic use in the treatment of osteoarthritis, rheumatoid arthritis, and juvenile rheumatoid arthritis in patients who weigh ≥60 kg.

The Office of Clinical Pharmacology (OCP) team identified that the meloxicam Cmax for the proposed product Symbravo (AXS-07) is slightly higher than the acceptable range, with the upper 90% confidence interval at 135% compared to the standard cut-off of 125% after a single dose, and 1.9 times higher than the listed drug (Mobic tablets) at steady state.

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.

The dose 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 bioavailability (BA) study described 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 a long-term extension study. Thus, the Applicant has established a scientific bridge to justify reliance on FDA's previous finding of safety for the LD Mobic and has provided adequate data to demonstrate the safety of a higher dose of meloxicam in this indicated population.

Refer to the OCP review in DARRTS dated April 15, 2022, for the review of the original submission and for information related to the acceptable bridging data provided for reliance on the LDs Maxalt and Anjeso.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Dr. Viveca Livezey conducted the clinical efficacy review for the original application. Dr. Shawna Cutting conducted the clinical review for this resubmission. Dr. Jinnan Liu conducted the biometrics review and Dr. John Lawrence was the biometrics Team Leader for both the original submission and the resubmission. The following is extracted from the Summary Review for the original submission dated April 29, 2022. No additional efficacy data were submitted in the resubmission.

Extracted from the Summary Review for the Original Submission

The Applicant conducted two placebo-controlled efficacy trials (Table 1) in adult migraine subjects with or without aura, Study 301, was conducted in subjects that experienced a

moderate to severe migraine attack and is considered the pivotal efficacy trial, and Study 303, conducted in subjects that experienced a mild migraine attack. In addition, an open-label long term safety study (AXS-07-302) was conducted to evaluate safety up to 12 months in subjects that treated on average 2 migraines a month with AXS-07.

Table 1: Phase 3 Clinical Studies

	Treatment Duration	Treatment arms
Study 301	Double-blind (DB) randomized treatment of a single migraine attack (moderate-severe pain) using a factorial design	AXS-07 (20 mg meloxicam, 10 mg rizatriptan), rizatriptan 10 mg, meloxicam 20 mg, placebo orally once
Study 303	DB randomized treatment of a single migraine attack (mild pain)	AXS-07, Placebo orally once
Study 302	Open-label, multicenter, long-term safety study	AXS-07 orally, treat all migraine attacks, up to 12 months. Maximum dose in 24 hours is 1 tablet.

Study 301

Study 301 was a multicenter, randomized, double-blind, placebo-controlled, 4-arm, parallel-group, single dose study designed to evaluate the efficacy and safety of AXS-07 for the acute treatment of migraine (associated with moderate to severe pain) and to establish a contribution of individual components of the combination product to the overall effect using a factorial design. Subjects were randomized in a 2:2:2:1 ratio to receive either AXS-07, rizatriptan 10 mg, meloxicam 20 mg, or placebo. Subjects did not have the option of using another tablet within the same day for either rescue or recurrence. Subjects were told not to take more than one tablet a day or more than 10 tablets a month. This study was conducted under a Special Protocol Assessment agreement.

Subjects eligible for enrollment into the trials were adults 18-65 years of age with a diagnosis of migraine with or without aura, and with 2-8 moderate or severe migraine attacks per month (but not more than 10 migraine days per month) for at least the last 3 months, but a history of migraine for at least 1 year. Subjects with chronic daily headache (greater or equal to 15 migraines per month for the past 3 months) were excluded.

The protocol had inclusion criterion as follows: History of inadequate response to prior acute migraine treatments, defined as a score of less than or equal to 7 on the Migraine Treatment Optimization Questionnaire (m-TOQ-4), which the Applicant proposes corresponds to moderate or worse response to prior treatments over the prior 4 weeks screening period. Given that the m-TOQ-4 was a measure that was not previously reviewed by the Division, the clinical outcome assessment (COA) team was consulted to determine the acceptability of this scale as a measure for treatment failure, as proposed by the Applicant. During development, the Applicant was informed that (b) (4)

(b) (4)

Instead, the Applicant chose to use the m-TOQ-4 to attempt to enrich this trial with subjects that failed treatment based on the Applicant's pre-specified threshold.

The co-primary endpoints used to evaluate efficacy were the proportion of subjects who were headache pain-free at 2 hours, and the proportion of subjects who were most bothersome symptom (MBS)-free at 2 hours, following the initial dose. Pain freedom was defined as the absence of migraine pain at 2 hours following the treatment of a qualifying migraine attack (defined below). The pain freedom endpoint was assessed using a 0-3 scale, where 0=no pain, 1=mild, 2=moderate, and 3=severe. The MBS for a qualifying migraine attack was defined as either nausea, phonophobia, or photophobia. The MBS endpoint was assessed in a binary fashion, as either present or absent. The key secondary endpoint, sustained pain freedom (SPF) 2- 24 hours, was used to measure a contribution of each individual component of the combination product to the overall effect. SPF 2 -24 hours was 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. In order to support this conclusion, AXS-07 had to demonstrate superiority over the individual components on sustained pain freedom 2- 24 hours. The efficacy of a second dose of study medication to treat either an unresolved headache or a headache that returned after initial resolution was not tested.

The intent to treat (ITT) population was the efficacy analysis population and was defined as all randomized subjects who had a qualifying migraine. The multiplicity adjustment method was pre-specified and deemed to be adequate. To adjust for multiplicity, the null hypothesis for the following 4 claims (item 1 has 2 claims for the co-primary efficacy variables) were tested in a stepdown hierarchical fashion, at a 2-sided significance level of 0.05:

1. AXS-07 versus placebo for the 2 co-primary endpoints
2. AXS-07 versus meloxicam for the key secondary endpoint (SPF 2-24 hours)
3. AXS-07 versus rizatriptan for the key secondary endpoint (SPF 2-24 hours)

If the above claims were established, the following secondary endpoints were to be examined in the pre-specified hierarchical order:

1. AXS-07 versus placebo for percentage of subjects with pain relief at hour 2
2. AXS-07 versus placebo for time to pain relief
3. AXS-07 versus placebo for 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 reported greater than none at baseline
4. AXS-07 over rizatriptan for percentage of subjects with pain freedom at hour 2
5. AXS-07 over rizatriptan for percentage of subjects with freedom from MBS at hour 2

If one of the analyses is not statistically significant, then all subsequent analyses will be exploratory rather than confirmatory.

Study 303

Study 303 was a multicenter, randomized, double-blind, placebo-controlled, 2-arm, parallel-group, single dose study designed to evaluate the efficacy and safety of AXS-07 for the acute treatment of migraine (associated with mild pain). Subjects were randomized in a 1:1 ratio to receive either AXS-07 or placebo. Subjects did not have the option of using another tablet within the same day for either rescue or recurrence.

Eligibility criteria were similar to that of Study 301. The co-primary endpoints used to evaluate efficacy were the proportion of subjects who were headache pain-free at 2 hours, and the proportion of subjects who were most bothersome symptom (MBS)-free at 2 hours, following the initial dose. The definitions of pain-free and MBS-free as described above for Study 301 are consistent with the definitions used in Study 303.

The intent to treat (ITT) population was the efficacy analysis population and was defined as all randomized subjects who had a qualifying migraine. The multiplicity adjustment method was pre-specified and deemed to be adequate.

