CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215431Orig1s000

STATISTICAL REVIEW(S)

NDA 215431 SN 25 Resubmission (SN01 Stats Review Addendum)

Relevant Background:
This NDA 215431 SN 01 was submitted on 6/30/2021, and statistical review was completed and filed into DARRTS on 4/27/2022 (https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8065ba7f) A CR letter citing nonclinical and CMC deficiencies was issued on April 29, 2022.The applicant has addressed the issues in the CR letter and sent in a resubmission SN 25 on 7/31/2024. Please note that there are no new efficacy data in this resubmission. The main purpose for stats team in this NDA resubmission is to support the labeling discussion. We have a few addendum tables for efficacy results in Section 14 of the labeling.

1) To follow the example of Trximet labeling section 14, which is also a trial with 4 arms for a combinatory product of 2 approved drugs, the clinical team would like to present the efficacy results for all 4 arms in one table while limiting p value reporting to those prespecified in SAP as footnotes. Here's the table in the desired format and layout. All analysis results needed for this table have been provided by the applicant in the submission, in multiple places and tables, and verified by stats reviewer, as noted in the footnotes.

Table 3 Migraine Efficacy Endpoints in Study 1 [a]

	AXS-07 (N=428)	Rizatriptan (N=419)	Meloxicam (N=421)	Placebo (N=209)
Co-Primary Endpoints				
Pain Free at Hour 2	19.9%[b]	17.4%	11.6%	6.7%
MBS Free at Hour 2	36.9%[b]	35.8%	32.5%	24.4%
Key-Secondary Endpoint				
24 Hour Sustained Pain Freedom	16.1%[c]	11.2%	8.8%	5.3%
Other Secondary Endpoints				
Pain Relief at Hour 2	69.2%[b]	65.6%	62.0%	54.5%
Able to Perform Normal Daily Activities at Hour 2	32.0%[b]	30.3%	24.5%	21.1%

[a] *P* values provided only for prespecified comparisons.
[b] *P*<0.01 versus placebo.
[c] *P*<0.05 versus rizatriptan, and meloxicam.
(Source: Table 14.2.1.1, 14.2.2.1, 14.2.3, 14.2.4, 14.2.10 of CSR 301, verified by stats reviewer.)

2) Here's a Table 4A as addendum to Table 4 of stats review filed into DARRTS on 4/27/2022, to show the baseline MBS (Most Bothersome Symptom) breakdown for study 301, (b) (4) (b) (4) I was able to use MBSBL from ADSL to get the counts and percentages.

Table 4A Patient Baseline MBS (Most Bothersome Symptom) - mITT - Study AXS-07-301

N %	MBSBL (MBS at Baseline) Nausea	 Sensitivity to light	 Sensitivity to sound	 Total
AXS07	90 21.03	267 62.38	71 16.59	428
Meloxicam	95 22.57	244 57.96	82 19.48	421
Placebo	37 17.7	129 61.72	43 20.57	209
Rizatriptan	72 17.18	260 62.05	87 20.76	419
Total	294 19.91	900 60.93	283 19.16	1477

(Source: stats reviewer's own analysis using ADAM data ADSL provided by the applicant.)

3) Correction of a Typo in Table 3 of stats review filed into DARRTS on 4/27/2022:
The Maximum age for Meloxicam group in study 301 should be 67, not 57.

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/

JINNAN LIU
01/28/2025 11:45:44 AM

JOHN P LAWRENCE
01/28/2025 11:57:54 AM

HSIEN MING J HUNG
01/28/2025 12:14:09 PM

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	NDA 215431
Drug Name:	AXS-07 (Meloxicam and Rizatriptan)
Indication(s):	Acute treatment of Migraine in adults
Applicant:	Axsome Therapeutics
Date(s):	Stamp date: 6/30/2021 (date received by CDER) PDUFA date: 4/29/2022
Review Priority:	Standard Review
Biometrics Division:	Division of Biometrics 1
Statistical Reviewer:	Jinnan Liu, Ph.D., Statistical Reviewer
Concurring Reviewers:	John Lawrence, Ph.D., Statistical Team Leader Hsien Ming Hung, Ph.D., Division Director
Medical Division:	Division of Neurology II
Clinical Team:	Viveca Livezey, M.D., Clinical Reviewer Heather Fitter, M.D., Clinical Team Leader Paul Lee, M.D., DN2 Deputy Division Director Nick Kozauer, M.D., DN2 Division Director
Project Manager:	Lana Chen

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

This NDA submission is to seek approval of AXS-07 for the acute treatment of migraine in adults. The efficacy evidence for the AXS-07 is from two Phase III studies: AXS-07-301 and AXS-07-303.

This is a 505(b)(2) application. There are two component RLDs (Referenced Listed Drug): Meloxicam, or, Anjeso Injection, by Baudax Bio, Inc., approved in Feb 2020 for pain relief under NDA210583, and Rizatriptan benzoate, or, Maxalt Tablets, by Merck & Co., Inc., initial approved in 1998 for acute migraine under NDA020864.

1.1 Conclusions and Recommendations

The two studies AXS-07-301 and AXS-07-303 in patients with acute migraine presented statistical evidence that AXS-07 is efficacious for treating migraine based on pain free status and MBS free status at 2 hours post dose.

The intensity of migraine attacks treated in Study 303 were mild using the 4 points scale: 1-mild, 2-moderate, 3-severe or 0-none. The current guidance on migraine drug requires the intensity to reach moderate to severe in pivotal trials. Therefore study 303 is not considered as a pivotal study and its result may not be allowed in the labeling. Please see clinical review for more detailed comments.

1.2 Brief Overview of Clinical Study AXS-07-301 (Pivotal) and AXS-07-303 (Non Pivotal)

The pivotal Phase 3 study AXS-07-301 was a multi-center, 4-arm, randomized, double-blinded, parallel group and placebo-controlled study to evaluate the efficacy of AXS-07 (20 mg meloxicam-10 mg rizatriptan) in the acute treatment of migraine in adults.

The non-pivotal Phase 3 study AXS-07-303 was a multi-center, 2-arm, randomized, double-blinded, parallel group and placebo-controlled study to evaluate the efficacy of AXS-07 (20 mg meloxicam-10 mg rizatriptan) versus placebo in the acute treatment of migraine in adults.

Both studies are completed, and the study reports are included in the current submission.

1.3 Statistical Issues and Findings

No major statistical issues were found.

2 INTRODUCTION

Two studies AXS-07-301 and AXS-07-303 are included in this statistical review for efficacy evaluation.

2.1 Overview

AXS-07 (20 mg meloxicam-10 mg rizatriptan) is a fixed-dose combination of meloxicam and rizatriptan being developed for the acute treatment of migraine with or without aura in adults.

The rationale for combining meloxicam with rizatriptan is based on the potential additive efficacy of the distinct mechanisms of action of these two agents, and the improved pharmacokinetic properties of the meloxicam formulation in AXS-07.

AXS-07 tablets are formulated to provide faster dissolution and absorption of meloxicam as compared to standard oral preparations, enabling the use of meloxicam for the acute treatment of migraine.

Table 1 List of All Studies included in Review

Trial ID	Design*	Treatment/ Sample Size	Endpoint/ Analysis	Preliminary Findings
AXS-07-301	MC, R, DB, PG, PC	Placebo / 209 AXS-07 / 428	Pain Freedom at 2 hours post-dose	6.7% in Placebo group 19.9% in AXS-07 group with p-value <0.001
			MBS Freedom at 2 hours post-dose	24.4% in Placebo group 36.9% in AXS-07 group With p-value = 0.002
AXS-07-303**	MC, R, DB, PG, PC	Placebo / 135 AXS-07 / 132	Pain Freedom at 2 hours post-dose	16.3% in Placebo group 32.6% in AXS-07 group with p-value = 0.002
			MBS Freedom at 2 hours post dose	26.7% in Placebo group 43.9% in AXS-07 group With p-value =0.003

*MC: multi-center, R: randomized, DB: double-blinded, PG: parallel group, PC: placebo controlled.
** The intensity of migraine attacks treated in Study 303 were mild using the 4 points scale: 1-mild, 2-moderate, 3-severe or 0-none. The current guidance on migraine drug requires the intensity to reach moderate to severe in pivotal trials. Please see clinical review for more detailed comments.

