Comparative Efficacy of AXS-07 (MoSEIC™ Meloxicam/Rizatriptan) versus Rizatriptan in the Acute Treatment of Migraine

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AXSOME THERAPEUTICS

BACKGROUND

Unmet Need in the Acute Treatment of Migraine

- **Migraine is a highly disabling neurological disorder:**
- Characterized by recurrent attacks of pulsating head pain accompanied by nausea and sensitivity to light and sound
- These symptoms are often severe and incapacitating, requiring bed rest[1]
- The World Health Organization classifies severe migraine attacks as among the most disabling illnesses, comparable to dementia, quadriplegia, and active psychosis[2,3]
- **Current treatments are suboptimal:**
- More than 70% of sufferers report dissatisfaction with existing acute treatments.
- The most commonly reported reasons for patient dissatisfaction are slow onset of pain relief, inconsistent pain relief, and recurrence of pain during the same day[4,5]
- **Suboptimal acute treatment is associated with an increased risk of chronic migraine:** which may be prevented by improving acute treatment outcomes[6]
- **Predictors of poor treatment response:** Allodynia (pain from normally non-painful stimuli, such as brushing hair, wearing glasses or taking a shower), severe migraine pain, obesity, and morning migraine, are all known risk factors for poor treatment outcomes
- **There is an urgent need for new acute treatments:** that provide rapid, sustained, and improved efficacy for this serious neurological disease

AXS-07: A Multi-mechanistic Approach

- **AXS-07 consists of MoSEIC™ meloxicam and rizatriptan**:
  - MoSEIC™ meloxicam is a potent, oral, rapidly absorbed, COX-2 preferential NSAID
  - Rizatriptan is a potent 5-$HT_{1B/1D}$ agonist and is considered one of the most effective and fastest-acting acute migraine therapies
- **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	✓ Decrease 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

MOMENTUM Study Objective

- The objective of this study was to evaluate the efficacy and safety of a single dose of AXS-07 compared to its individual components, MoSEIC™ meloxicam and rizatriptan, as well as placebo, for the treatment of a moderate or severe migraine attack in patients with a history of inadequate response to prior acute treatments

References

1. Dodick DW. Migraine. Lancet. 2018;391(10127):1315–1330. **2.** Menken et al. Arch Neurol. 2000;57:418-420. **3.** Shapiro and Goadsby. Cephalalgia. 2007;27:991-4. **4.** Smelt AF et al. PLoS One. 2014;9(6):e98933. **5.** Lipton RB, Stewart WF. Headache. 1999;39(suppl 2):S20-S26. **6.** Lipton RB et al. Neurology. 2015;84(7):688–695. **7.** Lipton RB et al. Cephalalgia. 2009;29(7):751-9. **8.** Lipton RB et al. The Journal of Headache and Pain. 2013;14(Suppl 1):P201. **9.** Lipton RB, et al. Ann Neurology. 2008;63:148–158.

METHODS

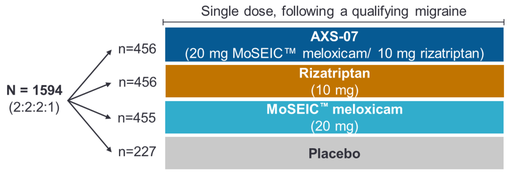
MOMENTUM Trial Design

- Randomized, double-blind, multicenter, active-and placebo-controlled, single-dose trial in patients with a history of inadequate response to prior acute migraine treatments
- Eligible patients were randomized in a 2:2:2:1 ratio to treatment with AXS-07 (20 mg MoSEIC™ meloxicam/10 mg rizatriptan), rizatriptan (10 mg), MoSEIC™ meloxicam (20 mg), or placebo

Key inclusion criteria:
- Male or female, 18 to 65 years of age
- Established diagnosis of migraine (at least one year) with or without aura as defined by ICHD-3 criteria
- Average of 2 to 8 migraines per month
- History of inadequate response as assessed by a score of ≤ 7 on the Migraine Treatment Optimization Questionnaire (mTOQ-4)

