CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215431Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology

Clinical Pharmacology review

NDA Number	215431
Regulatory Pathway	505(b)(2)
Link to EDR	\\CDSESUB1\EVSPROD\nda215431\0024
Submission Date(s)	06/28/2024
Submission Type	505(b)(2) (Standard Review)
Brand Name	Symbravo®
Generic Name	AXS-07 (Meloxicam-Rizatriptan)
Formulation and Strength	(b) (4) tablet: Fixed dose combination of 20 mg meloxicam, and 10 mg rizatriptan
Route of Administration	Oral
Proposed Indication	Acute treatment of migraine with or without aura in adults
Sponsor	Axosome Therapeutics, Inc.
Associated IND	135972
Primary Reviewer	Ping Du, Ph.D.
Team Lead	Anantha Ram Nookala, Ph.D.
Final Signatory	Mehul Mehta, Ph.D.

Contents

1. Executive Summary

AXS-07 (proposed trade name Symbravo®) is a fixed-dose combination product [redacted] (b) (4) tablet) consisting of 20 mg meloxicam and 10 mg rizatriptan developed for acute treatment of migraine with or without aura in adult population. The NDA was submitted on June 30, 2021, via the 505(b)(2) regulatory pathway using Maxalt tablets (NDA 020864, rizatriptan), and Anjeso intravenous injection (NDA 210583, meloxicam) as Listed Drugs (LDs). From OCP perspective, an adequate bridge between AXS-07 and LDs Anjeso (Meloxicam; 30 mg intravenous dose) and Maxalt (Rizatriptan; 10 mg tablets) was established. Please refer to OCP review in DARRTS dated 04/15/2022. However, a complete response was issued on 29 April, 2022 due to product quality deficiencies and inadequate information to support the safety of meloxicam for chronic use. In a Type A end of review meeting held on 29 August, 2022, the applicant proposed to establish a PK-based bridge to Mobic® tablets (new Listed Drug for meloxicam, NDA 020938) to support the safety of meloxicam for chronic use as Anjeso is not approved for chronic use.

The NDA was resubmitted on 28 June, 2024, via the 505(b)(2) regulatory pathway using Maxalt tablets (NDA 020864, rizatriptan), Anjeso intravenous injection (NDA 210583, meloxicam) and Mobic® tablets (new Listed Drug for meloxicam, NDA 020938) as Listed Drugs (LDs). In this resubmission, the Applicant provided the detailed study report for the relative bioavailability (rBA) study (AXS-07-104) to support the bridging to the LD, Mobic® for the safety of meloxicam for chronic use. Study AXS-07-104 is a randomized, open label, two-way crossover study to evaluate the pharmacokinetics of meloxicam in AXS-07 compared to the Mobic® tablets. The listed drug, Mobic® tablets were 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 primary focus of this review is to verify the results of the rBA study for supporting the PK bridge between meloxicam in AXS-07 and Mobic® tablets to support the chronic safety of Symbravo® (AXS-07).

1.1 Recommendation

The Division of Neuropsychiatric Pharmacology has reviewed the submitted application and 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. These results indicate that the PK bridge to support the chronic safety for Symbravo® (AXS-07) has not been established. However, the applicant submitted additional data from an open label long-term extension (LTE) study and nonclinical studies to support chronic safety. Therefore, the OCP team defers to nonclinical and clinical review teams for the evaluation of chronic safety of Symbravo® (AXS-07).

2. Comprehensive Clinical Pharmacology Review

2.1 Overview of the Product and Regulatory Background

Symbravo® (AXS-07) is a fixed-dose combination of 20 mg meloxicam and 10 mg rizatriptan formulated into immediate release (b) (4) tablets for oral administration.

12 August, 2020: Type B Pre-NDA Meeting

In the meeting package, the applicant proposed to rely on the FDA's findings of safety and efficacy for both Mobic® (meloxicam) oral tablets and Anjeso® (meloxicam) IV. However, during the meeting discussion, they clarified that only Anjeso® will be referenced.

29 April, 2022

The applicant was issued a complete response letter (CRL) for Symbravo® (AXS-07) for the acute treatment of migraine. The applicant was informed of multiple CMC and non-clinical deficiencies. Since Anjeso® is not approved for chronic use, the agency recommended the applicant to provide information to support the safety of meloxicam for chronic use. Suggested approaches for providing such information include relying on FDA's findings of safety for a listed drug that contains meloxicam for chronic use,

providing the information by right-of-reference, or by submitting 6- and 9-month oral toxicity studies of meloxicam in rodent and nonrodent, respectively.

29 August, 2022: Type A End of Review Meeting

Applicant proposed to rely on the FDA's findings of safety for the LD Mobic® which is approved for chronic daily administration and literature. Applicant proposed to (b) (4) (b) (4) (b) (4) The agency did not agree with the proposal to (b) (4) (b) (4) (b) (4) The agency recommended the applicant to evaluate the relative bioavailability of meloxicam in AXS-07 and Mobic® to support a PK-based bridge in order to rely on the FDA's previous findings of safety for the listed drug Mobic.

10 January, 2024: Type D Guidance Meeting

FDA reiterated that a (b) (4) is generally not suitable for quantitative comparison of plasma concentrations between products. In addition, since the approved meloxicam dose of Mobic® (15 mg) is lower than that in Symbravo® (AXS-07) (20 mg), safety data, such as that obtained from the long-term extension study (Study AXS-07-302), would be needed to supplement any potentially adequate scientific bridge.

28 June, 2024: NDA re-submission

The applicant resubmitted the NDA 215431, including the data from a relative bioavailability study (Study AXS-07-104) comparing the pharmacokinetics of Symbravo® (AXS-07) to listed drug Mobic® tablets.