2.2 Data Sources

All documents reviewed for this NDA submission are in electronic form. At the time of review, the following is the link to the EDR Location:
\\CDSESUB1\evsprod\NDA215431\0001

The SAS codes for efficacy analyses were submitted on 7/30/2021:
\\CDSESUB1\evsprod\NDA215431\0002

SAS program files received in SN2 for study 301 and 303:

Study 301	Study 303
t-14-2-1.sas t-14-2-1-2.sas t-14-2-3-2.sas t-14-2-5.sas t-14-2-6.sas t-14-2-7.sas t-14-2-11.sas t-14-2-14.sas t-14-2-15.sas	t-14-2-1.sas t14-2-1-2.sas t14-2-9-1.sas t14-2-18.sas t14-2-19.sas t14-2-20.sas t14-2-21.sas t-14-2-22.sas t-14-2-23.sas t14-2-32.sas t14-2-33.sas

3 STATISTICAL EVALUATION

Two studies AXS-07-301 and AXS-07-303 are included in this statistical review.

3.1 Data and Analysis Quality

There are some minor issues with data/analysis and documentation process.

(1) For both study 301 and 303, the rescue medication use before 2 hours should not be treated same as missing data (Pain/MBS status missing), yet the sensitivity analyses result has included imputation for rescue mediation use before 2 hours which implies that those were considered as missing, in the sponsor's study reports. We may need to tease out those with rescue medication use before 2 hours from missing and repeat the sensitivity analyses during review. This will only decrease the amount of missing data. This is a minor analysis issue.

(2) The intensity of migraine attacks treated in Study 303 were mild using the 4 points scale: 1-mild, 2-moderate, 3-severe or 0-none. The current guidance on migraine drug requires the intensity to reach moderate to severe in pivotal trials. Therefore study 303 is not considered as a pivotal study and its result may not be allowed in the labeling. At a lower data level, we notice that Site 805 alone has more than half of the missing of the entire study, although removing this site did not seem to alter the conclusion. The reason for missing was only recorded using a general umbrella phrase as protocol violation, so we could not understand the reason behind these missing data. This is potentially concerning despite the overall low missing data. The e-Dairy data is centralized so we usually do not see missingness related to any one site for migraine trials. Removing site 805 does not change the efficacy conclusion. This is a minor data issue.

(3) The sample size planning and randomization ratio for Study 301 were inconsistent between the study protocol and the study report. The study protocol planned to randomize 125 in placebo, and 250 in each of the 3 drug arms, however the study turned out to have randomized 227 in placebo and 456, 455, 456 in AXS-07, Meloxicam, and Rizatriptan arm. We note that this partially reflected what had been planned earlier at the pre-IND stage, to randomize 400 per arm. We also do not see a clear rationale for the deviation away from the usual 1:1 randomization ratio.

It seems that sample size planning was to meet both the goal of winning against placebo for the two co-primary endpoints, and against the two component drugs (or at least one of them for the key secondary endpoint). The main drive for the large sample size needed was the need to prove the drug is relatively better comparing to each of the 2 component drugs. Placebo group was planned at half of the size of each of the 3 drug groups to save some sample size without losing too much power for the overall goal of the study.

This thinking/rationale was not recorded in the sample size planning section of the final study protocol. This is a minor documentation issue.

3.2 Evaluation of Efficacy Study – AXS-07-301 (Pivotal)

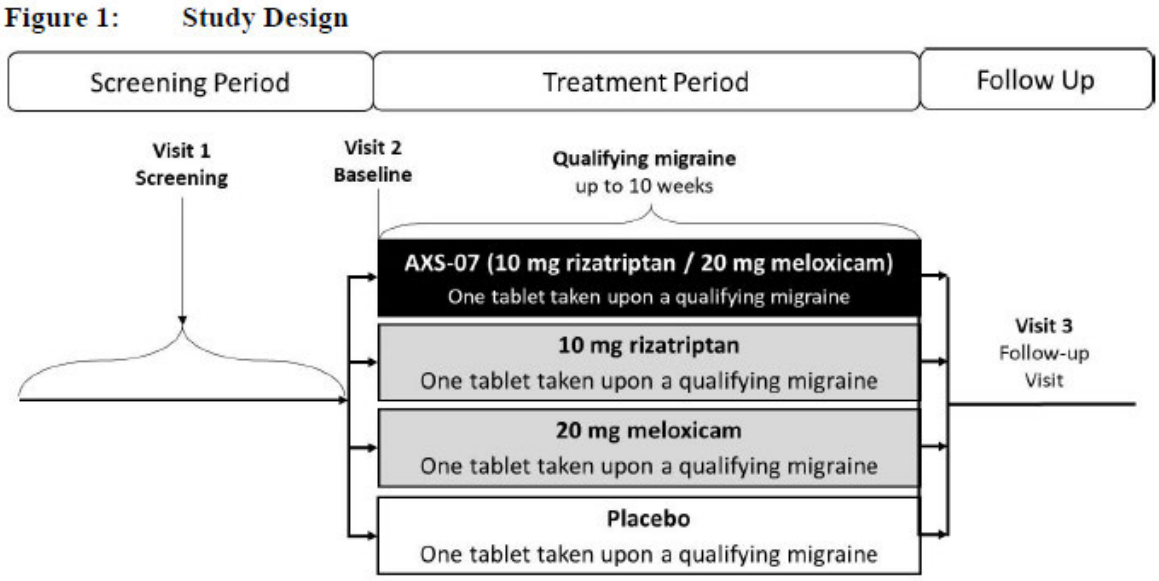
3.2.1 Study Design and Endpoints

The study AXS-07-301 was a Phase 3, 4-arm, multicenter, randomized, double-blind, placebo-control, parallel group study. Subjects who met the study entry criteria were randomly assigned in a 2:2:2:1 ratio to AXS-07, meloxicam, rizatriptan or placebo.

The two Co-Primary Endpoints for this study were the pain freedom and MBS freedom at 2 hours post dose. The Key Secondary Endpoint for this study was the pain freedom between hour 2 and hour 24, i.e., 24 hour sustained pain freedom.

The study design (double blinded, randomized, placebo controlled, parallel group) and the choice of the primary endpoint(s) definition (pain freedom and MBS freedom at 2 hours post dose) are considered appropriate.

Figure 1 Study Design – AXS-07-301



(Source: Sponsor's study protocol)

AXS-07, meloxicam, rizatriptan, and placebo tablets for this study were manufactured to be identical in appearance, shape, smell, and taste. A single dose of study drug was to be taken upon the onset of moderate or severe pain during a qualifying migraine. The study drug was to be taken orally with water without regard to meals.

Headache pain intensity (measured using a 4-point rating scale: 0-none, 1-mild, 2-moderate, or 3-severe), was recorded by the subject in the Headache Diary. Pain intensity was collected after randomization, upon occurrence of a qualified migraine attack.

During the treatment phase, the pain intensity was recorded by the subject in the Headache Diary immediately prior to taking study drug and at the following timepoints after taking medication: 15, 30 and 45 minutes, and 1, 2, 4, 12, 16, 24, and 48 hours after dosing.

The presence or absence of the following migraine symptoms was recorded by the subject in the Headache Diary: MBS (nausea, photophobia, or phonophobia). Prior to dosing, the subject defined the MBS and assessed the presence or absence of each symptom at the following time points: 30 minutes, and 1, 2, and 4 hours after dosing.