Key exclusion criteria:
- Cluster headaches or other types of migraines
- Chronic daily headache (≥ 15 non-migraine headache days per month)
- History of significant cardiovascular diseases
- Uncontrolled hypertension

Inadequate treatment response determined by mTOQ-4: The mTOQ is a validated, reliable, self-reported, easy-to-use, 4-item questionnaire that assesses the adequacy of current treatment efficacy for the purpose of optimizing treatment[6-9]



Co-Primary Endpoints (AXS-07 vs placebo)
- Pain Freedom at 2 hours
- Freedom from most bothersome symptom (MBS) at 2 hours

Key Secondary Endpoint (AXS-07 vs rizatriptan and MoSEIC™ meloxicam)
- Sustained pain freedom 2-24 hours after dosing

Demographics and Baseline Characteristics

	AXS-07 (20 mg MoSEIC Mlx / 10 mg Riz)	Rizatriptan (10 mg)	MoSEIC Meloxicam (20 mg)	Placebo
	n=428	n=419	n=421	n=209
Age, years	41.2 (11.52)	41.4 (10.68)	41.0 (12.07)	40.8 (11.47)
Female gender, n (%)	346 (80.8%)	353 (84.2%)	355 (84.3%)	177 (84.7%)
Race, n (%)				
White	337 (78.7%)	320 (76.4%)	324 (77.0%)	154 (73.7%)
Black or African American	73 (17.1%)	83 (19.8%)	86 (20.4%)	47 (22.5%)
Asian	10 (2.3%)	6 (1.4%)	9 (2.1%)	5 (2.4%)
Prior triptan use, n (%)	171 (40.0%)	163 (38.9%)	147 (34.9%)	73 (34.9%)
Total mTOQ-4 Score, mean (SD)	3.5 (2.17)	3.6 (2.25)	3.8 (2.14)	3.6 (2.19)
Presence of Allodynia, n (%)	336 (78.5%)	305 (72.8%)	322 (76.5%)	150 (71.8%)
Severe Pain Intensity, n (%)	184 (43.0%)	155 (37.0%)	181 (43.0%)	88 (42.1%)
Obese (>30mg/kg²), n (%)	184 (43.0%)	197 (47.0%)	174 (41.3%)	90 (43.1%)
Morning Migraine, n (%)	162 (36.7%)	158 (36.4%)	159 (36.7%)	76 (34.9%)

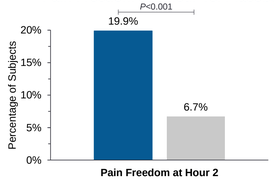
Abbreviations: BMI = body mass index, Mlx = meloxicam; mTOQ-4 = Migraine Treatment Optimization Questionnaire; Riz = rizatriptan

- Overall, demographics and baseline characteristics were consistent across treatment groups
- Enrolled patients exhibited a high rate of characteristics associated with poor treatment outcomes including allodynia, severe pain intensity, obesity and morning migraine

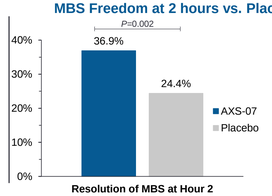
RESULTS

AXS-07 Achieved Co-primary Endpoints

Pain Freedom at 2 hour vs. Placebo

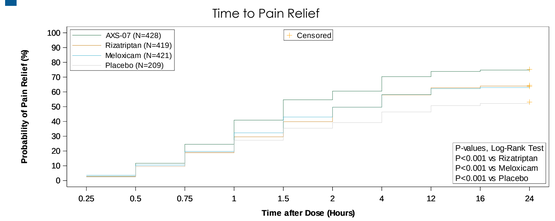


MBS Freedom at 2 hours vs. Placebo



- AXS-07 demonstrated statistically significant superiority to placebo on 2-hour pain freedom (20% vs. 7%; p<0.001) with a placebo corrected difference of 13%
- AXS-07 demonstrated statistically significant superiority to placebo on freedom from MBS at Hour 2 (37% vs. 24%; p=0.002) with a placebo corrected difference of 13%