The results are presented as the percentage of responders for each of the co-primary efficacy endpoints. The primary comparison was AXS-07 versus placebo. Between treatment group comparisons were performed via chi-square tests.

The two key secondary efficacy endpoints were examined in hierarchical order:

1. 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 reported greater than none at baseline
2. Time to pain freedom

If one of the analyses is not statistically significant, then all subsequent analyses will be exploratory rather than confirmatory.

Results

Study 301

The median age of the subjects was 41-42 years. Eighty-one to 85% of subjects were female, and 74%-78% were White. Demographic characteristics were generally balanced between treatment groups in each study with no clinically significant differences.

Baseline disease characteristics were balanced between treatment groups. 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.

Table 2 presents the results of the efficacy analyses for Study 301.

Table 2: Study AXS-07-301: Efficacy Endpoints

	Placebo (N=209) (n,%)	Meloxicam 20 mg (N=421) (n,%)	Rizatriptan 10 mg (N=419) (n,%)	AXS-07 (N=428) (n,%)
Co-Primary Endpoint				
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	<0.001	<0.001
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		0.0355	0.0039	0.002
Secondary Endpoint				
24-hour Sustained Pain Freedom*	11 (5.3%)	37 (8.8)	47 (11.2)	69 (16.1)
p-value vs AXS-07	<0.001	0.001	0.038	

Source: modified from Dr. Liu's review, Tables 5 and Table 12

*The prespecified endpoint was the comparison of AXS-07 to rizatriptan

Study 301 demonstrated a robust effect on both co-primary endpoints, and a significantly increased treatment effect on 24-hour sustained pain freedom of the combination product over both rizatriptan and meloxicam, thereby satisfying the combination therapy regulations.

Table 3 displays the results of the two secondary endpoints appropriate for inclusion in labeling, pain relief at 2 hours, and percentage of subjects able to perform normal daily activities at 2 hours.

Table 3: Study AXS-03-301: Secondary Endpoints

	Placebo (N=209)	AXS-07 (N=428)
Pain Relief at 2 Hours	n=114	n=296
%	54.5	69.2
p-value		<.001
Able to Perform Normal Daily Activities at 2 Hours	44	137
%	21.1	32.0
p-value		0.004

Source: modified from Dr. Liu 's review, Tables 14 and 18

A significant treatment effect on pain relief at 2 hours and the percentage of subjects able to perform normal daily activities at 2 hours, based on a 4-point scale, was seen for AXS-07 as compared to placebo. Although statistical significance was achieved on the endpoint, time to pain relief, due to deficiencies in the measurements, this endpoint should not be included in labeling. Specifically, the secondary endpoint, time to pain relief was calculated based on ten uneven time intervals, and, therefore, presenting the median value for this analysis is misleading.

Study 303

The median age of the subjects was 41-43 years. Eighty-five percent of subjects were female, and 81-84% were White. Demographic characteristics otherwise were generally balanced between treatment groups in each study with no clinically significant differences.

Baseline disease characteristics were balanced between treatment groups.

Table 4 presents the co-primary efficacy analyses.

Table 4: Study AXS-07-303: Primary Endpoint Analysis

Co-Primary Endpoint	**Placebo (N=135)**	**AXS-07 (N=132)**
2-hour Pain Freedom	22 (16.3)	43 (32.6)
Difference from AXS-07		16.3%
p-value vs placebo		0.002
2-hour MBS Freedom	36 (26.7)	58 (43.9)
Difference from AXS-07		17.2%
p-value vs placebo		0.003

Source: modified from Dr. Liu's review, Table 22

Study 303 demonstrates a robust effect on the co-primary endpoints of pain freedom and MBS freedom at 2 hours. The test for the first of the two prespecified key secondary endpoints was not significant, and so the testing stopped as per the statistical analysis plan.

Efficacy by subgroups

Dr. Liu performed analyses of the treatment effect across subgroups for both Studies 301 and 303 and concludes that the trend in treatment success appears to be similar across subgroups. (age, [redacted] and race). The study was conducted in the US; so, no analysis by region was performed.

Efficacy Conclusions

The Applicant has provided evidence to support efficacy of AXS-07 for the acute treatment of migraine with or without aura in adults based on the results from a single adequate and well-controlled investigation (Study 301). This study demonstrated statistically significantly greater

proportions of AXS-07 treated subjects who were pain-free and MBS-free at 2 hours post-dose, relative to placebo-treated patients. In addition, Study 301, demonstrated a statistically significantly greater proportion of AXS-07 subjects with SPF 2-24 hours as compared to rizatriptan, and meloxicam, thereby satisfying the combination therapy regulations. These findings were further supported by a positive treatment effect on the secondary endpoints, pain relief at 2 hours, and the percentage of subjects able to perform normal daily activities at 2 hours.

A single study was deemed acceptable to support this application because the product under review is a combination product for which one component is already approved for the treatment of migraine and the second component is an analgesic.

In addition, the Applicant provided an additional trial demonstrating that treatment of subjects with AXS-07 during a mild migraine attack leads to a statistically significantly greater proportion of subjects who were pain and MBS free at 2 hours, as compared to placebo.

The data provided in this application clearly demonstrate an effect of AXS-07 on pain freedom and migraine associated symptoms, as well as an effect on the SPF 2-24 hour endpoint demonstrating an improved effect for the combination over the individual components. Given these robust findings, and previous findings of efficacy of the LDs, Maxalt (that contains the same active ingredient as one component of this combination product and is marketed for the same indication) and Anjeso (containing the other component of this combination product and marketed as an analgesic) further supports its efficacy for the acute treatment of migraine without the need to replicate these findings in an additional efficacy trial.

8. Safety

Dr. Viveca Livezey conducted the clinical safety review of the original application. The safety information is this review is extracted from the Summary Review of the original submission. The Applicant submitted additional safety information in response to an Information Request. Dr. Shawna Cutting reviewed this additional information as part of the safety review of the resubmission.

Extracted from the Original Summary Review

As discussed by Dr. Livezey, the Applicant provided safety data from the controlled clinical trials (301 and 303), and the open label long term safety study (302). She reports that 1098 subjects were exposed to at least one dose of AXS-07 in the current development program. In order for subjects to be counted in the long-term safety database, subjects had to treat an average of 2 migraines a month. Four hundred and ninety-six subjects were treated for at least 6 months, and 132 subjects were treated for at least 12 months.

Dr. Livezey reports that there were no deaths in the development program. There was one serious adverse event (SAE) reported in the controlled clinical trials, and 8 reported in the open-label long-term safety study. None of the SAEs reported seemed to be related to AXS-

07. Dr. Livezey notes that there were no cardiovascular and/or gastrointestinal related SAEs. There were no subjects in the controlled efficacy trials that discontinued AXS-07 due to an adverse event (AE). In the open label long-term safety study, 5 subjects discontinued due to nausea or vomiting, and one subject discontinued due to sedation. Dr. Livezey concludes, based on her review, that the SAEs and AEs that led to discontinuations in this application do not warrant description in labeling.

Upon review of the treatment-emergent AEs, Dr. Livezey notes that dizziness and somnolence occurred at equal or greater than 1% higher than placebo. Refer to Table 5 below.