Figure 2 Schedule of Assessments – AXS-07-301

	Visit 1	Visit 2	Visit 3
	Screening	Randomization	Follow-up[d] / EOS
	Day – 14 to Day -1	Day 1	Within 7 days of dosing
Informed Consent	X		
Inclusion/Exclusion Criteria	X	X	
Demographics	X		
Medical History	X		
Migraine Headache History	X	X	
Medications, Prior and Concomitant, or Non-drug Therapy	X	X	X
m-TOQ-4	X		
Physical Examination, including height and weight	X		X
Vital Signs (seated blood pressure, pulse, oral body temp.)	X	X	
ECG	X		
Clinical Laboratory Tests	X		
Urine Pregnancy Test[a]	X	X	X
Urine Drug Screen	X	X	
ASC-12		X	
Randomization		X	
Dispense Headache Diary and Instruct on Use	X	X	
Review Compliance with Headache Diary	X	X	
Dispense Study Drug & Provide Dosing Instructions		X	
Subject Completes Diary Data[b]		X	
Phone call contact[c]		X	
Return Headache Diary			X
Collect/Inventory Study drug			X
Adverse Events[e]		X	X

ASC-12=12-item Allodynia Symptom Checklist; ECG=electrocardiogram; EOS=end of study, m-TOQ-4=Migraine Treatment Optimization Questionnaire, 4-item; PGI-C=Patient Global Impression-Change.
a For women of child-bearing potential only. Test results must have been negative at screening and randomization for the subject to continue in the study.
b Headache Diary data was collected at the following times: Baseline (at onset of moderate to severe migraine pain, [pre- dose]) and 15, 30 and 45 minutes, and 1, 2, 4, 12, 16, 24, and 48 hours after dosing. The PGI-C was captured at Hour 2.
c The subject should have been contacted within 24 hours after administering study drug. During the post-dose call, the site re-confirmed study drug dosing, assessed compliance with the headache diary, checked for changes in concomitant medications and rescue medication use, and to schedule the follow up appointment.
d Final visit after treating one attack (scheduled as soon as possible but within 7 days of dosing), or within 10 weeks after Visit 2 if the study drug not used.
e Adverse events were not required to be collected if subjects did not receive a dose of study drug.
(Source: Sponsor's study protocol)

The study population included male or female, 18 to 65 years of age. Eligible patients were those who had an established diagnosis of migraine (history indicating the presence of migraine for at

least 1 year) with or without aura as defined by ICHD-3 criteria, had a diagnosis of migraine presenting before age 50, had a history on average of 2 to 8 moderate to severe migraine attacks per month over the past 3 months, had a history of usual migraine duration of > 3 hours untreated (by history) for the 3 months prior to screening, and had experienced an inadequate response to prior acute treatments over the preceding 4 weeks, defined as a score of <=7 on the m-TOQ-4 (Migraine Treatment Optimization Questionnaire, 4-item) at screening, and were willing and able to complete the Headache Diary.

The m-TOQ-4 is a self-reported 4-item questionnaire. For each of the 4 questions the responses include 4 frequency-based options (never [0], rarely [0], <half the time [1], and ≥ half the time [2]). The maximum total score is 8, representing maximal treatment efficacy.

The sample size planning and randomization ratio for Study 301 were inconsistent between the study protocol and the study report. The study protocol planned to randomize 125 in placebo, and 250 in each of the 3 drug arms, however the study turned out to have randomized 227 in placebo and 456, 455, 456 in AXS-07, Meloxicam, and Rizatriptan arm. We note that this partially reflected what had been planned earlier at the pre-IND stage, to randomize 400 per arm. One concern about a much larger than planned sample size is that the study might be over-powered to detect small changes that may or may not be clinically meaningful. We also do not see a clear rationale for the deviation away from the usual 1:1 randomization ratio and why the changes back-and-forth. There might be other considerations behind the choice of the randomization ratio. This will be a review issue.

The sample size planning of “400 in the AXS-07 arm and each of the two active control arms, and the 200 in the placebo group”, was a balance to ensure the study to have adequate overall power for the main goal which consists of the primary comparison of AXS-07 versus placebo for the two co-primary endpoints, and the key secondary comparisons of AXS-07 versus the two active control arms. While each of the two individual test appears to have power about 90%, the combined power to win both tests can be derived as about 80% (from 90%*90%). Similarly, 95%*95% = 90% indicates that each of the test needs to be powered at 95% if there are 4 tests.

Keep in mind the AXS-07 is a combination of two components with one component being an approved drug for acute migraine, so the primary comparison between AXS-07 to placebo does not require a large sample size. But AXS-07 is also involved in the key secondary to show the contribution of each of the two component drugs, i.e., the two active control arms, so the sample size in AXS-07 needs to be the maximum of the 2 needed: 200, 400. The placebo group is the only place to save some resource without suffering power loss, so the sample size planned for placebo is about 200.

Section “**9.8.1. Changes in the Conduct of the Study**” of the study report indicates such “over-enrollment” was a change implemented after the study started but still very early on in the study with only about 5% enrolled to account for the potentially increased variability. See below for the language:

“

This study aimed to enroll approximately 250 treated subjects per active treatment arm, and 125 subjects in the placebo arm. Approximately 450 subjects per active treatment arm and 250 subjects in the placebo arm were ultimately randomized. The over-enrollment was to account for the potentially increased variability related to the eligible patient population, which were subjects who had an inadequate response to prior migraine treatments. This potential variability was identified early in the enrollment period, when less than 5% of the total population was enrolled. In order to further reduce inter-subject variability, a mid-study diary update was made to ensure collection of sufficient baseline information about the headache to verify that the qualifying headache was indeed a migraine.

“

3.2.2 Statistical Methodologies

The two co-primary endpoints were rate of pain freedom at 2 hours and MBS free at 2 hours post the first dose treating a qualifying acute migraine attack during the double-blind treatment phase.

The primary comparison was AXS-07 versus placebo. Between treatment group comparisons were performed via chi-square tests.

The Key Secondary Endpoint for this study was the pain freedom between hour 2 and hour 24, i.e., 24 hour sustained pain freedom. To be treated as a responder, the subject must have met all 4 of the following conditions:

1) all reported pain intensity between Hours 2 and 24 must have been 0
2) pain intensity at Hours 2 and 24 must have been 0
3) pain intensity must have been available for at least Hours 12 or 16
4) no rescue medication could have been used through Hour 24

Subjects who met any of the following conditions were considered as missing:

1) Took rescue medication between Hours 2 and 24
2) Missed either Hour 2 or Hour 24 assessment
3) Missed both Hour 12 and Hour 16 assessments

Efficacy analyses were based on the ITT population which consisted of all randomized subjects who had a qualifying migraine. The primary efficacy analysis was based on the ITT population. Subjects were grouped based on the assigned treatment.

The multiplicity adjustment method was pre-specified and deemed to be adequate. To adjust for multiplicity, the null hypotheses for the following 4 claims (Item 1 has 2 claims for the 2 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
3. AXS-07 versus Rizatriptan for the key secondary endpoint

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.

3.2.3 Patient Disposition, Demographics and Baseline Characteristics

This study had its first patient enrolled on 01 Mar 2019, and last patient complete on 01 Dec 2019. The study report was created on the date of 09 Jun 2021.

A total of 1594 subjects were randomized: 456 to AXS-07group, 227 to the placebo group, 455 to the Meloxicam group and 456 to the Rizatriptan group.

Overall, 1526 subjects (95.7%) completed study: 441 subjects (96.7%) in the AXS-07 group, 218 subjects (96.0%) in the placebo group, 433 subjects (95.2%) in the meloxicam group, and 434 subjects (95.2%) in the rizatriptan group.

In the Randomized population, a total of 68 subjects (4.3%) discontinued from the study and the primary reasons for discontinuation in the total group was 'other' in 32 subjects (2.0%) and failure to meet continuation criteria in 22 subjects (1.4%).

Subject disposition for the Randomized population is summarized in the table below.

Table 2 Subject Disposition (randomized population) – AXS-07-301

	No. of Subjects (%)				
	AXS-07 (20 mg MLX /10 mg RIZ) (N=456)	**Placebo (N=227)**	**Meloxicam 20 mg (N-455)**	**Rizatriptan 10 mg (N=456)**	**Total (N=1594)**
Completed	441 (96.7)	218 (96.0)	433 (95.2)	434 (95.2)	1526 (95.7)
Completed with qualifying migraine[a]	428 (93.9)	209 (92.1)	421 (92.5)	419 (91.9)	1477 (92.7)
Completed without qualifying migraine	13 (2.9)	9 (4.0)	12 (2.6)	15 (3.3)	49 (3.1)
Discontinued	15 (3.3)	9 (4.0)	22 (4.8)	22 (4.8)	68 (4.3)
Primary Reason for Discontinuation					
Screen Failure	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.1)
Failure to Meet Continuation Criteria	7 (1.5)	3 (1.3)	7 (1.5)	5 (1.1)	22 (1.4)
Withdrawal by Subject	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.7)	4 (0.3)
Lost to Follow-Up	1 (0.2)	1 (0.4)	3 (0.7)	3 (0.7)	8 (0.5)
Other	6 (1.3)	5 (2.2)	10 (2.2)	11 (2.4)	32 (2.0)

(source: Table 4 in the CSR)

Of the 1477 subjects in the ITT population, majority were women (> 80.8%), white (>73.7%), and the mean age was 41 (18 to 65) years. The treatment groups were balanced for these baseline demographic characteristics.