2.2 Clinical Pharmacology Review Questions

2.2.1 Is the PK bridge with previously approved Mobic® tablets adequately established to support the chronic safety of AXS-07?

No. Exposure comparisons at steady state with Mobic® tablets do not support the chronic safety of Symbravo® (AXS-07) for the meloxicam component.

Study AXS-07-104, a randomized, open-label, two period, two-way crossover study was conducted to evaluate the pharmacokinetics (PK) of the meloxicam component after a single dose of AXS-07 (i.e., meloxicam with rizatriptan) to that of single and multiple doses of Mobic® (meloxicam) in healthy subjects. Enrolled subjects received each of the following treatments:

- Treatment A (study treatment): single dose of AXS-07 (20 mg meloxicam/10 mg rizatriptan)
- Treatment B (reference treatment): 5-day once daily (QD) Mobic® (15 mg meloxicam)

The summary of the statistical comparisons of ln-transformed meloxicam PK parameters following single dose AXS-07 versus Mobic® (meloxicam) first dose is provided in **Table 1**. The 90% CIs of the Geometric Least Square Mean (GLSM) ratios for Cmax and AUC_{0-24} were entirely above the standard bioequivalence range of 80% to 125%. The GLSM ratios indicated that peak plasma exposure (Cmax) and daily exposures (AUC_{0-24}) were approximately 106% and 64% higher, respectively, following single dose AXS-07 compared to the first dose of Mobic® (meloxicam).

Table 1: Summary of the Statistical Comparisons of Plasma Meloxicam Pharmacokinetic Parameters: Single Dose AXS-07 versus Mobic® (meloxicam) First Dose

PK Parameter (Units)	AXS-07 (Test) GLSM (n)	Meloxicam First Dose (Reference) GLSM (n)	GLSM Ratio (%)	90% CI
C_{max} (ng/mL)	2684 (10)	1304 (10)	205.82	170.22, 248.87
AUC_{0-24} (h·ng/mL)	32280 (10)	19690 (10)	163.89	139.31, 192.82
DNC_{max} (ng/mL)	134.2 (10)	86.92 (10)	154.37	127.66, 186.66
$DNAUC_{0-24}$ (h·ng/mL)	1614 (10)	1313 (10)	122.92	104.48, 144.61

Source: Sponsor's analysis. Study axs-07-104-csr-body.pdf, Table 15

The summary of the statistical comparisons of ln-transformed meloxicam PK parameters following single dose of AXS-07 versus Mobic® (meloxicam) at steady state is provided in **Table *2***. The GLSM for C_{max} (or $C_{max,ss}$) was higher while AUC_{0-24} (or AUC_{tau}) was lower for single dose of AXS-07 compared to Mobic® (meloxicam) at steady state, respectively. The upper bound for C_{max} and lower bound for AUC_{0-24} were outside the standard 80% to

125% reference interval. The GLSM ratios indicated peak exposure (C_{max}) was approximately 13% higher while daily exposure (AUC_{0-24}) was approximately 19% lower following single dose of AXS-07 compared to Mobic® (meloxicam) at steady state.

Table 2: Summary of the Statistical Comparisons of Plasma Meloxicam Pharmacokinetic Parameters: Single Dose AXS-07 versus Mobic® (meloxicam) Steady State

PK Parameter[a] (Units)	AXS-07 (Test) GLSM (n)	Meloxicam Steady State (Reference) GLSM (n)	GLSM Ratio (%)	90% CI
C_{max} (ng/mL)	2684 (10)	2370 (12)	113.24	94.69, 135.42
AUC_{0-24} (h·ng/mL)	32280 (10)	39880 (12)	80.94	69.46, 94.31
DNC_{max} (ng/mL)	134.2 (10)	158 (12)	84.93	71.01, 101.57
$DNAUC_{0-24}$ (h·ng/mL)	1614 (10)	2659 (12)	60.70	52.10, 70.73

Source: Sponsor's analysis. Study axs-07-104-csr-body.pdf, Table 16

Reviewer's Analysis

In the rBA study (Study AXS-07-104), a single dose of AXS-07 (20 mg meloxicam/10 mg rizatriptan) was selected as it is the dose used in the clinical development program with AXS-07, and a 5-day regimen of 15 mg Mobic® (meloxicam) was selected as the standard reference treatment to evaluate PK at steady state, aligning with the approved label. While the upper 90% CI of Cmax for meloxicam is slightly higher than the standard 125%, it is not expected to be clinically significant based on the safety data from open label study (AXS-07-304) and the lower AUC_{0-24} compared to Mobic® (meloxicam) is not expected to affect safety as well. Therefore, the exposure of meloxicam after single dose of AXS-07 to that of Mobic® (meloxicam) at steady state appears to be comparable.

According to the applicant's [redacted] (b) (4), AXS-07 is to be administered once daily at the onset of migraine, with no restrictions on taking the second dose on the following day. [redacted] (b) (4) it cannot be excluded that the patients may take AXS-07 every day for 5 consecutive days (time for meloxicam to reach steady state). In an information request (IR) dated 06 October, 2022, the applicant was asked to provide data on the monthly use of AXS-07 tablets from the open-label long-term trial. **Table 3** and **Table 4** below present the actual data of AXS-07 use in the safety population and long-

term open label extension trial, respectively. As shown in **Table 4**, under the 90th percentile, 6 tablets were used within one month.

