Combined Efficacy and Safety of AXS-07 (MoSEIC™ Meloxicam and Rizatriptan) in Two Phase 3 Clinical Trials

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Key Question

What is the pooled efficacy and safety profile of AXS-07 (MoSEIC™ meloxicam and rizatriptan) in the acute treatment of migraine headache across two phase 3 clinical studies?

Conclusions

- Based on pooled data from 2 randomized placebo-controlled trials (MOMENTUM and INTERCEPT):
  - AXS-07 was effective for the acute treatment of migraine.
  - AXS-07 was generally safe and well tolerated.

References

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Acknowledgments

The clinical trials and the current study were supported by Axsome Therapeutics, developer of AXS-07. Medical writing services were provided by Shuang Li, PhD, CMPP, of Envision Pharma Group, funded by Axsome Therapeutics. The authors would like to express their appreciation to the study participants and their families as well as the investigators and site personnel.

Disclosures

ST, RBL are consultants to Axsome Therapeutics.

AC, CS, GP, and HT are full-time employees of Axsome Therapeutics and may hold stock or stock options.

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American Academy of Neurology (AAN) 2024 Annual Meeting, Denver, CO, USA April 13–18, 2024

Background

Better Acute Treatments of Migraine Are Needed

- All patients with migraine require acute treatment.[1]
- Current treatments are suboptimal, as approximately 70% of people with migraine are not fully satisfied with current treatment.[2]
- Suboptimal acute treatment of migraine is associated with an increased risk of medication overuse, progression to chronicity, and poor treatment outcomes.[3,4]
- There is a substantial unmet need for new acute treatments that provide rapid, sustained response for patients with migraine.

AXS-07 Uses a Multi-Mechanistic Approach to Treat Migraine

- AXS-07 is a novel, oral, rapidly absorbed, multi-mechanistic investigational medicine, consisting of MoSEIC™ meloxicam and rizatriptan (**Supplementary Figure 1**).
- Meloxicam is a cyclooxygenase-2 (COX-2) preferential non-steroidal anti-inflammatory drug and rizatriptan is a 5-$HT_{1B/1D}$ agonist.
- In AXS-07, meloxicam is enabled by the proprietary MoSEIC™ technology, which results in rapid absorption while maintaining a long half-life.

AXS-07 Demonstrated Efficacy in Clinical Trials

- MOMENTUM (NCT0389600, **Supplementary Information**):
  - AXS-07 improved clinical outcomes in patients with a history of inadequate response to acute migraine treatment compared with placebo, MoSEIC™ meloxicam, and rizatriptan.[5,6]
- INTERCEPT (NCT04163185, **Supplementary Information**):
  - AXS-07 resulted in rapid, substantial, and sustained pain relief as an early treatment of migraine.[7]
- MOVEMENT (NCT04068051):
  - AXS-07 consistently improved clinical outcomes across multiple headache episodes and was well tolerated in long-term episodic treatment of acute migraine.[8]

Methods

Study Design

- MOMENTUM and INTERCEPT were randomized, double-blind, multicenter, active- (MOMENTUM) and placebo- (MOMENTUM and INTERCEPT) controlled trials in participants with migraine.
- In MOMENTUM, 1594 participants were randomized (2:2:2:1) to take a single dose of AXS-07, 20 mg MoSEIC™ meloxicam, 10 mg rizatriptan, or placebo to treat a single migraine attack of moderate or severe intensity.[5,6]
- In INTERCEPT, 302 participants were randomized (1:1) to take a single dose of AXS-07 or placebo at the earliest onset of migraine pain.[7]

Participants

- Key inclusion criteria:
  - Adults (male or female) aged 18 to 65 years
  - Established diagnosis (≥1 year) of migraine with or without aura
  - 2 to 8 migraines per month on average
  - **For MOMENTUM only**, history of inadequate response as assessed by a score of ≤7 on the Migraine Treatment Optimization Questionnaire (mTOQ-4)
- Key exclusion criteria:
  - Cluster headaches, tension headaches, or other types of migraines
  - Chronic daily headache (≥15 non-migraine headache days per month)
  - History of significant cardiovascular disease
  - Uncontrolled hypertension

Outcomes

- Co-primary endpoints for both studies were pain freedom at Hour 2 post dose and freedom from most bothersome symptom (MBS) at Hour 2 post dose.
- AXS-07 results from the 2 studies, MOMENTUM and INTERCEPT, compared with placebo were pooled for the present analysis.

Results

Demographics and Baseline Characteristics

- Demographics and baseline characteristics were generally balanced between treatment groups; rates of characteristics associated with poor treatment outcomes were high (**Table 1**).