Table 3 Patient Baseline Demographics – ITT – Study AXS-07-301

	AXS-07 N=428	Placebo N=209	Meloxicam N=421	Rizatriptan N=419
Age (years), n				
Mean (SD)	41.2 (11.52)	40.8 (11.68)	40.9 (12.08)	41.4 (10.72)
Median	41.0	42.0	41.0	42.0
Minimum	18	18	18	18
Maximum	65	65	57	64
n (%)				
Female	346 (80.8)	177 (84.7)	355 (84.3)	353 (84.2)
Male	82 (19.2)	32 (15.3)	66 (15.7)	66 (15.8)
Race, n (%)				
White	337 (78.7)	154 (73.7)	324 (77.0)	320 (76.4)
Black or African American	72 (16.8)	45 (21.5)	83 (19.7)	81 (19.3)
Asian	8 (1.9)	4 (1.9)	9 (2.1)	6 (1.4)
American Indian or Alaska Native	4 (0.9)	0	1 (0.2)	2 (0.5)
Multiple	3 (0.7)	4 (1.9)	4 (1.0)	5 (1.2)
Other	3 (0.7)	2 (1.0)	0	5 (1.2)
Not reported	1 (0.2)	0	0	0
BMI (kg/m2), n				
Mean (SD)	29.2 (5.67)	29.3 (5.33)	28.9 (5.69)	29.7 (5.67)
Median	28.7	29.2	28.3	29.7
Minimum	16.3	18.2	16.7	17.6
Maximum	43.0	39.9	43.2	40.0

BMI = body mass index
(Source: Table 8 in the study report, verified by the statistical reviewer.)

Baseline disease characteristics were well balanced across the treatment groups.

Table 4 Patient Baseline Disease Characteristics - mITT - Study AXS-07-301

	AXS-07 N=428	Placebo N=209	Meloxicam N=421	Rizatriptan N=419
Total m-TOQ-4 score				
Mean (SD)	3.5 (2.17)	3.5 (2.21)	3.8 (2.14)	3.6 (2.25)
Median	3.0	3.0	4.0	4.0
Minimum	0	0	0	0
Maximum	7	7	7	7
Allodynia (ASC-12 score ≥3), n (%)	336 (78.5)	150 (71.8)	322 (75.5)	305 (72.8)
Severe migraine pain at Baseline, n (%)	184 (43.0)	88 (42.1)	181 (43.0)	155 (37.0)
Nausea at Baseline, n (%)	195 (45.6)	100 (47.8)	195 (46.3)	192 (45.8)

m-TOQ-4 = Migraine Treatment Optimization Questionnaire, 4-item.
(Source: Table 9 in the study report, verified by the statistical reviewer.)

3.2.4 Results and Conclusions

3.2.4.1 Efficacy Results of the Primary Endpoints

The results reported by the sponsor were confirmed. The primary analysis included 637 patients.

Table 5 Primary Endpoint Analyses - Study AXS-07-301

	AXS-07 (N=428)	Placebo (N=209)
Pain Free at 2 hours	85	14
%	19.9%	6.7%
p-value	<.001	
MBS Free at 2 hours	158	51
%	36.9%	24.4%
p-value	.002	

P value was from Chi-square test.
(Source: reviewer's own analysis and sponsor's analysis Table 12, Table 13 verified by the reviewer.)

There was a statistically significant increase in the rate of pain free at 2 hours without rescue medication from 6.7% in the placebo group to 19.9% in the AXS-07 group. The p-value versus placebo was < .001.

There was a statistically significant increase in the rate of MBS free at 2 hours without rescue medication from 24.4% in the placebo group to 36.9% in the AXS-07 group. The p-value versus placebo was .002.

Patients with missing data at 2-hour time point were counted as treatment failures.
As a clinical rule, patients with rescue medication use prior to the 2-hour time point were considered as treatment failures.

3.2.4.2 Missing Data and Sensitivity Analyses

The overall missing rate was relatively low for this study and similar among the treatment groups as can be seen in the following table which shows the missing data patient counts for each group.

Table 6 Patient Counts at Time of Dosing and Two Hours (rescue= failure) – StudyAXS-07- 301

	Patient Count at time 0	Pain score Missing at 2 hours	Pain Status Still Missing after rescue=failure	Missing %	MBS Status Missing at 2 hours	MBS Status Still Missing after rescue=failure	Missing %
AXS-07	428	15	14	3.3%	15	14	3.3%
placebo	209	8	7	3.3%	8	7	3.3%
Meloxicam	421	24	20	4.8%	24	20	4.8%
Rizatriptan	419	20	17	4.1%	20	17	4.1%

(Source: Reviewer's own analysis.)

If the subject did not record a pain severity rating at 2 hours post dosing, then this subject's pain free status at 2 hours was set as missing. If the subject failed to record a symptom rating at 2 hours post dosing, then this subject's MBS status at 2 hours post dosing was set as missing.

As a clinical rule, if the subject took any recue medication prior to the 2 hours timepoint, then this patient was considered as treatment failure.

In the primary efficacy analysis, subjects with missing data at 2 hours timepoint were counted as treatment failures.

The breakdown of patient counts with only "pain score at 2 hours missing", or only "rescue medication before 2 hours", or both, can be seen from the table below, with similar breakdown for MBS the secondary co-primary endpoint.

Table 7 Breakdown of Patients for Different Missing Patterns – Study AXS-07-301

Pattern of Missing	AXS-07	Placebo	Meloxicam	Rizatriptan
Only Pain score at 2 hours missing	14	7	20	17
Only rescue before 2 hours	19	11	16	22
Both rescue and missing pain score at 2 hours	1	1	4	3
Either rescue or missing pain score at 2 hours	34	19	40	42
Still Missing pain after applying clinical rule of "rescue = failure"	*14*	*7*	*20*	*17*
Only MBS status at 2 hours missing	14	7	20	17
Only rescue before 2 hours	19	11	16	22
Both rescue and missing MBS status at 2 hours	1	1	4	3
Either rescue or missing MBS status at 2 hours	34	19	40	42
Still Missing MBS after applying clinical rule of "rescue = failure"	*14*	*7*	*20*	*17*
Randomized	428	209	421	419

(Source: Reviewer's own analysis.)

Table 8, 9 and 10 show the breakdown of patient counts with or without actual efficacy measurements at 2 hours (Yes/No/Missing); the rescue medication use; and the patient efficacy results after applying the clinical rule of rescue medication use before 2 hours = failure.

Table 8 Patient Counts for Data Status at 2 Hours –ITT- Study 301

			Pain			MBS
AXS-07	428	89	Yes	428	158	Yes
		324	No		255	No
		15	2-Hour missing		15	2-Hour Missing
Placebo	209	14	Yes	209	51	Yes
		187	No		150	No
		8	2-Hour missing		8	2-Hour Missing
Meloxicam	421	52	Yes	421	137	Yes
		345	No		260	No
		24	2-Hour missing		24	2-Hour Missing
Rizatriptan	419	77	Yes	419	150	Yes
		322	No		249	No
		20	2-Hour missing		20	2-Hour missing

(Source: Reviewer's own analysis.)

Table 9 Patient Counts for Rescue Meds before 2 Hours –ITT- Study 301

			Pain			MBS
AXS-07	20	4	Yes	20	0	Yes
		15	No		19	No
		1	2-Hour missing		1	2-Hour Missing
Placebo	12	0	Yes	12	0	Yes
		11	No		11	No
		1	2-Hour missing		1	2-Hour Missing
Meloxicam	20	3	Yes	20	0	Yes
		13	No		16	No
		4	2-Hour missing		4	2-Hour Missing
Rizatriptan	25	4	Yes	25	0	Yes
		18	No		22	No
		3	2-Hour missing		3	2-Hour missing

(Source: Reviewer's own analysis.)

Table 10 Counts for Patients' Data Status at 2H (rescue* = failure) –ITT- Study 301

			Pain			MBS
AXS-07	428	85	Yes	428	158	Yes
		329	No		256	No
		14	2-Hour missing		14	2-Hour Missing
Placebo	209	14	Yes	209	51	Yes
		188	No		151	No
		7	2-Hour missing		7	2-Hour Missing
Meloxicam	421	49	Yes	421	137	Yes
		352	No		264	No
		20	2-Hour missing		20	2-Hour Missing
Rizatriptan	419	73	Yes	419	150	Yes
		329	No		252	No
		17	2-Hour missing		17	2-Hour missing

(Source: Reviewer's own analysis.)