Table 3: Overall Summary of Treatment Exposure (Safety Population)

	AXS-07 Overall[a] (N=1066)
Months of Exposure	
Mean (SD)	4.9 (4.4)
Median	5.7
Min - Max	0.0 - 13.0
Total Drug Exposure (Tablet)	
Mean (SD)	23.6 (21.6)
Median	22
Min - Max	1 - 108

Max=maximum; Min=minimum; N=number of subjects; SD=standard deviation.
a AXS-07 Overall is defined as subjects who received at least one dose of AXS-07 in controlled clinical trials (AXS-07-301 or AXS-07-303) or the long-term trial (AXS-07-302).
Source: ISS Table 2.1.0

Source: Sponsor's analysis. Report, 1-11-3-clinical-info-amendment.pdf, Page 2, Table 20

Table 4: Summary of Monthly AXS-07 Table Using During the Long-Term Open-Label Safety Trial

Statistic	Monthly AXS-07 Tablet Usage*
N	706
Mean	4.44
SD	1.402
Min	1.33
25th Percentile (1st Quartile)	3.33
50th Percentile (2nd Quartile)	4.44
75th Percentile (3rd Quartile)	5.33
90th Percentile	6.00
Max	10.00

* The monthly AXS-07 tablet usage is derived as the total tablets taken divided by the total duration of exposure (last exposure date-first exposure date +1) in months, where the month is defined as 30 days.

Source: Sponsor's analysis. Report, 1-11-3-clinical-info-amendment.pdf, Page 3 (No Table number provided in the report)

Based on the actual exposure statistics provided by the sponsor from the open-label extension, it remains possible that the patients may take AXS-07 every day for up to 5 consecutive days. To evaluate this scenario, the reviewer simulated the worst-case scenario to compare the exposures of meloxicam at steady state between AXS-07 and Mobic® (meloxicam). The steady state exposures of meloxicam for AXS-07 were estimated using Phoenix® nonparametric superposition (NPS). **Table** summarizes the

PK Parameters for meloxicam at steady state for AXS-07 (calculated) and Mobic® (observed). The steady state Cmax for meloxicam with AXS-07 was 4755.8 ng/mL, almost 1.9-fold higher than that of Mobic® tablets, which was 2497.7 ng/mL. Thus, Mobic® doesn't provide adequate coverage for meloxicam exposure from AXS-07 at steady state, suggesting that an adequate PK bridge between AXS-07 and Mobic® for meloxicam at steady state has not been established.

Table 5: Summary of PK Parameters between AXS-07 and Mobic® for meloxicam at steady state

Parameter	AXS-07 (20 mg meloxicam)		Mobic (15 mg meloxicam)	
	Mean	%CV	Mean	%CV
AUC_{24h} (h*ng/mL)	72767.28	56.6	44028.09	46.2
Cmax (ng/mL)	4755.805	38.0	2497.661	34.6

Source: Reviewer's Independent Analysis

3. Appendices

3.1 Summary of bioanalytical method validation

A validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method was employed for determining the plasma concentrations of meloxicam in the relative bioavailability study (AXS-07-104). The sample analysis was conducted in accordance with the FDA guidance for the industry, Bioanalytical Method Validation, 2018.

Reviewer's Comments:

The validation and performance of the assay was reviewed individually for the relative bioavailability study (**Table**). Accuracy and precision of QC samples were ≤15%, and calibration curves for the LC-MS/MS bioanalytical assay were within the accepted limits.

Table *6*: Bioanalytical method validation reports for meloxicam

Validation Parameters	**Results:**
Linearity:	$r^2 \geq 0.9896$
Calibration Curve Range:	10.00 to 3999.20 ng/mL
Calibration Curve Accuracy and Precision:	Biases: -3.82 to 3.87% CV: 4.57 to 7.66%
Between-Run Accuracy and Precision:	Biases: -1.84 to 5.86% CV: 5.27 to 13.14%
Within-Run Accuracy and Precision:	Biases: -2.70 to 1.45% CV: 6.55 to 14.32%
Run Size Evaluation (288 samples):	Biases: -6.41 to 7.04% CV: 2.52 to 3.86%
Recovery of Analyte:	74.50, 76.14 and 73.17%
Recovery of Internal Standard:	83.40%

Validation Parameters	**Results:**
Dilution Integrity:	Bias: 10.51% CV: 1.90%
Lower Limit of Quantitation:	Signal to noise ratio at 10.07 ng/mL: 56
Matrix Selectivity (Including Hyperlipemic Matrix and Hemolyzed Matrix at 5%):	No significant interference observed in 8 out of 8 tested matrices for meloxicam and its IS No effect on the quantitation of the analyte
Potentially Interfering and Commonly Used Drugs:	No effect on the quantitation of the analyte
Specificity (Rizatriptan):	No significant interference observed in BLKF No effect on the quantitation of the analyte
Matrix Effect (Matrix Factor) (Including Hyperlipemic Matrix and Hemolyzed Matrix at 5%):	Mean IS-Normalized matrix factor: 0.9964539 and 0.9979904 CV: 1.21% and 0.55%
Matrix Effect (Spiked QCs): (Including Hyperlipemic Matrix and Hemolyzed Matrix at 5%):	No effect on the quantitation of the analyte Refer to validation report
Carryover of Analyte and IS:	No significant carryover observed
Reinjection Reproducibility:	59h14min at room temperature
Freeze and Thaw Stability in Matrix:	4 cycles at -20°C
Freeze and Thaw Stability in Matrix (Fortified with Rizatriptan):	4 cycles at -20°C
Short-Term Stability of Analyte in Matrix:	23h45min at room temperature
Short-Term Stability of Analyte in Matrix (Fortified with Rizatriptan):	23h17min at room temperature
Long-Term Stability of Analyte in Matrix:	673 days at -20°C
Long-Term Stability of Analyte in Matrix (Fortified with Rizatriptan):	28 days at -20°C
Stability of Analyte in Whole Blood:	240 minutes in an ice/water bath