Table 5: Study AXS-07-301: Adverse Reactions Occurring at Greater than 1% and Greater than Placebo

	Placebo N=218 n(%)	**Meloxicam 20 mg N=433 n(%)**	**Rizatriptan 10 N=434 n(%)**	**AXS-07 N=441 n(%)**
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: Dr. Livezey's safety review, Table 23

Additional information provided in an Information Request response

In order to better understand the safety database in terms how many doses per month of Symbravo subjects in the long-term extension trial took, the Division sent an Information Request, and the response is summarized below.

In Study AXS-07-302, the majority (approximately 88%) of subjects treated 2-5 attacks per month on average. Table 6 shows the distribution of subjects who treated a given number of attacks per month over the entire duration of the study.

Table 6: Study AXS-07-302: Average Number of Treated Attacks per Month

Average number of treated attacks per month	Symbravo N=706 n (%)
1	68 (10%)
2-3	332 (47%)
4-5	287 (41%)
6-7	10 (1%)
8-9	0 (0%)
10 or more	0 (0%)

Source: Modified from Dr. Cutting's Clinical Review, Information Request response from the Applicant (January 6, 2025).

In Study AXS-07-302, the maximum number of attacks treated was higher than the average, with 30% treating 6 or 7 attacks at maximum. Refer to Table 7 that shows the distribution of subjects by maximum number of attacks treated within a month.

Table 7: Study AXS-07-302: Maximum Number of Treated Attacks per Month

Maximum number of treated attacks per month	Symbravo N = 706 n (%)
1	23 (3.3%)
2-3	117 (16.5%)
4-5	309 (43.6%)
6-7	218 (30.8%)
8-9	38 (5.4%)
10 or more	1 (0.1%)

Source: Modified from Dr. Cutting's Clinical Review, Information Request response from the Applicant (January 6, 2025).

Based on the review of the data provided on the number of monthly attacks that subjects treated, there are adequate safety data to support the use of up to seven doses of Symbravo per month, which represents more than the average monthly use in the trial and approximately 95% of the trial's treatment experience.

9. Advisory Committee Meeting

There was no advisory committee for this505(b)(2) application.

10. Pediatrics

This application triggered the Pediatric Research Equity Act (PREA) requirements because of the new indication and therefore the application included an Agreed iPSP. The Division met

with the Pediatric Review Committee (PeRC) on December 17, 2024. The PeRC concurred with the Division's recommendations to impose the PREA post marketing requirements (PMRs) listed in Section 13 of this review.

11. Other Relevant Regulatory Issues

Division of Medication Error Prevention and Analysis (DMEPA)

Dr. Beverly Weitzman was the primary reviewer and Dr. Stephanie DeGraw was Team Leader for the DMEPA review. DMEPA concludes that the final agreed-upon PI, medication guide, container labels are acceptable.

DMEPA reviewed the proposed proprietary name, Symbravo, and determined that this name was found conditionally acceptable on October 9, 2024.

Office of Scientific Investigations (OSI)

As per the OSI review of the original NDA submission, Dr. Cara Alfaro was the primary OSI reviewer for this application and Dr. Phillip Kronstein was the Team Leader. Dr. Alfaro stated that 3 clinical sites were inspected in support of this NDA, specifically for Studies 301 and 303. Dr. Alfaro concluded that despite some protocol deviations, the studies appear to have been conducted adequately, and the data generated by these sites appeared acceptable.

Division of Clinical Outcome Assessment (DCOA) Team

As per the DCOA team's review of the original NDA submission, Dr. Robert Fieo was the clinical reviewer for the COA consult, and Dr. David Reasner conducted the secondary review. Dr. Fieo was asked to provide an opinion on the interpretability of the Migraine Treatment Optimization Questionnaire (M-TOQ-4) as a screening tool for the Applicant's enrichment strategy, (b) (4). Dr. Fieo stated that the M-TOQ-4 was reviewed for content validity, as well as measurement properties. He concluded that the M-TOQ-4 values may be difficult to interpret meaningfully due to insufficient evidence pertaining to content comprehensiveness and measurement properties.

12. Labeling

Refer to the final negotiated product label. Labeling negotiations with the Applicant have been completed, and the Applicant has accepted all recommended changes.

There is an established drug-drug interaction between propranolol and rizatriptan, specifically that propranolol can increase the plasma AUC of rizatriptan by 70% which would increase the likelihood of adverse events associated with rizatriptan, including potentially serious outcomes. While other rizatriptan products have different approved doses, there is only one formulation of Symbravo (meaning there is no way to adjust the rizatriptan dose strength,) and there is no way to predict when a migraine would occur to allow for advising of a safe interval

between administration of propranolol and Symbravo. Therefore, the decision was made to contraindicate concomitant use of propranolol with Symbravo out of a concern for safety.

13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

There is no need for a Risk Evaluation and Management Strategy (REMS) for this drug product because the LDs used to establish safety for Symbravo in the context of this 505(b)(2) submission do not have a REMS, and the additional data submitted for Symbravo did not identify any new safety signals for Symbravo.

- Other Postmarketing Requirements and Commitments

The following PREA PMRs and pregnancy PMRs will be imposed with this application:

- 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.

- 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.

- 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.

- A pregnancy outcomes study using a different study design than provided for in PMR 3 (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.

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/

HEATHER D FITTER
01/30/2025 11:11:56 AM

PAUL R LEE
01/30/2025 12:31:06 PM

Summary Review

Date	April 29, 2022
From	Heather Fitter, MD Nick Kozauer, MD
Subject	Summary Review
NDA #	215431
Applicant	Axsome Therapeutics Inc.
Date of Submission	June 30, 2021
PDUFA Goal Date	April 29, 2022
Proprietary Name	Symbravo
Established or Proper Names	AXS-07, rizatriptan/meloxicam
Dosage Form	Oral Tablet (10 mg rizatriptan/20 mg meloxicam)
Recommended Dosing Regimen	One tablet at the onset of migraine
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s)	Acute treatment of migraine with or without aura in adults

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

AXS-07 (Symbravo) is a fixed dose combination product of 20 mg meloxicam and 10 mg rizatriptan for oral administration as a tablet. Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) currently marketed 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-$HT_{1B/1D}$ agonist that is marketed for the acute treatment of migraine with or without aura.

The Applicant is seeking an indication for the acute treatment of migraine with or without aura in adults. This application includes two efficacy trials. One that is required for approval and is considered a pivotal efficacy trial in which patients treat a migraine attack when the pain is moderate to severe, and a second trial in which patients are instructed to treat a migraine when the associated pain is mild. The standard for products approved for the acute treatment of migraine is to evaluate the treatment when administered during a migraine attack associated with pain of moderate to severe intensity. During development the Division told the Applicant 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 reviewing data from a single adequate and well controlled efficacy trial to support a marketing application for AXS-07.

Therefore, the Applicant has included in this application a single adequate and well-controlled pivotal trial with AXS-07 to support efficacy for the migraine indication, and largely relies on the Maxalt (rizatriptan) and Anjesco (meloxicam) label to support the safety of its product, using a 505(b)(2) approach. In addition, long term safety data was included in this application for AXS-07 that meet ICH guidelines for chronically administered drugs.

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

The efficacy of AXS-07 was demonstrated a single adequate and well-controlled study (AXS-07-301). The study used well-validated and clinically meaningful co-primary endpoints to establish efficacy; the proportion of patients who were pain-free and the proportion of patients who

were most bothersome symptom (MBS)-free at 2 hours after dosing for the acute treatment of a migraine attack. In addition, the study addressed the combination rule regulations (CFR 21 300.50) and demonstrated a contribution of each individual component to the overall effect, demonstrating superiority of the combination over meloxicam and rizatriptan when given individually on the endpoint, sustained pain freedom at 24 hours.