In the sensitivity analysis performed by the sponsor, the MI (multiple imputation) – "Average" was used:

> Subjects with missing data (either missing assessment at 2 hours or rescue meds before 2 hours) were assumed to respond at the average rate of the two response rates of the treated subjects and the placebo subjects with available data. The imputed responder counts in the placebo group would be rounding up if not an integer in the calculation process, while the drug group would be rounding down.

Results for the sensitivity analyses using MI – "Average" were consistent with those observed for the primary analysis. Please note that the rescue medication use before 2 hours as clinical rule should be treated as failure and not missing data. The sponsor's sensitivity analysis, either rescue or missing pain assessment was counted as missing data for the imputation, however, the difference is so small it has almost none impact on the efficacy conclusion.

In addition, the more conservative imputation assuming the "Worst case" also produced similar efficacy result as the primary analysis, as can be seen in the table below. The "worst case scenario" imputation is the most conservative method by imputing placebo subjects with missing data as responders, while active subjects with missing data as non-responders.

Table 11 Sensitivity Analysis for Co-Primary endpoints - Study AXS-07-301

	MI – "Average"		**Imputation - "Worst case"**		**Primary**	
	AXS-07 (N=428)	**Placebo (N=209)**	**AXS-07 (N=428)**	**Placebo (N=209)**	**AXS-07 (N=428)**	**Placebo (N=209)**
Pain Free at 2 hours	89	17	85	21	85	14
%	20.8%	8.1%	19.9%	10.1%	19.9%	6.7%
p-value	<.001		.002		<.001	
MBS Free at 2 hours	169	58	158	58	158	51
%	39.5%	27.8%	36.9%	27.8%	36.9%	24.4%
p-value	.004		.02		.002	

(Source: Reviewer's own analysis and Table 14, Table 15 in the study report.)

In this study, only the 7 missing in the placebo was to be moved into 'responder' counts under the "worst case scenario", since the 14 missing in the AXS-07 group has already been counted as 'non-responders' in the primary analysis. As can be seen from the table above, the p value for MBS2H under "worst' was .02 still under .05 although being much larger than the .002.

3.2.4.3 Efficacy Results of the Key Secondary Endpoint

Subjects with Sustained Pain Freedom between Hours 2 and 24 (AXS-07 versus Meloxicam, AXS-07 versus Rizatriptan)

The Key Secondary Endpoint for this study was the pain freedom between hour 2 and hour 24, i.e., 24 hour sustained pain freedom. Two tests were performed in the following order using 2-sided .05 significance level:

1. AXS-07 versus Meloxicam
2. AXS-07 versus Rizatriptan

16.1% of AXS-07 subjects had 24 hours sustained pain freedom, compared to 8.8% of Meloxicam subjects with p = 0.001, and 11.2% of rizatriptan subjects with p .038.

Table 12 Key Secondary Endpoint: 24H Sustained Pain Freedom – AXS-07-301

	AXS-07 (N=428)	Meloxicam (N=421)	Rizatriptan (N=419)
Sustained pain freedom between 2 and 24 hours	69	37	47
%	16.1%	8.8%	11.2%
p-value	-	.001	.038

P value was based on Chi-square test. (Source: Table 16 in study report verified by the reviewer.)

In the sensitivity analysis performed by the sponsor, the similar MI (multiple imputation) – "Average" was used. Responder status for subjects who met any of the 3 conditions: 1) Took rescue medication between Hours 2 and 24; 2) Missed either Hour 2 or Hour 24 assessment; 3) Missed both Hour 12 and Hour 16 assessments; were imputed according to the similar procedures discussed above for the 2 co-primary efficacy variables.

The sensitivity analysis produced similar results as can be seen in the table below.

Table 13 Sensitivity Analysis for Key Secondary Endpoint – AXS-07-301

MI – "Average" Sensitivity Analysis	AXS-07 (N=428)	Meloxicam (N=421)	Rizatriptan (N=419)
Sustained pain freedom between 2 and 24 hours	69	32	45
%	16.1%	7.6%	10.7%
p-value	-	<.001	.022

P value was based on Chi-square test. (Source: Table 17 in study report verified by the reviewer.)

In the sensitivity analysis, 16.1% of AXS-07 subjects had 24 hours sustained pain freedom, compared to 7.6% of Meloxicam subjects with p < 0.001, and 10.7% of rizatriptan subjects with p .022.

3.2.4.4 Efficacy Results of Other Secondary Endpoints

3 out of the 5 tests (#1, #2, #3) for the prespecified secondary endpoints were significant.

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, did not test significantly, so the testing stopped. Results for #4 and #5 were exploratory only.

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.

1. Pain Relief at Hour 2 (AXS-07 versus Placebo)

Table 14 Secondary Endpoint: Pain Relief at Hour 2– Study 301

	AXS-07 (N=428)	Placebo (N=209)
Pain Relief at Hour 2	296	114
%	69.2%	54.5%
p-value	<.001	-

P value was based on Chi-square test. (Source: Table 18 in the study report verified by the reviewer.)

Subjects who provided values at Hour 2 and did not take rescue medication were treated as responders.

2. Time to Pain Relief Through Hour 24 (AXS-07 versus Placebo)

Subjects pain score were collected at 10 timepoints through Hour 24: 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 12, 16, and 24 Hours. The rate of having pain relief at one or more of the 10 timepoints were higher in the AXS-07 group at 75.2%, comparing to the 53.1% in the placebo group (p<.001).

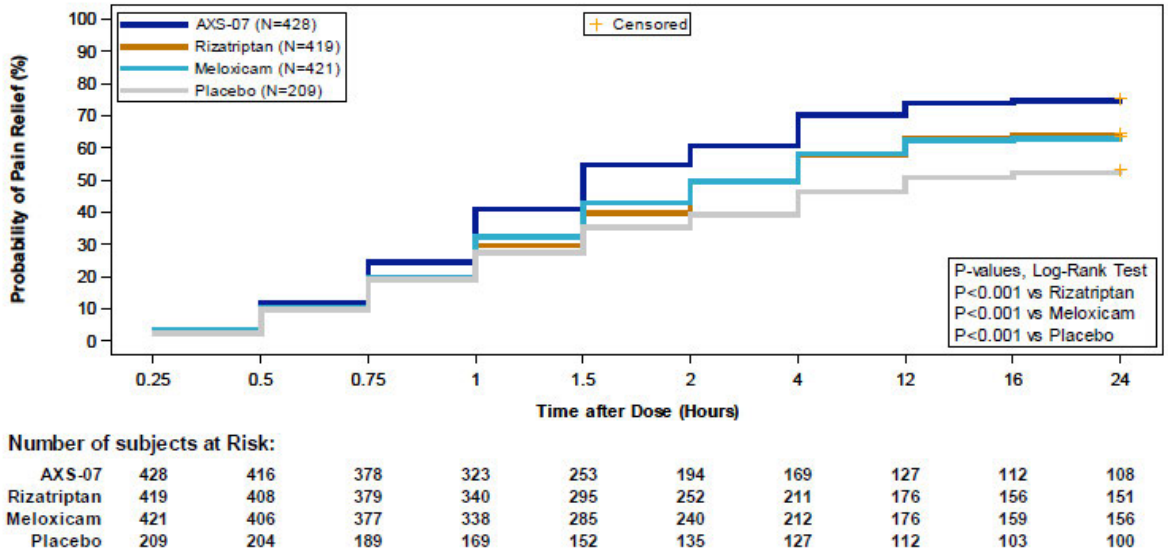
Table 15 Secondary Endpoint: Time to Pain Relief Through Hour 24– Study 301

Pain Relief at	AXS-07 (N=428)	Placebo (N=209)
one or more of the 10 timepoints through Hour 24	322	111
%	75.2%	53.1%
*p-value vs placebo	<.001	-
*p-value vs AXS-07	-	<.001
Event Free Survival (Hours)		
25^{th} percentile	1	1
Median	1.5	12
75^{th} percentile	24	NE
**p-value vs AXS-07	-	<.001

NE =Not Estimable *p value was based on Chi-square test. **p value was based on log-rank test after adjusting for multiple comparison. (Source: Table 19 in the study report verified by the reviewer.)

We suggest to present the result using Kaplan Meier Plot to show the different patient counts included at each of the 10 timepoint, and the further slight gain of patients achieving pain relief at the latter hours till Hour 24.