Validation Parameters	Results:
Pre-Automated Extraction Stability:	03h05min at 4°C
Post-Preparative Stability:	72h30min at room temperature
Short-Term Stability of Analyte in Solution (High Concentration):	20h13min at room temperature
Short-Term Stability of IS in Solution (High Concentration):	20h35min at room temperature
Short-Term Stability of Analyte in Solution (Intermediate Concentration):	24h56min at room temperature
Short-Term Stability of Analyte in Solution (Low Concentration):	24h56min at room temperature
Short-Term Stability of IS in Solution (Low Concentration):	22h25min at room temperature
Long-Term Stability of Analyte in Solution (High Concentration):	321 days at -20°C
Long-Term Stability of IS in Solution (High Concentration):	413 days at -20°C
Long-Term Stability of Analyte in Solution (Intermediate Concentration):	321 days at -20°C
Long-Term Stability of Analyte in Solution (Low Concentration):	321 days at -20°C
Long-Term Stability of IS in Solution (Low Concentration):	413 days at -20°C

3.2 Individual Study Summary

Study AXS-07-104 was a randomized, open-label, two-period, two-way crossover study to evaluate the pharmacokinetics of meloxicam in AXS-07 and meloxicam in healthy subjects.

The main objectives of the study were to evaluate the pharmacokinetics (PK) of the meloxicam component in a single dose of AXS-07 (i.e., meloxicam with rizatriptan) to that of single and multiple doses of meloxicam.

- Treatment A (study treatment): single dose of AXS-07 (20 mg meloxicam/10 mg rizatriptan)
- Treatment B (reference treatment): 5-day once daily (QD) meloxicam (15 mg meloxicam)

A dose of AXS-07 (20 mg meloxicam/10 mg rizatriptan) was selected for this PK study since it is the dose used in the clinical development program with AXS-07. This dose has been studied in 3 completed and ongoing Phase 3 studies and found to be safe and well tolerated.

A 5-day regimen of meloxicam 15 mg dose was selected as the standard reference treatment in order to evaluate PK at steady state. Dosing of meloxicam occurred according to the US Prescribing Information as one 15 mg tablet given QD over 5 days, which would achieve anticipated steady state for the drug.

Blood samples were collected for concentration analysis. PK samples were collected pre-dose and at 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 36, 48, 72, and 96 hours post-dose in each period relative to the following doses.

- Period 1:
    - Sequence 1: AXS-07 on Day 1
    - Sequence 2: Meloxicam on Days 1 through 5
- Period 2:

- Sequence 1: Meloxicam on Days 6 through 10
- Sequence 2: AXS-07 on Day 10

Table 7: Summary of Plasma Meloxicam Pharmacokinetic Parameters (Pharmacokinetic Population)

PK Parameter[a] (Units)	Geometric Mean (Geometric CV%)[b]		
	AXS-07 (n = 10)	Meloxicam First Dose (n = 10)	Meloxicam Steady State (n = 12)[c]
C_{max} (ng/mL)	2602 (22.5)	1285 (39.1)	2370 (34.6)
T_{max} (h)	1.007 (0.50, 2.02)	2.030 (2.00, 8.00)	2.045 (2.00, 6.00)
T_{lag} (h)	0.000 (0.00, 0.00)	0.000 (0.00, 0.00)	NA
$C_{min,ss}$ (ng/mL)	NA	NA	1035 (66.8)
$C_{avg,ss}$ (ng/mL)	NA	NA	1662 (48.5)
AUC_{0-6} (h·ng/mL)	10970 (19.6)	5440 (33.3)	11220 (42.9)
AUC_{0-12} (h·ng/mL)	19040 (18.5)	11110 (26.5)	22240 (41.8)
AUC_{0-24} (h·ng/mL)	30330 (17.2)	18910 (28.7)	39880 (48.5)
AUC_{0-t} (h·ng/mL)	52140 (33.3)	NA	75720 (78.4)
$AUC_{0-\infty}$ (h·ng/mL)	56350 (40.4)	NA	NA
DNC_{max} (ng/mL/mg)	130.1 (22.5)	85.68 (39.1)	158 (34.6)
$DNAUC_{0-24}$ (h·ng/mL/mg)	1517 (17.2)	1261 (28.7)	2659 (48.5)
$t_{1/2}$ (h)	21.46 (49.3)	NA	24.21 (56.0)
CL/F (L/h)	0.3549 (40.4)	NA	0.3761 (48.5)
V_z/F (L)	10.99 (15.6)	NA	13.14 (21.1)
RA,C_{max}	NA	NA	1.755 (20.0)
RA,AUC	NA	NA	1.93 (23.2)

Table 8: Summary of the Statistical Comparisons of Plasma Meloxicam Pharmacokinetic Parameters: AXS-07 versus Meloxicam First Dose (Pharmacokinetic Population)

PK Parameter (Units)	AXS-07 (Test) GLSM (n)	Meloxicam First Dose (Reference) GLSM (n)	GLSM Ratio (%)	90% CI
C_{max} (ng/mL)	2684 (10)	1304 (10)	205.82	170.22, 248.87
AUC_{0-24} (h·ng/mL)	32280 (10)	19690 (10)	163.89	139.31, 192.82
DNC_{max} (ng/mL)	134.2 (10)	86.92 (10)	154.37	127.66, 186.66
$DNAUC_{0-24}$ (h·ng/mL)	1614 (10)	1313 (10)	122.92	104.48, 144.61