The treatment effect size for pain freedom at 2 hours post-dose was 13.2% greater than placebo (AXS-07 responder rate of approximately 19.9%). The treatment effect size for MBS-freedom at 2 hours post-dose was 12.5% greater than placebo (AXS-07 responder rate of 36.9%). Sustained pain freedom in the AXS-07 treatment group was significantly higher than meloxicam (7.3%) and rizatriptan (4.9%) and this information supports the demonstration of a contribution of each individual component to the overall effect of the fixed-dose combination. The efficacy of a second dose was not studied in this development program. These data support the efficacy of AXS-07 for the proposed indication based on the established effect on pain and MBS freedom, and demonstration of a contribution of each individual component of the combination product to the overall effect, with an effect on sustained pain freedom at 24 hours. A second adequate and well-controlled study was submitted (AXS-07-303), although this study was not a required efficacy study for this application. This study evaluated the efficacy of AXS-07 when administered to patients during a migraine associated with mild pain using the standard co-primary endpoints to establish efficacy, the proportion of patients who were pain-free and the proportion of patients who were MBS-free at 2 hours after dosing for the acute treatment of a mild migraine attack.

The safety profile of AXS-07 was supported by both pharmacokinetic bridging to the listed drugs (LD), rizatriptan (Maxalt) and meloxicam (Anjeso) and data from the two placebo controlled trials (AXS-07-301 and AXS-07-303), as well as one long-term safety study (AXS-07-302).

Despite the ability of this application to reference safety of the LDs, the long-term extension study was required due to the following limitations to the safety information of the LDs. The Anjesco label supports acute but not chronic administration of meloxicam. Although there is a marketed meloxicam product (Mobic) administered as a tablet for chronic use up to 15 mg daily, the Applicant did not use Mobic as an LD, so the safety information in the Mobic PI could not be relied upon. In development, the Applicant discussed the possibility of using Mobic as an LD but then decided not to take that path. In addition, given that the LD's labels both include a Warning and Precaution in the prescribing information (PI) related to cardiovascular risk, an evaluation of long-term safety to determine if this risk is increased when both drugs are used together, was needed. If labeling negotiations had occurred, recommendations would have been to include the Warnings and Precautions listed in the LDs PIs and to describe an increased incidence of dizziness and somnolence reported with AXS-07 as compared to placebo, in the controlled clinical trials.

Although efficacy was demonstrated in the pivotal efficacy trial, and AXS-07 demonstrated an acceptable safety profile for the intended population, there were significant CMC and nonclinical deficiencies. The CMC deficiencies related to inadequate drug product specification to control potential impurities, inadequate manufacturing controls to ensure consistent product quality, and inadequate data to support the proposed dissolution test method. The nonclinical deficiencies related to the lack of nonclinical data to support chronic oral administration of meloxicam and the lack of data to qualify the proposed limit (b) (4)%) for the impurity, rizatriptan-N-oxide. Due to the CMC and nonclinical deficiencies, a Complete Response action will be taken on this application.

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 various associated symptoms. The typical headache of migraine is throbbing, unilateral, and aggravated by motion, but bilateral and/or non-throbbing headaches are also commonly reported. Typical migraine-associated symptoms include nausea, vomiting, photophobia, and phonophobia, but a myriad of other neurological symptoms may occur, and various degrees of cognitive impairment are often present. Migraine attacks typically last from 4 to 72 hours in adults. About one-third of people with migraine experience transient neurological symptoms before and/or during an attack, referred to as a migraine aura. • Migraine was found to be the second highest cause of disability in the Global Burden of Disease Study in 2016. The prevalence of migraine is approximately 9% in males and 20% in females in the U.S., thus resulting in a major impact to public health.	Migraine is a serious and frequently disabling condition that can impact the quality of patients' lives.
Current Treatment Options	• There are many FDA-approved therapies for acute migraine such as triptans, dihydroergotamine (DHE), lasmiditan, CGRP receptor antagonists and certain non-steroidal anti-inflammatory drugs (NSAIDs), the latter which can be used alone or in combination with a triptan. In addition, there are several over-the-counter drugs marketed for migraine.	Several classes of drugs are indicated for the acute treatment of migraine with or without aura in adults. However, many patients still do not respond adequately to these therapies. AXS-07 offers another treatment option for migraine patients.
Benefit	• The efficacy of AXS-07 was demonstrated in an adequate and well-controlled clinical study (Study AXS-07-301). The study used well-validated and clinically meaningful endpoints to evaluate efficacy, the proportion of patients that are pain-free (PF) at 2 hours post-dose, and most bothersome symptom (MBS)-free at 2 hours post-dose. In addition, to demonstrate a contribution of the individual components of the combination	AXS-07 is effective for the acute treatment of a migraine with or without aura in adults. These data support the efficacy of AXS-07 for the proposed indication based on the established effect on pain

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	product to the overall effect, a higher treatment effect was seen on sustained pain freedom from 2 to 24 hours in the comparison of the AXS-07 group to the rizatriptan group, as well as in the comparison of the AXS-07 group to the meloxicam group. There was a statistically significant increase ($p \leq 0.001$) in the rate of pain freedom at 2 hours in the AXS-07 group (19.9%) as compared to the placebo group (6.7%). There was also a statistically significant increase ($p=0.002$) in the rate of MBS freedom at 2 hours in the AXS-07 group (36.9%) as compared to the placebo group (24.4%). • A second dose to treat a single migraine attack was not evaluated in the clinical efficacy study. • Rizatriptan has demonstrated efficacy for the acute treatment of migraine, such as Maxalt and Maxalt MLT. • Meloxicam is an NSAID with an acute pain indication. • The efficacy of AXS-07 was also demonstrated in one adequate and well controlled clinical study (Study AXS-07-303) that evaluated treatment during a mild migraine attack, rather than a moderate-severe migraine attack. Pain freedom at 2 hours was 32.6% in the AXS-07 treated group, compared to 16.3% in placebo ($p=0.002$). MBS freedom at 2 hours was 43.9% in the AXS-07 treated group, compared to 26.7% in the placebo group ($p=0.003$)	freedom and MBS freedom at 2 hours, in one trial in the context of the known efficacy of rizatriptan indicated for the same indication and of meloxicam with an acute pain indication. AXS-07 is a combination product of 20 mg meloxicam and 10 mg rizatriptan. The efficacy and safety of a second dose for a single migraine attack was not evaluated.
Risk and Risk Management	• The drug product specification is inadequate to control potential impurities, including potential (b) (4) degradants. In addition, manufacturing controls are inadequate to ensure consistent product quality, and the Applicant has not provided adequate data to support the proposed dissolution test method. • The nonclinical package did not include data to support chronic oral administration of meloxicam, and data were not provided to qualify the proposed limit (b) (4) %) for the impurity, rizatriptan-N-oxide. • Supportive safety data for AXS-07 is provided by the listed drugs, Anjesco and Maxalt.	There were no significant safety findings in the clinical studies that would preclude approval of AXS-07. CMC identified unresolved quality issues related to drug product, manufacturing, and biopharmaceutics disciplines. Nonclinical identified that adequate chronic toxicity data was not provided for meloxicam, and the impurity,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The Anjesco label includes a boxed warning for serious cardiovascular and gastrointestinal events, as well as Warnings and Precautions sections pertaining to hepatoxicity, hypertension, heart failure and edema, renal toxicity, anaphylactic reactions, exacerbation of asthma related to aspirin sensitivity, serious skin reactions, drug reaction with eosinophilia and systemic symptoms (DRESS), fetal toxicity, and hematologic toxicity. • The Maxalt label includes Warning and Precautions sections pertaining to myocardial ischemia, arrhythmias, Chest/throat/neck and/or jaw pain/pressure, cerebrovascular events, other vasospasm reactions, medication overuse headache, serotonin syndrome, and increase in blood pressure. • There were no serious safety issues identified in the controlled clinical trials conducted with AXS-07. • The incidence of dizziness (1.6% vs 0.9%) and somnolence (1.4% vs 0.5%) in the controlled clinical trials was increased in patients that received AXS-07 compared to placebo, respectively. Other uncertainties • Safety and efficacy in pediatric migraine patients has not been established.	rizatriptan-N-oxide was not adequately qualified. Due to the CMC and nonclinical deficiencies a Complete Response action will be taken for this application, therefore, labeling recommendations will not be made and PMRs will not be issued during this review cycle.