Figure 3 Kaplan Meier Plot for Time to Pain Relief – Study 301



(Source: Figure 4 in study report, verified by reviewer)

3. Subjects Able to Perform Normal Daily Activities at Hour 2 (AXS-07 versus Placebo)

Table 16 Secondary Endpoint: Normal Daily Activities at Hour 2– Study 301

	AXS-07 (N=428)	Placebo (N=209)
Able to Perform Normal Daily Activities at Hour 2	137	44
%	32.0%	21.1%
p-value	-	.004

P value was based on Chi-square test. (Source: Table 20 in the study report verified by the reviewer.)

3.3 Evaluation of Efficacy Study – AXS-07-303 (Non Pivotal)

3.3.1 Study Design and Endpoints

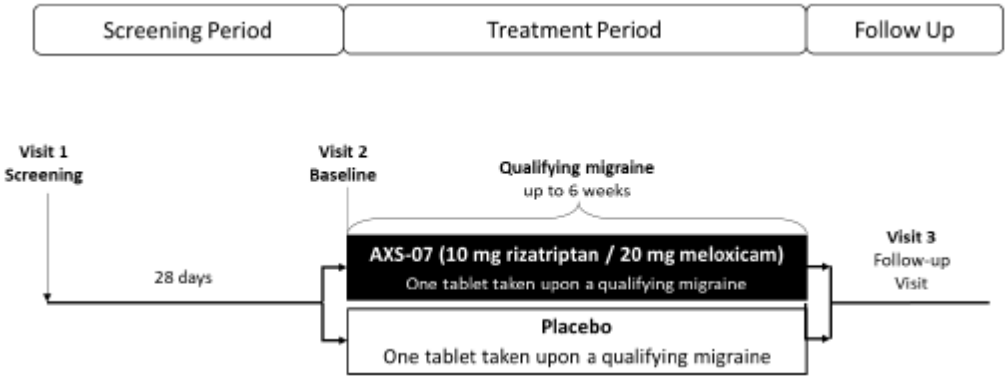
The study AXS-07-303 was a Phase 3, 2-arm, multicenter, randomized, double-blind, placebo-control, parallel group study. Subjects who met the study entry criteria were randomly assigned in a 1:1 ratio to AXS-07 or placebo.

The two Co-Primary Endpoints for this study were the pain freedom and MBS freedom at 2 hours post dose. The Key Secondary Endpoints for this study were Time to headache pain freedom, and the ability to perform normal activity (functional disability = none) at Hour 2.

The study design (double blinded, randomized, placebo controlled, parallel group) and the choice of the primary endpoint(s) definition (pain freedom and MBS freedom at 2 hours post dose) are considered appropriate.

The intensity of migraine attacks treated in Study 303 were mild using the 4 points scale: 1-mild, 2-moderate, 3-severe or 0-none. The current guidance on migraine drug requires the intensity to reach moderate to severe in pivotal trials. Therefore study AXS-07-303 is not considered as a pivotal trial and its result may not be allowed in the labeling. Please see clinical review for more detailed comments.

Figure 4 Study Design – Study AXS-07-303



(Source: Study protocol)

Headache pain intensity (measured using a 4-point rating scale: 0-none, 1-mild, 2-moderate, or 3-severe), was recorded by the subject in the Headache Diary. Pain intensity was collected after randomization, upon occurrence of a qualified migraine attack.

During the treatment phase, the pain intensity was recorded by the subject in the Headache Diary immediately prior to taking study drug and at the following timepoints after taking medication: 15, 30 and 45 minutes, and 1, 2, 4, 12, 16, 24, and 48 hours after dosing.

The presence or absence of the following migraine symptoms was recorded by the subject in the Headache Diary: MBS (nausea, photophobia, or phonophobia). Prior to dosing, the subject

defined the MBS and assessed the presence or absence of each symptom at the following time points: 30 minutes, and 1, 2, and 4 hours after dosing.

Figure 5 Schedule of Assessments – Study AXS-07- 303

	Visit 1	Visit 2	Visit 3
	Screening	Randomization	Follow-up[d] / EOS
	Day – 14 to Day -1	Day 1	Within 7 days of dosing
Informed Consent	X		
Inclusion/Exclusion Criteria	X	X	
Demographics	X		
Medical History	X		
Migraine Headache History	X	X	
Medications, Prior and Concomitant, or Non-drug Therapy	X	X	X
Physical Examination, including height and weight	X		X
Vital Signs (seated blood pressure, pulse, oral body temp.)	X	X	X
ECG	X		X
Clinical Laboratory Tests	X		X
Urine Pregnancy Test[a]	X	X	X
Urine Drug Screen	X	X	
MIDAS		X	
ASC-12		X	
Randomization		X	
Dispense Headache Diary and Instruct on Use	X	X	
Review Compliance with Headache Diary	X	X	
Dispense Study Drug & Provide Dosing Instructions		X	
Subject Completes Diary Data[b]		X	
Phone call contact[c]		X	
Return Headache Diary			X
Collect/Inventory Study Medication			X
Adverse Events[e]		X	X

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

a. For women of child-bearing potential only. Test results must be negative at Screening and Randomization for the subject to continue in the study.

b. Headache Diary data will be collected at the following times: Baseline (at onset of moderate to severe migraine pain, [predose]) and 20, 30 and 45 minutes, and 1, 1.5, 2, 4, 12, 16, 24, and 48 hours after dosing

c. The subject should be contacted within 24 hours after administering study medication. During the post-dose call, the site should re-confirm study drug dosing instructions and check for changes in concomitant medications. Following the onset of a qualifying migraine, assess compliance with migraine pain diary, rescue medication use, and to schedule the follow up appointment.

d. Final visit after treating one attack (to be scheduled as soon as possible but within 7 days of dosing), or within 10 weeks after Visit 2 if the study medication not used.

e. Adverse events are not required to be collected if subjects do not receive a dose of study medication.

(Source: Study protocol)

The study population included male or female, 18 to 65 years of age. Eligible patients were those who had an established diagnosis of migraine (history indicating the presence of migraine for at least 1 year) with or without aura as defined by ICHD-3 criteria, had a diagnosis of migraine presenting before age 50, had a history on average of 2 to 8 migraine attacks per month over the past 3 months, had a history of usual migraine duration of > 3 hours untreated (by history) for the 3 months prior to screening, must have reported at least 1, and no more than 8 migraines during the Screening Period, and had a body weight ≥ 45 kg and a BMI ≤ 40 kg/m2, and were willing and able to complete the Headache Diary.

Approximately 150 subjects per group was planned to provide 90% power to detect a treatment difference at a two-sided significance level of 0.05, assuming the responder rate for pain freedom at Hour 2 is ≤15% for placebo and ≥29% for AXS-07.

3.3.2 Statistical Methodologies

The two co-primary endpoints were rate of pain freedom at 2 hours and MBS free at 2 hours post the first dose treating a qualifying acute migraine attack during the double-blind treatment phase.

The primary comparison was AXS-07 versus placebo. Between treatment group comparisons were performed via chi-square tests.

The Key Secondary Endpoints for this study was time to the pain freedom and ability to perform normal daily activities at hour 2.

Efficacy analyses were based on the ITT population which consisted of all randomized subjects who had a qualifying migraine. The primary efficacy analysis was based on the ITT population. Subjects were grouped based on the assigned treatment.

The multiplicity adjustment method was pre-specified and deemed to be adequate.

The two key secondary efficacy endpoints were examined in hierarchical order, each at .05.

(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.

3.3.3 Patient Disposition, Demographics and Baseline Characteristics

This study had its first patient enrolled on 08 Oct 2019, and last patient completed on 16 Mar 2020. The study report was created on the date of 09 Jun 2021.

A total of 302 subjects were randomized: 456 to AXS-07group, 227 to the placebo group. Subject disposition for the Randomized population is summarized in the table below.

Table 17 Subject Disposition – Study AXS-07- 303

Population	AXS-07 (N=152)	Placebo (N=150)	Total (N=302)
Randomized[a]	152 (100.0%)	150 (100.0%)	302 (100.0%)
Safety[b]	140 (92.1%)	143 (95.3%)	283 (93.7%)
ITT[c]	132 (86.8%)	135 (90.0%)	267 (88.4%)

ITT=intent-to-treat
a The Randomized Population included all subjects randomized to study drug.
b The Safety Population included all subjects who received study drug.
c The ITT Population consisted of all randomized subjects who had a qualifying migraine.
(Source: Table 6 in CSR.)