Table 1. Baseline Characteristics (ITT Population)

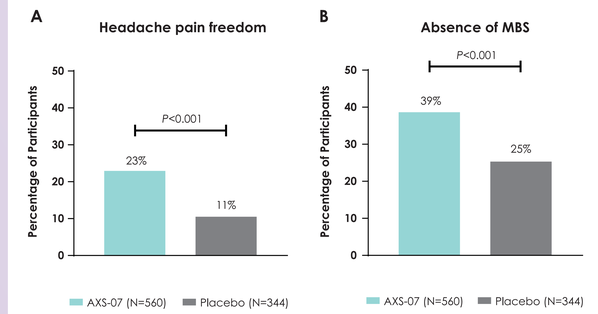
Characteristics	AXS-07 Pooled (N=560)	Placebo Pooled (N=344)
Participants of MOMENTUM, n	428	209
Participants of INTERCEPT, n	132	135
Age, years, mean (SD)	41.3 (11.51)	41.0 (11.29)
Sex, female, n (%)	459 (82.0)	292 (84.9)
Race, n (%)		
White	450 (80.4)	263 (76.5)
Black or African American	88 (15.7)	61 (17.7)
Asian	9 (1.6)	11 (3.2)
Other	13 (2.3)	9 (2.6)
Allodynia, n (%)		
Yes (ASC-12 ≥3)	438 (78.2)	246 (71.5)
No (ASC-12 <3)	122 (21.8)	98 (28.5)
Migraine pain, n (%)		
1 – mild	132 (23.6)	135 (39.2)
2 – moderate	244 (43.6)	121 (35.2)
3 – severe	184 (32.9)	88 (25.6)
Nausea, n (%)	244 (43.6)	159 (46.2)
Depression, n (%)	78 (13.9)	51 (14.8)
Obese (BMI ≥30 kg/m^2), n (%)	239 (42.7)	145 (42.2)

ASC-12=12-item Allodynia symptom Checklist; BMI=body mass index; ITT=intent-to-treat; SD, standard deviation.

Efficacy

- The percentage of participants with headache pain freedom at Hour 2 was significantly higher with AXS-07 compared with placebo (P<0.001) (**Figure 1A**).
- Absence of MBS (nausea, photophobia, or phonophobia) at Hour 2 was achieved by a significantly greater percentage of participants taking AXS-07 versus placebo (P<0.001) (**Figure 1B**).
- In the AXS-07 group, 60.5% of participants experienced headache pain relief 2 hours after dosing, compared with 39.5% in the placebo group (P<0.001).
- The percentage of participants achieving 24-hour and 48-hour sustained pain freedom was significantly greater in the AXS-07 group compared with the placebo group; the between-group difference was 10.6% and 9.9 %, respectively (both P<0.001) (**Figures 2A** and **2B**).
- Participants receiving AXS-07 had reduced rescue medication use through 24 hours compared with placebo (P<0.001) (**Figure 3**).
- More participants receiving AXS-07 returned to normal functioning than those taking placebo, starting at 1 hour after dosing and maintained at every timepoint thereafter (P<0.05 or P<0.001) (**Figure 4**).

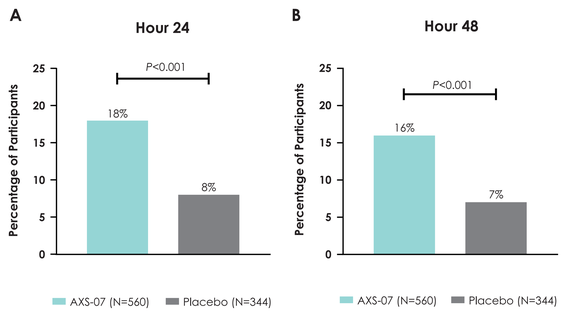
Figure 1. Headache Pain Freedom and Absence of MBS at Hour 2



AXS-07 effectively reduced headache pain and MBS at Hour 2

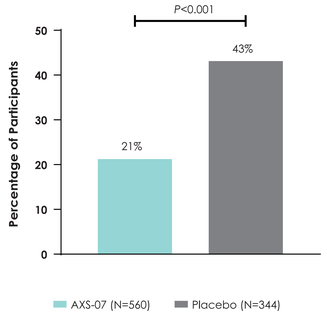
MBS=most bothersome symptom.

Figure 2. Sustained Pain Freedom



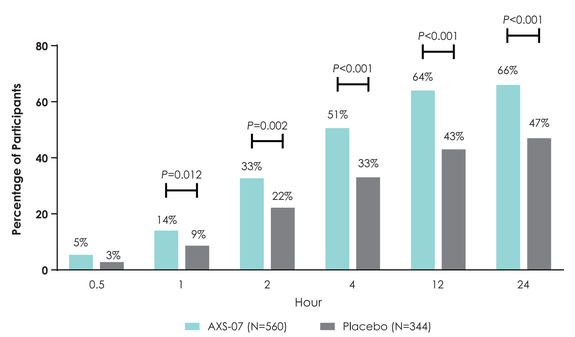
AXS-07 improved 24-hour and 48-hour sustained pain freedom

Figure 3. Rescue Medication Use in the First 24 Hours Post-dose



AXS-07 effectively reduced the usage of rescue medication

Figure 4. Percentage of Participants Able to Perform Normal Activity Over Time



AXS-07 promoted the resumption of normal activity

Safety

- Treatment-emergent adverse events (TEAEs) were experienced by 12.7% of participants taking AXS-07 compared with 6.6% of participants on placebo (**Table 2**).
- The most frequently reported TEAEs in the AXS-07 and placebo groups were nausea, somnolence, and dizziness (**Table 2**).