Table 9: Summary of the Statistical Comparisons of Plasma Meloxicam Pharmacokinetic Parameters: AXS-07 versus Meloxicam Steady State (Pharmacokinetic Population)

PK Parameter[a] (Units)	AXS-07 (Test) GLSM (n)	Meloxicam Steady State (Reference) GLSM (n)	GLSM Ratio (%)	90% CI
C_{max} (ng/mL)	2684 (10)	2370 (12)	113.24	94.69, 135.42
AUC_{0-24} (h·ng/mL)	32280 (10)	39880 (12)	80.94	69.46, 94.31
DNC_{max} (ng/mL)	134.2 (10)	158 (12)	84.93	71.01, 101.57
$DNAUC_{0-24}$ (h·ng/mL)	1614 (10)	2659 (12)	60.70	52.10, 70.73

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Office of Clinical Pharmacology

Integrated Clinical Pharmacology Review

NDA Number	215431
Link to EDR	\\CDSESUB1\evsprod\NDA215431\0001
Applicant	Axosome Therapeutics, Inc.
Submission Date	06/30/2021
Submission Type	505(b)(2)
Generic Name	AXS-07 (Meloxicam-Rizatriptan)
Brand Name	SYMBRAVO
Dosage Form (Strength)	(b) (4) tablet: Fixed dose combination of 20 mg meloxicam, and 10 mg rizatriptan
Route of Administration	Oral
Indication	Acute treatment of migraine with or without aura in adults
Associated IND	135972
OCP Review Team	Muzeeb Syed, Ph.D., Gopichand Gottipati, Ph.D.
OCP Division	Division of Neuropsychiatric Pharmacology (DNP)
OND Division	Division of Neurology II (DN2)

Table of Contents

1. Executive Summary

In this original New Drug Application (NDA), the Applicant, Axosome Therapeutics Inc., is seeking approval for SYMBRAVO (AXS-07) via 505(b)(2) regulatory pathway for acute treatment of migraine with or without aura in adult population. The proposed product, AXS-07, is a fixed-dose combination product [redacted] (b) (4) tablet) consisting of 20 mg meloxicam and 10 mg rizatriptan. The two listed drugs (LDs) used in this application, Maxalt tablets[1] (NDA 020864, rizatriptan), and Anjeso intravenous injection[2] (NDA 210583, meloxicam) were originally approved in the US in 1998 and 2020 respectively. Meloxicam tablets were originally approved in 2000.

In this NDA, the applicant conducted a pivotal randomized, double-blinded, placebo-controlled studies: AXS-07-301 (MOMENTUM): a factorial single-dose study which included rizatriptan (10 mg) and meloxicam (20 mg) as active controls, AXS-07 and placebo arms for acute treatment of moderate or severe migraine pain, and a long-term, open-label safety extension (AXS-07-302). Additionally, the applicant conducted a single-dose, double-blind, placebo-controlled study AXS-07-303 (INTERCEPT) with AXS-07 and placebo arms for acute treatment of mild migraine 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 (LD for rizatriptan), meloxicam component of AXS-07 to Anjeso intravenous injection (LD for meloxicam), and impact of high-fat-high-calorie meal intake on 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. OSIS noted that the inspection was not warranted for these sites because they were inspected previously and issued a No Action Indicated (NAI) classification (DARRTS dated 11/15/2021).

The primary focus of this review is 1) to verify the results of the relative bioavailability studies for supporting the PK bridge between the individual components of AXS-07 to respective LDs and allowing the reliance of FDA's previous findings as it pertains to relevant clinical pharmacology sections in respective labels of LDs; and 2) to verify the impact of food-intake on PK of individual components of AXS-07.

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[1] USPI for Maxalt tablets:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020864s023,020865s024lbl.pdf

[2] USPI for Anjeso intravenous injection:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/210583s001lbl.pdf

2. Recommendation

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). The key review topics with specific recommendations/comments are summarized below.

Review Issues	Recommendations and Comments
Pivotal evidence of effectiveness	The primary evidence of effectiveness of AXS-07 for treatment of acute treatment of migraine with or without aura in adults was demonstrated in a double-blind, randomized, placebo-controlled, single-dose study AXS-07-301 for acute treatment of moderate or severe migraine pain based on co-primary endpoints: percent of subjects who achieved headache pain freedom and freedom from most-bothersome-symptoms (MBS) at 2 hours post-dose. Additional evidence of effectiveness of AXS-07 was demonstrated in a double-blinded, randomized, placebo-controlled, single-dose study AXS-07-303 for acute treatment of mild migraine pain based on co-primary efficacy endpoints noted above.
PK Bridging between each component of AXS-07 and respective LDs	In study AXS-07-102, a single-dose of AXS-07 (10 mg rizatriptan component), and a single-dose of 10 mg Maxalt tablet (LD for Rizatriptan) in healthy subjects were administered under fasting conditions. The results showed that the mean relative bioavailability estimate for rizatriptan component was 115%. However, the maximum allowed total daily dosage of Maxalt (30 mg in any 24 hour period) is higher than the rizatriptan dosage in AXS-07 (10 mg). 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. In study AXS-07-103, single-dose of AXS-07 (20 mg meloxicam component) given orally under fasting conditions, and single-dose of 30 mg Anjeso intravenous injection (LD for meloxicam) in healthy subjects. The results showed that the mean relative bioavailability estimate for meloxicam component was 95%. However, the dose of the listed drug is higher than that recommended for AXS-07, providing adequate exposure coverage and bridge between AXS-07 and Anjeso for meloxicam component. Administration of AXS-07 under fed conditions (high-fat high-calorie meal) did not result in significant changes in exposures relative to those under fasted conditions, and therefore, bridging conclusions noted above are not affected under fed conditions.

3. Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

AXS-07 is a fixed-dose combination of 20 mg meloxicam and 10 mg rizatriptan formulated into immediate release (b) (4) tablets for oral administration. The applicant noted that meloxicam is a Bio-pharmaceutical Classification System class II compound, and AXS-07 tablets were formulated using MoSEIC™ (Molecular Solubility Enhanced Inclusion Complex), (b) (4) to improve the solubility and enhance the absorption of meloxicam. Further, the applicant noted that rizatriptan solubility is suitable across a wide pH, the formulation development for rizatriptan component focused on (b) (4)

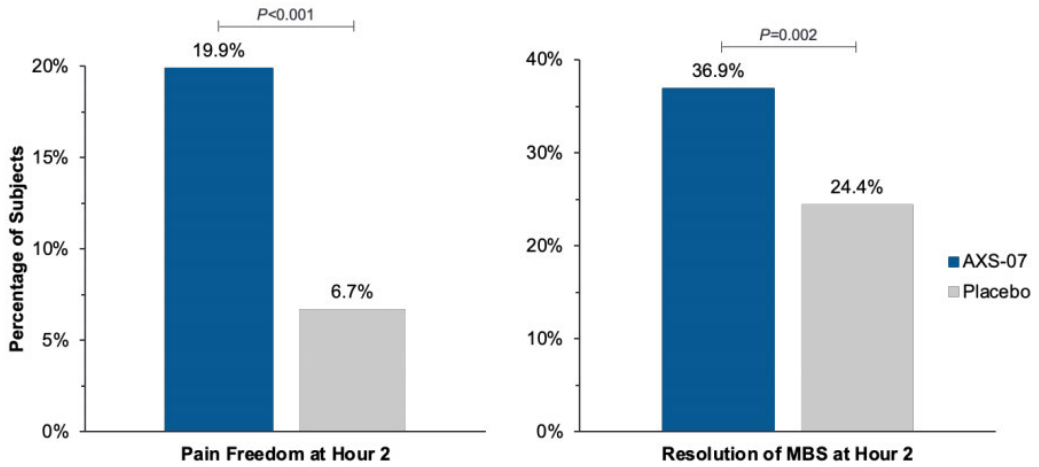
In 2017, the agency provided written responses in a Type B Meeting (PIND) to applicant's questions on proposed Phase 3 efficacy and the appropriateness of PK bridging strategy. An agreement letter for Special Protocol Assessment (SPA) for the applicant's phase 3 pivotal study was issued in January 2019. At the End-of-Phase 2 meeting, the agency advised about the appropriateness of listed drugs for the purposes of bridging to the individual components of AXS-07 and need for a long-term safety assessment (meeting minutes in DARRTS dated 06/25/2019). In the pre-NDA meeting (dated August 2020), the applicant discussed with the agency about the proposed 505(b)(2) regulatory drug development program, Phase 3 efficacy studies (AXS-07-301 and AXS-07-303), QT assessment, reliance on the listed drug labels for information pertinent to drug-interactions and special populations sections.

3.2 Summary of Evidence of Effectiveness Findings

The primary evidence of effectiveness was evaluated in AXS-07-301 (MOMENTUM) – a randomized, double-blind, 4-arm, parallel-group, single-dose, pivotal phase 3 study. The study subjects were 18 – 65 years of age, who had a history of migraine with or without aura, defined by the ICHD-3, first diagnosed at < 50 years, and an average of 2 to 8 moderate to severe migraines per month (not more than 10 migraine days per month) over the past 3 months. An additional inclusion criterion was subjects with a history of inadequate response to prior acute migraine treatments, defined as a score of ≤ 7 on the Migraine Treatment Optimization Questionnaire (m-TOQ-4*), corresponding to moderate or worse response to prior treatments over prior 4 weeks at screening. A total of 1594 subjects were randomized to 4 arms: placebo, meloxicam 20 mg, rizatriptan 10 mg and AXS-07. The study included a 2 week screening period, a 10-week period for treatment of moderate to severe migraine attack. The co-primary efficacy endpoints: percent of subjects with headache pain freedom at 2 hours and percentage of subjects with absence of Most Bothersome Symptoms (MBS) [nausea, photophobia, phonophobia] at 2 hours showed statistically significant benefit (placebo-corrected) for AXS-07.

Please refer to the statistical review by Drs. Minjeong Park and Jinnan Liu, and clinical review by Drs. Viveca Livezey and Heather Fitter for additional details on efficacy/safety assessments.

Figure 1: Study AXS-07-301: Results of Co-Primary Efficacy Endpoints



MBS=most bothersome symptom (nausea, photophobia, or phonophobia).
Note: p-value was based on Chi-square test.

Source: Clinical Study Report AXS-07-301; pg-51

The applicant also conducted AXS-07-303 (INTERCEPT) – a randomized, double-blind, single-dose, placebo-controlled study to evaluate the safety and efficacy of AXS-07 for acute treatment of mild migraine in subjects with episodic migraine with or without aura (≤ 8 migraines per month). Please refer to the statistical review by Drs. Jinnan Liu and John Lawrence, and clinical review by Drs. Viveca Livezey and Heather Fitter for additional details on study design and co-primary efficacy endpoints results from study AXS-07-303, and long-term safety study AXS-07-302.

3.3 Summary of Relative Bioavailability and Food-Effect Assessments

Summary of PK bridging between AXS-07 and Maxalt (Listed Drug for Rizatriptan)

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 non-compartmental 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.