2. Background

This review discusses the data presented by Axsome Therapeutics Inc. (the Applicant) in support of a 505(b)(2) new drug application (NDA) for AXS-07 (Symbravo), a fixed dose combination product of an oral tablet of meloxicam 20 mg and rizatriptan 10 mg, for the acute treatment of migraine with or without aura in adults. The Applicant is relying on the listed drugs (LD), Anjesco (NDA 210583) and Maxalt (NDA 20864) to support the safety of its product, in addition to data from a 12 month long-term safety study using AXS-07.

Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) marketed for the management of moderate to severe pain as Anjesco and as tablets/capsules in other applications with indications for the relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis treatment. Rizatriptan is a 5-$HT_{1B/1D}$ agonist marketed for the proposed indication for this application and marketed as Maxalt (tablets) and Maxalt MLT (orally disintegrating tablets, NDA 20865). During development the Division told the Applicant 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 reviewing data from a single adequate and well controlled efficacy trial to support a marketing application for AXS-07.

Migraine is a primary headache disorder characterized by recurrent headaches that are moderate to severe, accompanied by various associated symptoms. The typical headache of migraine is throbbing, unilateral, and aggravated by motion, but bilateral and/or non-throbbing headache is also commonly reported. Typical migraine-associated symptoms include nausea, vomiting, photophobia, and phonophobia, but a range of other neurological symptoms may occur, with various degrees of cognitive impairment often present. Migraine attacks typically last between 4 to 72 hours in adults. About one-third of individuals with migraine experience transient neurological symptoms before and/or during a migraine attack, referred to as migraine aura. Generally accepted diagnostic criteria for migraine are presented in the International Classification of Headache Disorders-3 (ICHD-3).

Many products are FDA-approved for the acute treatment of migraine in adults. These products include a number of different triptans, dihydroergotamine, NSAIDs used alone or in combination with a triptan, a 5-HT_{1F} agonist (lasmiditan), and CGRP receptor antagonists (ubrogepant and rimegepant). There are also many over-the-counter medications that are labeled for the acute treatment of migraine. Despite the availability of numerous products, not all migraineurs respond well to the available therapies, the use of which can also be limited by safety concerns (e.g., restrictions for the use of triptans, ergotamines, and NSAIDs in patients with cardiovascular (CV) disease and driving restrictions for lasmiditan).

The Applicant provides data from a single placebo-controlled efficacy trial, Study AXS-07-301 (referred to as Study 301 in this review) in adult patients with migraine with or without aura to support the efficacy of AXS-07 for the proposed indication. In addition, a second placebo-controlled efficacy trial, Study AXS-07-303 (referred to as Study 303 in this review)

was submitted that evaluates the efficacy of AXS-07 for the acute treatment of migraine in patients that experienced a mild attack.

3. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Martha Heimann (refer to her review for the entire OPQ list of participants in the review of this application). The Applicant has developed a fixed dose combination tablet for oral administration composed of 20 mg meloxicam and 10 mg rizatriptan (equivalent to 14.53 mg as benzoate salt).

Dr. Heimann states that regarding the drug substance and facilities, the current application meets applicable standards to support its identity, strength, quality, and purity. 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.

Dr. Heimann recommends a Complete Response action be taken for this application from a product quality perspective.

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer for this application was Dr. Ed Nesti, with Dr. Lois Freed performing the secondary review. Dr. Nesti concludes that the nonclinical NDA package does not support approval of AXS-07, because 1) the Applicant has not provided data to support chronic oral administration of meloxicam, and 2) data were not provided to qualify the proposed limit (b) (4) %) for the impurity, rizatriptan-N-oxide.

Dr. Nesti reports that clinical development was allowed to proceed without the chronic toxicology studies because under the IND the Applicant had expressed plans to rely on Mobic (meloxicam) tablets, which are approved for chronic administration. However, Mobic was not given as a listed drug in the NDA.

5. Clinical Pharmacology

The primary reviewer from the Office of Clinical Pharmacology (OCP) was Dr. Muzeeb Syed and Dr. Gopichand Gottipati was the team leader. Dr. Syed states that the Applicant is seeking approval for Symbravo via a 505(b)(2) regulatory pathway. The proposed product, AXS-07, is a fixed dose combination product consisting of 20 mg meloxicam and 10 mg rizatriptan. The two LDs used in this application are Maxalt (rizatriptan) tablets (NDA 020864) and Anjesco (meloxicam) intravenous injection (NDA 210583), originally approved in the US in 1998 and 2020, respectively. Meloxicam tablets are also marketed in the US and were originally approved in 2000. The Applicant conducted two efficacy studies to support this application. A

factorial single dose study which included AXS-07, rizatriptan 10 mg, meloxicam 20 mg and placebo to evaluate the acute treatment of migraine associated with moderate to severe pain. In addition, the Applicant conducted a single dose double blind placebo controlled study with AXS-07 vs placebo to evaluate the acute treatment of migraine associated with mild pain. The Applicant also conducted two single dose clinical pharmacology studies, AXS-07-102 and AXS-07-103 to evaluate the relative bioavailability of rizatriptan component of AXS-07 to Maxalt tablets, meloxicam component of AXS-07 to Anjesco, and the impact of high fat high calorie meal intake on the pharmacokinetics (PK) of each component of AXS-07.

The Office of Study Integrity and Surveillance (OSIS) was consulted for clinical and analytical site inspections for the pivotal relative bioavailability studies AXS-07-102 and AXS-07-103 and stated that the inspection was not warranted for these sites since they were previously inspected and issued a No Action Indicated classification on (b) (4)

PK bridging between AXS-07 and Maxalt (LD for Rizatriptan)

Dr Syed reports that in Study AXS-07-102, a single-dose of AXS-07 (10 mg rizatriptan component), and a single-dose of 10 mg Maxalt tablet (listed drug for Rizatriptan) in 20 healthy subjects (10 subjects per treatment arm) were administered under fasting conditions. The PK samples were collected up to 60 hours post dose and were analyzed for rizatriptan and N-desmethyl rizatriptan (active metabolite) exposures. PK parameters C_{max}, AUC_{0-t} and AUC_{0-inf} were calculated for rizatriptan and N-desmethyl rizatriptan using noncompartmental analyses.