Of the 267 subjects in the ITT population, majority were women (> 85%), white (>80%), and the mean age was 42 (18 to 65) years. The treatment groups were balanced for these baseline demographic characteristics.

Table 18 Patient Demographics – Study AXS-07-303

	AXS-07 N=132	Placebo N=135	Total N=267
Age (years), n			
Mean (SD)	41.6 (11.51)	41.4 (10.68)	41.5 (11.08)
Median	43.0	41.0	42.0
Minimum	19	19	19
Maximum	63	65	65
n (%)			
Female	113 (85.6)	1115 (85.2)	228 (85.4)
Male	19 (14.4)	20 (14.8)	39 (14.6)
Race, n (%)			
White	113 (85.6)	109 (80.7)	222 (83.1)
Black or African American	16 (12.1)	16 (11.9)	32 (12.0)
Asian	1 (0.8)	7 (5.2)	8 (3.0)
American Indian or Alaska Native	1 (0.8)	0	1 (0.4)
Multiple	1 (0.8)	3 (2.2)	4 (1.5)
BMI (kg/m2), n			
Mean (SD)	28.5 (5.56)	28.5 (5.79)	28.5 (5.67)
Median	28.6	27.8	28.3
Minimum	17.7	17.2	17.2
Maximum	39.8	39.9	39.9

BMI = body mass index (Source: Table 7 in the study report, verified by the statistical reviewer.)

Baseline disease characteristics were well balanced across the treatment groups.

Table 19 Patient Baseline Disease Characteristics – Study AXS-07-303

	AXS-07 N=132	**Placebo N=135**	**Total N=267**
Monthly Migraine Frequency			
Mean (SD)	4.6 (1.76)	4.5 (1.56)	4.6 (1.67)
Median	4	4	4
Minimum	2	2	2
Maximum	8	8	8
Allodynia (ASC-12 score ≥3), n (%)	102 (77.3)	96 (71.1)	198 (74.2)
Morning migraine (onset before or at 10 am), n (%)	55 (41.7)	51 (37.8)	106 (39.7)
Nausea at Baseline, n (%)	49 (37.1)	59 (43.7)	108 (40.4)
Depression at baseline, n (%)	25 (18.9)	21 (15.6)	46 (17.2)
Obese (BMI>= 30), n (%)	54 (40.9)	52 (38.5)	106 (39.7)
MIDAS			
Mean (SD)	25.8 (23.41)	21.9 (15.11)	23.8 (19.72)
Median	19	19	19
Minimum	1	0	0
Maximum	166	79	166
Pain Score at baseline (1 - Mild), n (%)	132 (100)	135 (100)	267 (100)
MBS at baseline, n (%)			
Nausea	26 (19.7)	30 (22.2)	56 (21.0)
Sensitivity to light	89 (67.4)	80 (59.3)	169 (63.3)
Sensitivity to sound	17 (12.9)	25 (18.5)	42 (15.7)

(Source: Table 8 in the study report, verified by the statistical reviewer.)

3.3.4 Results and Conclusions

3.3.4.1 Efficacy Results of the Primary endpoints

The results reported by the sponsor were confirmed. The primary analysis included 267 patients.

Table 20 Primary Endpoint Analyses – Study AXS-07-303

	AXS-07 (N=132)	Placebo (N=135)
Pain Free at 2 hours	43	22
%	32.6%	16.3%
p-value	.002	
MBS Free at 2 hours	58	36
%	43.9%	26.7%
p-value	.003	

P value was from Chi-square test.
(Source: reviewer's own analysis and sponsor's analysis Table 11 and Table 12 verified by the reviewer.)

There was a statistically significant increase in the rate of pain free at 2 hours without rescue medication from 16.3% in the placebo group to 32.6% in the AXS-07 group. The p-value versus placebo was .002.

There was a statistically significant increase in the rate of MBS free at 2 hours without rescue medication from 26.7% in the placebo group to 43.9% in the AXS-07 group. The p-value versus placebo was .003.

Patients with missing data at 2-hour time point were counted as treatment failures.
As a clinical rule, patients with rescue medication use prior to the 2-hour time point were considered as treatment failures.

3.3.4.2 Missing Data and Sensitivity Analyses

The overall missing rate was relatively low for this study and similar among the treatment groups as can be seen in the following table.

Table 21 Patient Counts at Time of Dosing and Two Hours (rescue= failure) – Study AXS-07- 303

	Patient Count at time 0	Pain score Missing at 2 hours	Pain Status Still Missing after rescue=failure	Missing %	MBS Status Missing at 2 hours	MBS Status Still Missing after rescue=failure	Missing %
AXS-07	132	8	8	6.1%	8	8	6.1%
placebo	135	5	4	3.0%	5	4	3.0%
Total	267	13	12	4.5%	13	12	4.5%

(Source: Reviewer's own analysis.)

In the sensitivity analysis performed by the sponsor, the MI (multiple imputation) – "Average" was used:

> Subjects with missing data (either missing assessment at 2 hours or rescue meds before 2 hours) were assumed to respond at the average rate of the two response rates of the treated subjects and the placebo subjects with available data. The imputed responder counts in the placebo group would be rounding up if not an integer in the calculation process, while the drug group would be rounding down.

Results for the sensitivity analyses using MI – "Average" were consistent with those observed for the primary analysis.

Table 22 Sensitivity Analyses – 303

	MI – "Average"		**Imputation - "Worst case"**		**Primary**	
	AXS-07 (N=132)	**Placebo (N=135)**	**AXS-07 (N=132)**	**Placebo (N=135)**	**AXS-07 (N=132)**	**Placebo (N=135)**
Pain Free at 2 hours	46	25	43	26	43	22
%	34.8%	18.5%	32.6%	19.3%	32.6%	16.3%
p-value	.003		.013		.002	
MBS Free at 2 hours	63	41	58	40	58	36
%	47.7%	30.4%	43.9%	29.6%	43.9%	26.7%
p-value	.004		.015		.003	

(Source: Reviewer's own analysis and Table 13, Table 14 in the study report.)

In addition, the more conservative imputation assuming the "Worst case" also produced similar efficacy result as the primary analysis, as can be seen in the table below. The "worst case scenario" imputation is the most conservative method by imputing placebo subjects with missing data as responders, while active subjects with missing data as non-responders.

In this study, only the 4 missing in the placebo was to be moved into 'responder' counts under the "worst case scenario", since the 8 missing in the AXS-07 group has already been counted as 'non-responders' in the primary analysis. As can be seen from the table above, the p value for MBS2H under "worst' was .015 still under .05 although being much larger than the .003.

3.3.4.3 Efficacy Results of the Key Secondary Endpoints

The Key Secondary Endpoints for this study were the ability to perform normal activity (functional disability = none) at Hour 2 and Time to headache pain freedom.

The test for the first of the two prespecified key secondary endpoints was not significant, so the testing stopped. The results for the two key secondary endpoints were exploratory only.

3.3.4.4 Efficacy Results of other Secondary Endpoints

The results for the secondary endpoints were exploratory only since the first key secondary endpoint did not achieve statistical significance and the testing stopped.

3.4 Evaluation of Safety

Please refer to the clinical review for details on safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 [redacted] Race, Age and Geographic Region

In Study 301, the median age of the subjects was about 41 to 42 years, with the percentage of female as 80.8% in the AXS-07 group and 84.7% in the placebo group, and the majority being either black or white, with the percentage of being white 78.7% and 73.7%, being black as 16.8% and 21.5%. Age 65+ subgroup was very small with 9 subjects out of total 1477 subjects for entire study 301.

Table 23 Age, [redacted] and Race Summaries by Treatment Group - Study AXS-07-301

	Age (Median)	Patient count with Age 65+	[redacted] (%F)	Race (%White)	Race (%Black)
AXS-07 (N=428)	41	4	80.8	78.7	16.8
Placebo (N=209)	42	1	84.7	73.7	21.5
Meloxicam (N=421)	41	4	84.3	77.0	19.7
Rizatriptan (N=419)	42	0	84.3	76.4	19.3
Total (N=1477)	41	9	83.3	76.8	19.0

%White +%Black < 100%. (Reviewer's result.)

There is no need to conduct subgroup analysis by region since the entire study was conducted in the US. Analyses for the treatment effect across subgroups such as age, [redacted] and race were performed. The trend in treatment success appears to be similar across subgroups.