Table 1: Study results from AXS-07-102: Relative bioavailability assessment between AXS-07 and Maxalt for rizatriptan (Reviewer's independent analyses)

Parameter	Geometric LSM (Least Square Means)		Geometric LS Means Ratio	90% Confidence Interval of Geometric LS Mean Ratio	
	AXS-07	Maxalt	Ratio (%)	Lower (%)	Upper (%)
AUC_{0-t} (h*pg/ml)	84423	73511	116.34	92.02	147.09
AUC_{0-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 results from AXS-07-102: Relative bioavailability assessment between AXS-07 and Maxalt for N-desmethyl rizatriptan (Reviewer's independent analyses)

Parameter	Geometric LSM (Least Square Means)		Geometric LS Means Ratio	90% Confidence Interval of Geometric LS Mean Ratio	
	AXS-07	Maxalt	Ratio (%)	Lower (%)	Upper (%)
AUC_{0-t} (h*pg/ml)	6667	5858	115.84	94.81	141.55
AUC_{0-inf} (h*pg/ml)	6768	5940	115.89	94.79	141.69
Cmax (pg/ml)	1815	1544	120.47	98.86	146.81

Reviewer's comments:

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 Anjeso (Listed Drug for Meloxicam)

In study AXS-07-103, a single-dose of AXS-07 (20 mg meloxicam component) given orally under fasting conditions, and a single-dose of 30 mg Anjeso 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 the table below.

Table 3: Study results from AXS-07-103: Summary of PK Parameters between AXS-07 and Anjeso for meloxicam (Reviewer's independent analyses)

Parameter	**AXS-07 (20 mg meloxicam) Fasted state**		**Anjeso 30 mg meloxicam intravenous injection**	
	Mean	**%CV**	**Mean**	**%CV**
AUC_{0-t} (h*ng/ml)	47419	22.4	72087	25.2
AUC_{0-inf} (h*ng/ml)	53532	27.3	83746	33.2
Cmax (ng/ml)	2936	27.9	4852	17.0

Reviewer's comments:

Sensitivity analysis: The applicant excluded 2 subjects in fasted state from the PK analysis of meloxicam data. Reviewer conducted independent sensitivity analysis to evaluate the potential impact of exclusion of these subjects from PK analyses [on the exposure (Cmax, AUClast, AUC0-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 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.

Summary of food-effect assessment

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 non-compartmental 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. The PK metrics for food-effect assessment are summarized below.

Table 4: Study results from AXS-07-103: Summary of PK parameters for food-effect assessment of rizatriptan and N-desmethyl rizatriptan (Reviewer's independent analyses)

Parameter	Rizatriptan		N-Desmethyl Rizatriptan	
	Fed	**Fasted**	**Fed**	**Fasted**
AUC_{0-t} (h*pg/ml)	90829 (21)	79992 (28)	8701 (22)	6893 (20)
AUC_{0-inf} (h*pg/ml)	93054 (21)	81509 (27)	8900 (21)	7074 (20)
Cmax (pg/ml)	27395 (42)	28519 (32)	2083 (29)	1904 (22)

Estimates presented as mean (%CV)

Table 5: Study results from AXS-07-103: Summary of PK parameters for food-effect assessment of meloxicam (Reviewer's independent analyses)

Parameter	Meloxicam	
	Fed	**Fasted**
AUC_{0-t} (h*ng/ml)	45817 (26)	47419 (22)
AUC_{0-inf} (h*ng/ml)	52272 (32)	53532 (27)
Cmax (ng/ml)	2132 (19)	2936 (28)

Estimates presented as mean (%CV)

Reviewer's comments:

The study results of food-effect assessment from AXS-07-103 showed that administration of AXS-07 with 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.

4. Appendices

4.1 Summary of Bioanalytical Method Validation

Bioanalytical methods used for the essential clinical pharmacology studies of Meloxicam and Rizatriptan are summarized in the Tables below,

Analyte	**Meloxicam**	**A: Rizatriptan** **B: N-Desmethyl Rizatriptan**
Report Number	*105142ABXR **187064ASZP	#165144AOWT ## 187064ASZQ
Study Number Supported	AXS-07-101, AXS-07-102, AXS-07-103	AXS-07-101, AXS-07-102, AXS-07-103
LLOQ	10 (ng/mL)	A: 100 pg/mL B: 10 pg/mL
Linear Range	10 – 3999.20 (ng/mL)	A: 100 to 8000 pg/mL B: 10 to 8000 pg/mL
QC Concentrations	10.07, 30.21, 604.20, 3021.0 (ng/mL)	A; 300, 14000, 30000 pg/mL B: 30.30, 1414, 3030 pg/mL
Intra-day Accuracy for QC (%RE)	-2.70 to 1.45	A:0.12 to 11.79 B:1.13 to 19.12
Intra-day Precision for QC (%CV)	6.55 to 14.32	A: 2.51 to 10.88 B: 2.64 to 10.59
Inter-day Accuracy for QC (%RE)	-1.84 to 5.86	A: -1.87 to 7.02 B: 0.55 to 5.74
Inter-day Precision for QC (%CV)	5.27 to 13.14	A:3.68 to 8.31 B:3.48 to 14.99
Post preparative stability	72 Hours and 30 min at room temperature	71 Hours and 52 min at room temperature
Freeze/Thaw Stability in Plasma	4 Cycles at -20°C and -90°C	4 Cycles at -20°C and -80°C