The relative bioavailability assessment was conducted by log-transforming PK parameters using an analysis of variance (ANOVA) model, which includes treatment as fixed effect. The ratio of the geometric mean ratio (test to reference), and the 90% confidence intervals were reported. All 20 subjects were included in PK analysis. The results are displayed in Table 1and Table 2 below.

Table 1: Study AXS-07-102: Relative Bioavailability Assessment Between AXS-07 and Maxalt for rizatriptan (source: Dr. Syed's review Table 1)

Parameter	Geometric LSM (Least Square Means)		Geometric LS Means Ratio	90% Confidence Interval of Geometric LS Mean Ratio	
	AXS-07	Maxalt	Ratio (%)	Lower (%)	Upper (%)
AUC0-t (h*pg/ml)	84423	73511	116.34	92.02	147.09
AUC0-inf (h*pg/ml)	85781	74300	116.94	92.53	147.78
Cmax (pg/ml)	31684	24807	129.07	97.07	171.62

Table 2: Study AXS-07-102: Relative Bioavailability Assessment between AXS-07 and Maxalt for N-desmethyl rizatriptan (source: Dr. Syed's review Table 2)

Parameter	Geometric LSM (Least Square Means)		Geometric LS Means Ratio	90% Confidence Interval of Geometric LS Mean Ratio	
	AXS-07	Maxalt	Ratio (%)	Lower (%)	Upper (%)
AUC0-t (h*pg/ml)	6667	5858	115.84	94.81	141.55
AUC0-inf (h*pg/ml)	6768	5940	115.89	94.79	141.69
Cmax (pg/ml)	1815	1544	120.47	98.86	146.81

Dr. Syed concludes that the study results from AXS-07-102 showed that the mean relative bioavailability estimate for rizatriptan component was 115%, and N-desmethyl rizatriptan was 116%. However, the approved USPI for Maxalt notes that the maximum allowed total daily

dosage of 30 mg in any 24 hour period, exceeding the rizatriptan component dose of 10 mg in AXS-07. Thus, Maxalt provides adequate coverage for rizatriptan exposure from AXS-07, suggesting that an adequate PK bridge between AXS-07 and Maxalt for rizatriptan component has been established. This allows the Applicant to rely upon FDA's previous findings of the listed drug for relevant sections of Maxalt label.

Summary of PK Bridging between AXS-07 and Anjesco (LD for meloxicam)

Dr. Syed reports that in Study AXS-07-103, a single-dose of AXS-07 (20 mg meloxicam component) was given orally under fasting conditions, and a single-dose of 30 mg Anjeso was given intravenously in 16 subjects. The PK samples were collected up to 60 hours post dose and were analyzed for meloxicam exposures. PK parameters C_{max}, AUC_{0-t} and AUC_{0-inf} were calculated for meloxicam using non-compartmental analyses. The Applicant excluded data from two subjects who received AXS-07 based on pre-specified criteria (pre-dose concentration higher than 5% of the respective C_{max}), while no data was excluded for Anjeso administration. The PK metrics for meloxicam component from AXS-07 and Anjeso are summarized in Table 3 below.

Table 3: Study AXS-07-103: Summary of PK Parameters between AXS-07 and Anjesco for meloxicam (source: Dr. Syed's review Table 3)

Parameter	**AXS-07 (20 mg meloxicam) Fasted state**		**Anjeso 30 mg meloxicam intravenous injection**	
	Mean	**%CV**	**Mean**	**%CV**
AUC0-t (h*ng/ml)	47419	22.4	72087	25.2
AUC0-inf (h*ng/ml)	53532	27.3	83746	33.2
Cmax (ng/ml)	2936	27.9	4852	17.0

Dr. Syed states that the Applicant excluded 2 subjects in the fasted state from the PK analysis of meloxicam data. He conducted an independent sensitivity analysis to evaluate the potential impact of exclusion of these subjects from the PK analyses [on the exposure (C_{max}, AUC_{last} and AUC_{0-inf})] of meloxicam on the overall conclusions. These sensitivity analyses showed exclusion of these subjects had a minimal impact on meloxicam exposures and the overall conclusions remain unaffected.

The study results from AXS-07-103 showed that meloxicam exposures were higher following 30 mg Anjeso intravenous injection compared to those following AXS-07 (20 mg meloxicam) administration under fasting condition. The mean relative bioavailability estimate for the meloxicam component was 95%. However, the dose of Anjeso is higher than that recommended for AXS-07, providing adequate exposure coverage. This allows the Applicant to rely upon FDA's previous findings of the listed drug for relevant sections of Anjeso label.

Food Effect Assessment

Dr. Syed reports that in Study AXS-07-103, a single-dose of AXS-07 was given orally under fasting conditions, and with high-fat, high-calorie meal conditions in 16 subjects. The PK samples were collected up to 60 hours post dose and were analyzed for rizatriptan, N-desmethyl rizatriptan, and meloxicam exposures. PK parameters C_{max}, AUC_{0-t} and AUC_{0-inf} were calculated for rizatriptan, N-desmethyl rizatriptan, and meloxicam using noncompartmental analyses. The Applicant excluded data from five subjects (two in fasted state and three in fed state), when analyzing the food-effect assessment on meloxicam component, based on pre-specified criteria (pre-dose concentration higher than 5% of the respective C_{max}), while no data was excluded for rizatriptan component.

Dr. Syed concludes that the study results of food-effect assessment from AXS-07-103 showed that administration of AXS-07 with a high-fat high-calorie meal did not significantly affect rizatriptan, N-desmethyl rizatriptan, and meloxicam (except Cmax, which was slightly lower) exposures. Overall, these changes in exposures under fed conditions relative to those under fasting conditions, are not expected to be clinically significant, in the context of efficacy findings from study AXS-07-301. Additionally, subjects in the pivotal Phase 3 study AXS-07-301 were instructed that the single-dose of AXS-07 can be taken without regards to meal intake. In summary, the bridging conclusions noted above are not affected under fed conditions.

The Office of Clinical Pharmacology team reviewed the information submitted under this NDA and recommends approval of AXS-07 for the treatment of acute treatment of migraine headaches with or without aura in adults, pending appropriate labeling edits and negotiations with the Applicant.

The recommendation is based on demonstration of an adequate bridge between AXS-07 and LDs Anjeso (Meloxicam; 30 mg intravenous dose) and Maxalt (Rizatriptan; 10 mg tablets).

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical - Efficacy

Dr. Viveca Livezey conducted the clinical efficacy review for this application. Dr. Jinnan Liu conducted the biometrics review and Dr. John Lawrence was the biometrics team leader.

The Applicant conducted two placebo-controlled efficacy trials (Table 4) in adult migraine patients with or without aura, Study 301, was conducted in patients that experienced a moderate to severe migraine attack and is considered the pivotal efficacy trial, and Study 303, conducted in patients that experienced a mild migraine attack. In addition, an open-label long term safety study (AXS-07-302) was conducted to evaluate safety up to 12 months in patients that treated on average 2 migraines a month with AXS-07.

Table 4: Phase 3 Clinical Studies

	Treatment Duration	Treatment arms
Study 301	Double-blind (DB) randomized treatment of a single migraine attack (moderate-severe pain) using a factorial design.	AXS-07 (20 mg meloxicam, 10 mg rizatriptan), rizatriptan 10 mg, meloxicam 20 mg, placebo orally once
Study 303	DB randomized treatment of a single migraine attack (mild pain).	AXS-07, Placebo orally once
Study 302	Open-label, multicenter, long-term safety study	AXS-07 orally, treat all migraine attacks, up to 12 months. Maximum dose in 24 hours is 1 tablet.