Table 24 Findings in Subgroup Populations – Age, [redacted] and Race – Study AXS-07-301

	Pain Free at 2 Hours						MBS Free at 2 Hours					
	N	n	%	N	n	%	N	n	%	N	n	%
	Age < 65			Age >= 65			Age < 65			Age >= 65		
AXS-07	424	84	19.81%	4	1	25%	424	157	37.03%	4	1	25%
Placebo	208	14	6.73%	1	0	0	208	51	24.52%	1	0	0
Meloxicam	417	47	11.27%	4	2	50%	417	134	32.13%	4	3	75%
Rizatriptan	419	73	17.42%	0	0	0	419	150	35.80%	0	0	0
	[redacted] = Female			[redacted] = Male			[redacted] = Female			[redacted] = Male		
AXS-07	346	62	17.92%	82	23	28.05%	346	125	36.13%	82	33	40.24%
Placebo	177	12	6.78%	32	2	6.25%	177	45	25.42%	32	6	18.75$
Meloxicam	355	39	10.99%	66	10	15.15%	355	116	32.68%	66	21	31.82%
Rizatriptan	353	64	18.13%	66	9	13.64%	353	128	36.26%	66	22	33.33%
	Race = White			Race = Black			Race = White			Race = Black		
AXS-07	337	76	22.55%	72	5	6.94%	337	131	38.87%	72	20	27.78%
Placebo	154	9	5.84%	45	4	8.69%	154	37	24.03%	45	12	26.67%
Meloxicam	324	37	11.42%	83	10	12.05%	324	104	32.10%	83	28	33.73%
Rizatriptan	320	63	19.69%	81	6	7.41%	320	120	37.50%	81	22	27.16%

%White +%Black < 100%. (Reviewer's result)

In Study 303, the median age of the subjects was about 41 to 43 years, with the percentage of female as 85.6% in the AXS-07 group and 85.2% in the placebo group, and the majority being either black or white, with the percentage of being white 85.6% and 80.7%, being black as 12.1% and 11.9%. Age 65+ subgroup was 0 out of total 267 subjects for entire study 301.

Table 25 Age, [redacted] and Race Summaries by Treatment Group - Study AXS-07-303

	Age (Median)	Patient count with Age 65+	[redacted] (%F)	Race (%White)	Race (%Black)
AXS-07 (N=132)	43	0	85.6	85.6	12.1
Placebo (N=135)	41	0	85.2	80.7	11.9
Total (N=267)	42	0	85.4	83.1	12.0

%White +%Black < 100%. (Reviewer's result.)

There is no need to conduct subgroup analysis by region since the entire study was conducted in the US. Analyses for the treatment effect across subgroups such as age, [redacted] and race were performed. The trend in treatment success appears to be similar across subgroups.

Table 26 Findings in Subgroup Populations – Age, [redacted] and Race – Study AXS-07-303

	Pain Free at 2 Hours						MBS Free at 2 Hours					
	N	n	%	N	n	%	N	n	%	N	n	%
	Age < 65			Age >= 65			Age < 65			Age >= 65		
AXS-07	132	43	32.58%	0			132	58	43.94%	0		
Placebo	135	22	16.30%	0			135	36	26.67%	0		
	[redacted] = Female			[redacted] = Male			[redacted] = Female			[redacted] = Male		
AXS-07	113	41	36.28%	19	2	10.53%	113	54	47.79%	19	4	21.05%
Placebo	115	20	17.39%	20	2	10.00%	115	31	26.96%	20	5	25.00$
	Race = White			Race = Black			Race = White			Race = Black		
AXS-07	113	37	32.74%	16	4	25.00%	113	53	46.90%	16	3	18.75%
Placebo	109	18	16.51%	16	2	12.50%	109	31	28.44%	16	1	6.25%

%White +%Black < 100%. (Reviewer's result)

4.2 Other Special/Subgroup Populations

None.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

No major statistical issues were identified.

5.2 Conclusions and Recommendations

The two studies AXS-07-301 (pivotal) and AXS-07-303 (non-pivotal due to intensity of migraine treated not meeting what's required in the current migraine guidance) in patients with acute migraine presented statistical evidence that AXS-07 is efficacious for treating migraine based on pain free status and MBS free status at 2 hours post dose.

5.3 Labeling Recommendations

Table 27 Co-Primary Efficacy Result Study 301 – AXS-07 VS Placebo

Co-Primary Endpoints	AXS-07 (N=428)	Placebo (N=209)
Pain Free at 2 hours	85	14
%	19.9%	6.7%
p-value	<.001	
MBS Free at 2 hours	158	51
%	36.9%	24.4%
p-value	.002	

P value was from Chi-square test. (Source: reviewer's own analysis and sponsor's analysis Table 12, Table 13 verified by the reviewer.)

Table 28 Key Secondary Efficacy Result for Study 301 – Component VS AXS-07

Key Secondary Endpoint	AXS-07 (N=428)	Meloxicam (N=421)	Rizatriptan (N=419)
24 Hour Sustained Pain Freedom	69	37	47
%	16.1%	8.8%	11.2%
p-value	-	.001	.038

P value was from Chi-square test. (Source: reviewer's own analysis and sponsor's analysis Table 16 verified by the reviewer.)

6 REFERENCES

[1] FDA Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-clinical-evidence-effectiveness-human-drug-and-biological-products

[2] FDA Guidance for Industry, Migraine: Developing Drugs for Acute Treatment
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/migraine-developing-drugs-acute-treatment

7 APPENDIX

The drug of interest AXS-07 is a combination product of 2 existing drugs so pivotal Study 301 had 4 arms including the drug itself, the placebo, and each of the 2 component drugs.

Using the same study data, it is possible to carry out comparisons of the AXS-07 to the other 3 arms, or the comparison of the 3 drug arms to placebo.

It may be useful for the clinical review team to have all these comparisons within the same trial even though the 2 component drugs are existing drugs and have efficacy data from previous trials. Worth noting is that Study 301 by design had a relatively low placebo effect.

Table 29 Two Co-Primary Endpoint for Study AXS-07-301 – Each of the 3 Groups VS AXS-07

Co-Primary Endpoints	AXS-07 (N=428)	Placebo (N=209)	Meloxicam (N=421)	Rizatriptan (N=419)
Pain Free at 2 hours	85	14	49	73
%	19.9%	6.7%	11.6%	17.4%
p-value vs AXS-07	-	<.001	.001	.363
MBS Free at 2 hours	158	51	137	150
%	36.9%	24.4%	32.5%	35.8%
p-value vs AXS-07	-	.002	.181	.736

P value was from Chi-square test. (Source: Table 25, 30 in CSR)

Table 30 Two Co-Primary Endpoint for Study AXS-07-301 – Each of the 3 Groups VS Placebo

Co-Primary Endpoints	AXS-07 (N=428)	Placebo (N=209)	Meloxicam (N=421)	Rizatriptan (N=419)
Pain Free at 2 hours	85	14	49	73
%	19.9%	6.7%	11.6%	17.4%
p-value vs Placebo	<.001	-	.0516	<.001
MBS Free at 2 hours	158	51	137	150
%	36.9%	24.4%	32.5%	35.8%
p-value vs Placebo	.002	-	.0355	.0039

P value was from Chi-square test. (Source: reviewer's own analysis.)

Table 31 Key Secondary Endpoint for Study 301 – Each of the 3 Groups VS AXS-07

Key Secondary Endpoint	AXS-07 (N=428)	Placebo (N=209)	Meloxicam (N=421)	Rizatriptan (N=419)
24 Hour Sustained Pain Freedom	69	11	37	47
%	16.1%	5.3%	8.8%	11.2%
p-value vs AXS-07	-	<.001	.001	.038

P value was from Chi-square test. (Source: reviewer's own analysis.)

Table 32 Key Secondary Endpoint for Study 301 – Each of the 3 Groups VS Placebo

Key Secondary Endpoint	AXS-07 (N=428)	Placebo (N=209)	Meloxicam (N=421)	Rizatriptan (N=419)
24 Hour Sustained Pain Freedom	69	11	37	47
%	16.1%	5.3%	8.8%	11.2%
p-value vs Placebo	<.001	-	.1163	.015

P value was from Chi-square test. (Source: reviewer's own analysis.)

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/

JINNAN LIU
04/27/2022 11:52:38 AM

HSIEN MING J HUNG
04/27/2022 03:35:50 PM