Table 2. Most Frequently Reported Treatment-emergent Adverse Events (Safety Population)

Participants, n (%)	AXS-07 Pooled (N=581)	Placebo Pooled (N=361)
At least 1 TEAE	74 (12.7)	24 (6.6)
Nausea	14 (2.4)	9 (2.5)
Somnolence	12 (2.1)	4 (1.1)
Dizziness	11 (1.9)	4 (1.1)

TEAE=treatment-emergent adverse event.

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Supplementary Figure 1. Mechanism of Action of AXS-07

- **AXS-07 consists of MoSEIC™ meloxicam and rizatriptan.**
  - MoSEIC™ Meloxicam: T_{max} 1 hour; $t_{½}$: 18.2 hours; median time to therapeutic plasma concentration: 17 minutes.
  - Rizatriptan: T_{max} 0.64 hours; $t_{½}$: 1.98 hours.

(Source: O'Gorman, et al. Poster at 19th Congress of the International Headache Society 2019. IHC-PO-124.)

- **MoSEIC™ delivery technology.**
  - A proprietary technology which substantially increases the solubility and speed of absorption of meloxicam, after oral administration, while maintaining an extended plasma half-life.

- **Multiple mechanisms of actions.**
  - AXS-07 provides multiple mechanisms of action, which combined with a favorable PK profile, may result in improved efficacy in acute migraine treatment.

	AXS-07	
Migraine Process	Mechanism / Action	Component
CGRP Mediated	✓ Inhibition of CGRP release ✓ Reversal of CGRP-mediated vasodilation	Rizatriptan
Neuro-inflammation	✓ Cyclooxygenase inhibition ✓ PGE_2 synthesis inhibition	MoSEIC™ meloxicam
Pain Signal Transmission	✓ Decreased passage of pain signals to trigeminal nucleus caudalis	Rizatriptan
Central Sensitization	✓ Reversal of central sensitization	MoSEIC™ meloxicam

Mechanism of AXS-07 addresses multiple disordered physiological processes observed during migraine attacks

CGRP=calcitonin gene-related peptide.

Supplementary Information: Findings from the MOMENTUM and INTERCEPT Trials

MOMENTUM

- **Enrolled patients exhibited a high rate of characteristics associated with poor treatment outcomes including allodynia, severe pain intensity, obesity, and morning migraine.**
- **AXS-07 met the 2 co-primary endpoints (Supplementary Table 1).**
- **A significantly greater percentage of patients in the AXS-07 group achieved sustained pain freedom from 2 to 24 hours after dosing, compared with rizatriptan, MoSEIC™ meloxicam, and placebo (16.1%, 11.2%, 8.8%, and 5.3%, respectively; *P*=0.038, *P*=0.001, and *P*<0.001, respectively vs AXS-07).**
- **Rescue medication was used by 23.0% of patients treated with AXS-07, compared with 43.5% of placebo- and 34.7% of rizatriptan-treated patients (*P*<0.001 for each group vs AXS-07).**
- **The most commonly reported adverse events with AXS-07 were nausea, dizziness, and somnolence; none of the rates was greater than placebo or greater than 3%.**

INTERCEPT

- **AXS-07 met the 2 co-primary endpoints (Supplementary Table 1).**
- **Treatment with AXS-07 led to rapid and durable freedom from migraine pain.**
  - AXS-07 rapidly eliminated migraine pain compared with placebo.
    - A greater proportion of patients achieving pain freedom 30 minutes after a single dose.
    - There was a significant difference starting at 90 minutes (*P*=0.003) and at every timepoint thereafter.
  - 64% and 69% of patients treated with AXS-07 were pain free at 12 and 24 hours, versus 42% and 47% of placebo patients, respectively.
- **AXS-07 significantly prevented pain progression in 73.5% of patients treated with AXS-07 compared with 47.4% for placebo (*P*<0.001) and significantly reduced rescue medication use through 24 hours (15.3% vs 42.2%, *P*<0.001).**
- **73.5% of patients treated with AXS-07 returned to normal functioning at 24 hours post dosing versus 47.4% for placebo (*P*<0.001).**

Supplementary Table 1. Co-primary Endpoints in Phase 3 Trials of AXS-07 (% Participants)

	AXS-07	Placebo	Difference	*P* value
MOMENTUM[5,6]	N=428	N=209		
Pain freedom at Hour 2	19.9%	6.7%	-13.2%	<0.001
Absence of MBS at Hour 2	36.9%	24.4%	-12.5%	0.002
INTERCEPT[7]	N=132	N=135		
Pain freedom at Hour 2	32.6%	16.3%	-16.3%	0.002
Absence of MBS at Hour 2	43.9%	26.7%	-17.3%	0.003

MBS, most bothersome symptom