Long-term Storage Stability in Plasma	7, 70 and 673 Days at -20°C, 7 and 70 Days at -80°C	A: 34, 42, 675, 722 and 724 days at -20°C B: 34 and 722 days at -20°C A; 34, 675, 722 and 724 days at -80°C B: 34 and 722 days at -80°C
Potential interference	No effect of Meloxicam on the quantitation of the Rizatriptan and N-desmethyl Rizatriptan	No effect of Rizatriptan on Meloxicam on the quantitation

*105142ABXR-Method validation report of Meloxicam

**187064ASZP-Interference evaluation of Meloxicam on Rizatriptan and N-Desmethyl Rizatriptan

#165144AOWT- Method validation report of Rizatriptan

187064ASZQ-Interference evaluation of Rizatriptan on Meloxicam

Reviewer's comments: The validated assay performance was reviewed individually for the key clinical pharmacology studies. Accuracy and precision of QC samples were ≤15% (and ≤20% at LLQ), and calibration curves for the LC-MS/MS bioanalytical assay were within acceptable limits

4.2 Individual Study Summary

Study AXS-07-102

This was a single-center, randomized, single-dose, parallel-group, open-label study to establish the relative bioavailability of rizatriptan component of AXS-07 to listed drug, Maxalt, in healthy subjects under fasting conditions.

Number of Subjects (Planned and Analyzed)

A total of 20 healthy, adult male or female non-smokers subjects were included in this study. There were 10 subjects in each group and all the 10 subjects were analyzed. Subjects were randomized as 1:1 to receive either of the treatment, AXS-07 (20 mg meloxicam/10 mg rizatriptan) or Maxalt® (rizatriptan 10 mg)

PK Sampling

PK blood samples were collected at and 0.167, 0.333, 0.500, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 12 hours post-dose (Day-1); 24- and 36-hours post-dose (Day-2) and 48- and 60-hours post-dose (Day-3)

Table 6: Study results from AXS-07-102: Relative bioavailability assessment between AXS-07 and Maxalt for rizatriptan (Applicant's analyses)

Parameter	Geometric LSM (Least Square Means)		Geometric LS Means Ratio	90% Confidence Interval of Geometric LS Mean Ratio	
	AXS-07	Maxalt	Ratio (%)	Lower (%)	Upper (%)
AUC_{0-t} (h*pg/ml)	85223 (26)	74412(32)	116.07	91.85	146.68
AUC_{0-inf} (h*pg/ml)	86651 (26)	75229(32)	116.70	92.36	147.44
Cmax (pg/ml)	31684 (35)	24807(38)	129.07	97.07	171.62

Source: Study report AXS-07-102, Page 52 and 53

Study AXS-07-103

This was a randomized, cross-over, 3-period, single-dose to evaluate the relative bioavailability of AXS-07 administered with (high-fat-high calorie) or without meals, and assess the bioavailability of meloxicam component of AXS-07 (20 mg meloxicam component) compared to Anjeso, intravenous 30 mg meloxicam injection

Number of Subjects (Planned and Analyzed)

Total 16 subjects were doses in each treatment arm. For the Rizatriptan and N-Desmethyl Rizatriptan all the 16 subjects were included in the PK and BE analysis without exclusions. But in Meloxicam 3 subjects were excluded in fed state and 2 subjects in fasted state.

PK Sampling:

Blood samples were collected for concentration analysis of rizatriptan, meloxicam and N-desmethyl rizatriptan at 24 timepoints in the AXS-07 dosing periods, and for meloxicam only in the IV meloxicam period at the following timepoints:

Pre-dose, and 15, 30, 45 minutes, and 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 12, 24, 36, 48, and 60 hours post-dose.

Table 7: Study results from AXS-07-103: Summary of PK Parameters between AXS-07 and Anjeso for meloxicam (Applicant's analyses)

Parameter	AXS-07 (20 mg meloxicam) Fasted state		Anjeso 30 mg meloxicam intravenous injection	
	Mean	**%CV**	**Mean**	**%CV**
$AUC_{0\ t}$ (h*ng/ml)	48073	22.18	73745	24.54
$AUC_{0\text{-}inf}$ (h*ng/ml)	54185	26.97	85401	32.43
Cmax (ng/ml)	2936	27.86	4852	17.04

Source: Study report AXS-07-103; page 58 and 59

Table 8: Study results from AXS-07-103: Summary of PK parameters for food-effect assessment of rizatriptan and N-desmethyl rizatriptan (Applicant's analyses)

Parameter	Rizatriptan		N-Desmethyl Rizatriptan	
	Fed	**Fasted**	**Fed**	**Fasted**
AUC_{0-t} (h*pg/ml)	90787 (21)	79818(28)	8883 (22)	6963 (19)
AUC_{0-inf} (h*pg/ml)	93014 (21)	81334 (28)	9082 (22)	7143 (20)
Cmax (pg/ml)	27395 (42)	28520 (32)	2083 (29)	1904 (22)

Estimates presented as mean (%CV)

Source: Study report AXS-07-103; Page 53

Table 9: Study results from AXS-07-103: Summary of PK parameters for food-effect assessment of meloxicam (Applicant's analyses)

Parameter	Meloxicam	
	Fed	**Fasted**
AUC_{0-t} (h*ng/ml)	46467 (26)	48073 (22)
AUC_{0-inf} (h*ng/ml)	52912 (31)	54185 (27)
Cmax (ng/ml)	2132 (19)	2936 (28)

Estimates presented as mean (%CV)

Source: Study report AXS-07-103; Page 58

Reviewer's comments: Overall, the findings of Clinical Pharmacology reviewer's independent analyses, as summarized in section 3 of the review, were generally consistent with the applicant's analyses for relative bioavailability and food-effect evaluation of rizatriptan, N-desmethyl rizatriptan and meloxicam components of AXS-07.

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