Study 301

Study 301 was a multicenter, randomized, double-blind, placebo-controlled, 4-arm, parallel-group, single dose study designed to evaluate the efficacy and safety of AXS-07 for the acute treatment of migraine (associated with moderate to severe pain) and to establish a contribution of individual components of the combination product to the overall effect using a factorial design. Patients were randomized in a 2:2:2:1 ratio to receive either AXS-07, rizatriptan 10 mg, meloxicam 20 mg, or placebo. Patients did not have the option of using another tablet within the same day for either rescue or recurrence. Patients were told not to take more than one tablet a day or more than 10 tablets a month. This study was conducted under a Special Protocol Assessment agreement.

Patients eligible for enrollment into the trials were adults 18-65 years of age with a diagnosis of migraine with or without aura, and with 2-8 moderate or severe migraine attacks per month (but not more than 10 migraine days per month) for at least the last 3 months, but a history of migraine for at least 1 year. Patients with chronic daily headache (greater or equal to 15 migraines per month for the past 3 months) were excluded.

The protocol had an inclusion criterion as follows: History of inadequate response to prior acute migraine treatments, defined as a score of less than or equal to 7 on the Migraine Treatment Optimization Questionnaire (m-TOQ-4), which the Applicant proposes corresponds to moderate or worse response to prior treatments over the prior 4 weeks screening period. Given that the m-TOQ-4 was a measure that was not previously reviewed by the Division, the clinical outcome assessment (COA) team was consulted to determine the acceptability of this

scale as a measure for treatment failure, as proposed by the Applicant. During development, the Applicant was informed that (b) (4) (b) (4) (b) (4) Instead, the Applicant chose to use the m-TOQ-4 to attempt to enrich this trial with patients that failed treatment based on the Applicant's pre-specified threshold.

The co-primary endpoints used to evaluate efficacy were the proportion of patients who were headache pain-free at 2 hours, and the proportion of patients who were most bothersome symptom (MBS)-free at 2 hours, following the initial dose. Pain freedom was defined as the absence of migraine pain at 2 hours following the treatment of a qualifying migraine attack (defined below). The pain freedom endpoint was assessed using a 0-3 scale, where 0=no pain, 1=mild, 2=moderate, and 3=severe. The MBS for a qualifying migraine attack was defined as either nausea, phonophobia, or photophobia. The MBS endpoint was assessed in a binary fashion, as either present or absent. The key secondary endpoint, sustained pain freedom 2- 24 hours, was used to measure a contribution of each individual component of the combination product to the overall effect. SPF 2 -24 hours was 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. In order to support this conclusion, AXS-07 had to demonstrate superiority over the individual components on sustained pain freedom 2- 24 hours. The efficacy of a second dose of study medication to treat either an unresolved headache or a headache that returned after initial resolution was not tested.

The intent to treat (ITT) population was the efficacy analysis population and was defined as all randomized patients who had a qualifying migraine. The multiplicity adjustment method was pre-specified and deemed to be adequate. To adjust for multiplicity, the null hypothesis for the following 4 claims (item 1 has 2 claims for the co-primary efficacy variables) were tested in a stepdown hierarchical fashion, at a 2-sided significance level of 0.05:

1. AXS-07 versus placebo for the 2 co-primary endpoints
2. AXS-07 versus meloxicam for the key secondary endpoint (SBF 2-24 hours)
3. AXS-07 versus rizatriptan for the key secondary endpoint (SBF 2-24 hours)

If the above claims were established, the following secondary endpoints were to be examined in the pre-specified hierarchical order:

1. AXS-07 versus placebo for percentage of subjects with pain relief at hour 2
2. AXS-07 versus placebo for time to pain relief
3. AXS-07 versus placebo for 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 reported greater than none at baseline.
4. AXS-07 over rizatriptan for percentage of subjects with pain freedom at hour 2.
5. AXS-07 over rizatriptan for percentage of subjects with freedom from MBS at hour 2.

If one of the analyses is not statistically significant, then all subsequent analyses will be

exploratory rather than confirmatory.

Study 303

Study 303 was a multicenter, randomized, double-blind, placebo-controlled, 2-arm, parallel-group, single dose study designed to evaluate the efficacy and safety of AXS-07 for the acute treatment of migraine (associated with ***mild pain***). Patients were randomized in a 1:1 ratio to receive either AXS-07 or placebo. Patients did not have the option of using another tablet within the same day for either rescue or recurrence.

Eligibility criteria were similar to that of Study 301. The co-primary endpoints used to evaluate efficacy were the proportion of patients who were headache pain-free at 2 hours, and the proportion of patients who were most bothersome symptom (MBS)-free at 2 hours, following the initial dose. The definitions of pain-free and MBS-free as described above for Study 301 are consistent with the definitions used in Study 303.

The intent to treat (ITT) population was the efficacy analysis population and was defined as all randomized patients who had a qualifying migraine. The multiplicity adjustment method was pre-specified and deemed to be adequate.

The results are presented as the percentage of responders for each of the co-primary efficacy endpoints. The primary comparison was AXS-07 versus placebo. Between treatment group comparisons were performed via chi-square tests.

The two key secondary efficacy endpoints were examined in hierarchical order:

1. 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 reported greater than none at baseline.
2. Time to pain freedom

If one of the analyses is not statistically significant, then all subsequent analyses will be exploratory rather than confirmatory.

Results

Study 301

The median age of the patients was 41-42 years. Eighty-one to 85% of patients were female, and 74%-78% were White. Demographic characteristics were generally balanced between treatment groups in each study with no clinically significant differences.

Baseline disease characteristics were balanced between treatment groups. 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.

Table 2 presents the results of the efficacy analyses for Study 301.

Table 5: Study AXS-07-301: Efficacy Endpoints (source: modified from Dr. Liu's review Tables 5 and Table 12)

Co-Primary Endpoint	**Placebo (N=209) (n,%)**	**Meloxicam 20 mg (N=421) (n,%)**	**Rizatriptan 10 mg (N=419) (n,%)**	**AXS-07 (N=428) (n,%)**
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**	**<0.001**	**<0.001**
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**
Secondary Endpoint				
24-hour Sustained Pain Freedom*	**11 (5.3%)**	**37 (8.8)**	**47 (11.2)**	**69 (16.1)**
p-value vs AXS-07	**<0.001**	**0.001**	**0.038**	

***The prespecified endpoint was the comparison of AXS-07 to rizatriptan**

Study 301 demonstrated a robust effect on both co-primary endpoints, and a significantly increased treatment effect on 24-hour sustained pain freedom of the combination product over both rizatriptan and meloxicam, thereby satisfying the combination therapy regulations.

Table 6 displays the results of the two secondary endpoints appropriate for inclusion in labeling, pain relief at 2 hours, and percentage of subjects able to perform normal daily activities at 2 hours.