Rapid Relief of Migraine Pain with AXS-07

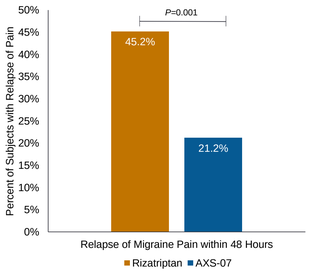


Number of subjects at Risk:

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

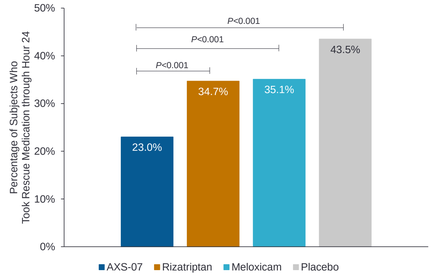
- Probability of achieving pain relief with AXS-07 was greater than with rizatriptan within 30 minutes after dosing, resulting in a median time to pain relief that was nearly 3x faster for AXS-07 compared to rizatriptan (1.5 vs. 4.0 hours, p<0.001)

Pain Relapse Significantly Reduced with AXS-07



- AXS-07 reduced pain relapse by greater than 50% compared to rizatriptan over 48 hours after dosing

Significant Reduction in Rescue Medication Use



- Rescue medication was used by 23% of AXS-07-treated patients, vs. 44% (placebo), 35% (MoSEIC meloxicam and rizatriptan) (p<0.001 for each group vs. AXS-07)
- Rescue medication use reflects need for rescue after a single dose of study drug

AXS-07 Superiority over Rizatriptan on Multiple Outcomes

	Results*		
Clinically Significant Endpoint	**AXS-07**	**Rizatriptan**	**P-value**
Time to Pain Relief (probability of relief greater with AXS-07 starting at 30 mins, median times shown)	1.5 hours	4.0 hours	<0.001
24-hour Sustained Pain Relief	53.3%	43.9%	0.006
48-hour Sustained Pain Relief	46.5%	36.5%	0.003
24-hour Sustained Pain Freedom	16.1%	11.2%	0.038
48-hour Sustained Pain Freedom	15.4%	8.8%	0.003
Pain Relapse	21.2%	45.2%	0.001
Rescue Medication Use within 24 hours	23.0%	34.7%	<0.001
PGI-C (Very Much/Much Improved at 2 hours)	47.3%	41.1%	0.022
Return to Normal Functioning at 24 hours	63.8%	56.1%	0.027

*Presented as percent of patients responding, except time to pain relief which is presented as median time.
Abbreviations: PGI-C = patient global impression of change.

Safety and Tolerability

	AXS-07 (N = 441)	Rizatriptan (N = 434)	Meloxicam (N = 433)	Placebo (N = 218)
Treatment-Emergent AE	**49 (11.1%)**	**67 (15.4%)**	**50 (11.5%)**	**13 (6.0%)**
Nausea	12 (2.7%)	21 (4.8%)	14 (3.2%)	8 (3.7%)
Dizziness	7 (1.6%)	9 (2.1%)	5 (1.2%)	5 (1.2%)
Somnolence	6 (1.4%)	9 (2.1%)	10 (2.3%)	6 (1.4%)

Adverse Events Occurring in ≥2% of Patients are Presented

- AXS-07 was generally safe and well tolerated. The most commonly reported adverse events with AXS-07 were nausea, dizziness and somnolence, none of which occurred at a rate greater than placebo or greater than 3 percent

CONCLUSIONS

- **AXS-07 met the co-primary endpoints of pain freedom and freedom from most bothersome symptoms at 2 hours, compared to placebo**
- **Statistically significant superiority of AXS-07 over rizatriptan was observed for time to pain relief, sustained pain relief and freedom, and pain relapse after a single dose**
- **Efficacy benefits of AXS-07 translated into statistically significantly better patient global assessment of response, return to normal functioning, and reduced rescue medication use as compared to rizatriptan**
- **AXS-07 was generally safe and well tolerated in this study**