Table 6: Study AXS-03-301: Secondary Endpoints (source: modified from Dr. Liu 's review Tables 14 and 18)

	Placebo (N=209)	**AXS-07 (N=428)**
Pain Relief at 2 Hours	n=114	n=296
%	54.5	69.2
p-value		<.001
Able to Perform Normal Daily Activities at 2 Hours	44	137
%	21.1	32.0
p-value		0.004

A significant treatment effect on pain relief at 2 hours and the percentage of patients able to perform normal daily activities at 2 hours, based on a 4 point scale, was seen for AXS-07 as compared to placebo. Although statistical significance was achieved on the endpoint, time to pain relief, due to deficiencies in the measurements, I do not recommend including this endpoint in labeling if future labeling negotiations are warranted. Specifically, the secondary endpoint, time to pain relief was calculated based on ten uneven time intervals and therefore, presenting the median value for this analysis is misleading.

Study 303

The median age of the patients was 41-43 years. Eighty-five percent of patients were female, and 81-84% were White. Demographic characteristics were generally balanced between treatment groups in each study with no clinically significant differences.

Baseline disease characteristics were balanced between treatment groups.

Table 4 presents the co-primary efficacy analyses.

Table 7: Study AXS-07-303: Primary Endpoint Analysis (source: modified from Dr. Liu's review Table 22)

Co-Primary Endpoint	Placebo (N=135)	AXS-07 (N=132)
2-hour Pain Freedom	**22 (16.3)**	**43, (32.6)**
Difference from AXS-07		**16.3%**
P value vs placebo		**0.002**
2-hour MBS Freedom	**36, (26.7)**	**58 (43.9)**
Difference from AXS-07		**17.2%**
P value vs placebo		**0.003**

Study 303 demonstrates a robust effect on the co-primary endpoints of pain and MBS freedom at 2 hours. The test for the first of the two prespecified key secondary endpoints was not significant, so the testing stopped.

Efficacy by subgroups

Dr. Liu performed analyses of the treatment effect across subgroups for both Studies 301 and 303 and concludes that the trend in treatment success appears to be similar across subgroups. (age, [redacted] and race). The study was conducted in the US, so no analysis by region was needed.

Efficacy Conclusions

The Applicant has provided evidence to support efficacy of AXS-07 for the acute treatment of migraine with or without aura in adults based on the results from a single adequate and well-controlled investigation (Study 301). This study demonstrated statistically significantly greater proportions of AXS-07 treated patients who were pain-free and MBS-free at 2 hours post-dose, relative to placebo-treated patients. In addition, Study 301, demonstrated a statistically significantly greater proportion of AXS-07 patients with SPF 2-24 hours as compared to rizatriptan, and meloxicam, thereby satisfying the combination therapy regulations. These findings were further supported by a positive treatment effect on the secondary endpoints, pain relief at 2 hours, and the percentage of subjects able to perform normal daily activities at 2 hours.

A single study was deemed acceptable to support this application because the product under review is a combination product for which one component is already approved for the treatment of migraine and the second component is an analgesic.

In addition, the Applicant provided an additional trial demonstrating that treatment of patients with AXS-07 during a mild migraine attack leads to a statistically significantly greater proportion of patients who were pain and MBS free at 2 hours, as compared to placebo.

This data provided in this application clearly demonstrates an effect of AXS-07 on pain freedom and migraine associated symptoms, as well as an effect on the SPF 2-24 hour endpoint demonstrating an improved effect for the combination over the individual components. Given these robust findings, and previous findings of efficacy of the LDs, Maxalt (that contains the same active ingredient as one component of this combination product and is marketed for the same indication) and Anjesco (containing the other component of this combination product and marketed as an analgesic) further supports its efficacy for the acute treatment of migraine without the need to replicate these findings in an additional efficacy trial.

8. Safety

Dr. Viveca Livezey conducted the clinical safety review of this application.

As discussed by Dr. Livezey, the Applicant provided safety data from the controlled clinical trials (301 and 303), and the open label long term safety study (302). She reports that 1098 patients were exposed to at least one dose of AXS-07 in the current development program. In order for patients to be counted in the long term safety database, patients had to treat an average of 2 migraines a month. Four hundred and ninety six patients were treated for at least 6 months, and 132 patients were treated for at least 12 months.

Dr. Livezey reports that there were no deaths in the development program. There was one serious adverse event (SAE) reported in the controlled clinical trials, and 8 reported in the open-label long-term safety study. None of the SAEs reported seemed to be related to AXS-07. Dr. Livezey notes that there were no cardiovascular and/or gastrointestinal related SAEs. There were no patients in the controlled efficacy trials that discontinued AXS-07 due to an adverse event (AE). In the open label long-term safety study, 5 patients discontinued due to

nausea or vomiting, and one patient discontinued due to sedation. Dr. Livezey concludes, based on her review, that the SAEs and AEs that led to discontinuations in this application do not warrant description in labeling.

Upon review of the treatment-emergent AEs, Dr. Livezey notes that dizziness and somnolence occurred at equal or greater than 1% higher than placebo. Refer to Table 8 below.

Table 8: Study AXS-07-301: Adverse Reactions Occurring at Greater than 1% and Greater than Placebo (source: Dr. Livezey's review Table 23)

	Placebo N=218 n(%)	Meloxicam 20 mg N=433 n(%)	Rizatriptan 10 N=434 n(%)	AXS-07 N=441 n(%)
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)**

Safety Conclusions
There are no safety issues that preclude approval.

AXS-07 has a favorable safety profile. There were no deaths or SAEs in the controlled trials associated with AXS-07. Common adverse events that occurred at a rate of at least 1% and greater than placebo were dizziness and somnolence. Labeling negotiations were not conducted with the Applicant due to CMC and nonclinical deficiencies in the application. In future review cycles if this product is marketed, the label will reflect the Warnings and Precautions described in the Anjesco and Maxalt label.

9. Pediatrics

This application triggered PREA but since a Complete Response action will be taken, pediatric post marketing requirements will not be issued with this action.

10. Other Relevant Regulatory Issues

Office of Scientific Investigations (OSI)
Dr. Cara Alfaro was the primary OSI reviewer for this application and Dr. Phillip Kronstein was the team leader. Dr. Alfaro states that 3 clinical sites were inspected in support of this NDA, specifically for Studies 301 and 303. Dr. Alfaro concludes that despite some protocol deviations, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable.

Division of Medication Error Prevention and Analysis (DMEPA)

Dr. Beverly Weitzman was the primary reviewer and Dr. Stephanie DeGraw was team leader for the DMEPA review. DMEPA concludes that the final agreed-upon PI, container labels, and carton labeling are acceptable.

Dr. Weitzman reviewed the proposed proprietary name, Symbravo and determined that this name was found conditionally acceptable on March 7, 2022. Dr. Weitzman identified medication error issues and provided recommendations to minimize the risk of medication errors.

Clinical Outcome Assessment (COA) Team

Dr. Robert Fieo was the clinical reviewer for the COA consult, and Dr. David Reasner conducted the secondary review. Dr. Fieo was asked to opine on the interpretability of the Migraine Treatment Optimization Questionnaire (M-TOQ-4) as a screening tool for the Applicant's enrichment strategy, (b) (4) Dr. Fieo states that the M-TOQ-4 was reviewed for content validity, as well as measurement properties. He concludes that the M-TOQ-4 values may be difficult to meaningfully interpret due to insufficient evidence pertaining to content comprehensiveness and measurement properties.

11. Labeling

Deficiencies in the application precluded discussion of labeling.

12. Postmarketing Recommendations

No post marketing requirements were issued since a Complete Response action will be taken for this application.

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/

HEATHER D FITTER
04/29/2022 04:33:31 PM

NICHOLAS A KOZAUER
04/29/2022 04:57:29 PM