

Comparative Efficacy of AXS-07 Versus Gepants for Acute Treatment of Migraine: A Network Meta-Analysis

American Academy of Neurology
(AAN) 77th Annual Meeting
April 5-9, 2025
San Diego, CA

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Key Objective

To compare the efficacy of AXS-07 (MoSEICTM meloxicam and rizatriptan) with rimegepant, ubrogepant, and zavegepant for acute migraine treatment using a network meta-analysis (NMA)

Introduction

- Migraine is a highly disabling neurological disorder for which patients require acute treatment¹
 - Pulsating head pain – a hallmark symptom frequently accompanied by nausea and sensitivity to light and sound – can be severe and incapacitating^{2,3}
- Multiple migraine treatments exist, but they often have limitations, such as inconsistent pain relief, slow onset, limited response, and high recurrence within 24 hours, resulting in patient dissatisfaction^{4,5}
 - Suboptimal treatments of acute migraine can lead to medication overuse, medication discontinuation, and progression of migraine from episodic to chronic, leading to increased healthcare utilization and costs^{6,7}
- There is a need for new acute migraine treatments with improved efficacy that provide rapid and sustained relief or freedom from pain and associated symptoms
 - Gepants are a class of calcitonin gene-related peptide receptor antagonists, with rimegepant, ubrogepant, and zavegepant approved for acute treatment of migraine in the United States (US)⁸
 - Though efficacy over placebo has been demonstrated for gepants, data analysis is needed to attempt to compare the efficacy of these currently available and widely used treatments with newer migraine treatments, such as AXS-07
 - AXS-07, consisting of 20 mg MoSEICTM (Molecular Solubility Enhanced Inclusion Complex) meloxicam and 10 mg rizatriptan, is a novel, oral, rapidly absorbed, multimechanistic medicine recently approved in the US for the acute treatment of migraine with or without aura in adults⁹

Plain Language Summary

- Many patients with migraine say their acute treatments do not work well enough, meaning new treatments that are more effective are needed
- A new acute treatment for migraine called AXS-07 is effective and safe, but it has not been compared with other available treatments, like another class of acute migraine medication called gepants
- In this study, existing information about AXS-07 and gepants is compared using an approach called a network meta-analysis (NMA), which allows for indirect comparisons between the results of different trials
- NMA showed AXS-07 was likely to be better than gepants for relieving pain and other migraine symptoms

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Acknowledgments

This study was funded by Axsome Therapeutics.

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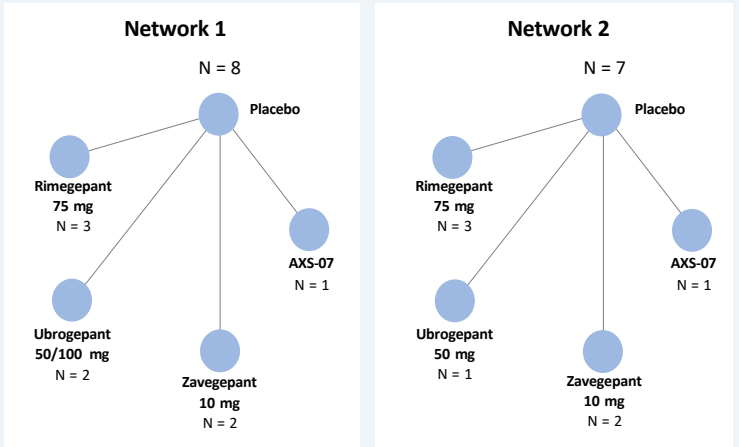
Disclosures

SN is an employee at the Jefferson Headache Center and in the Department of Neurology at Thomas Jefferson University and was served as a consultant or on an advisory board for Amgen, Axsome Therapeutics, AbbVie, Eli Lilly, Lundbeck, Pfizer, and Tonic. YZ is an employee of Axsome Therapeutics and may hold shares and/or stock options in the company. CG and AE are full-time employees of RTI Health Solutions, an independent nonprofit research organization; their compensation is unconnected to the studies on which they work. AB is an employee at the Los Angeles Headache Center and the San Diego Headache Center; serves as a consultant or on an advisory board for Allergan, AbbVie, Ason, Alder, Amgen, Axsome, BMS, Biohaven, Impel, Lundbeck, Lilly, Novartis, Pfizer, Revance, Teva, Tharionica, Zoscano; and has been a speaker for and/or received honoraria from Allergan, AbbVie, Amgen, BMS, Biohaven, Eli Lilly, Lundbeck, and Teva. RTI Health Solutions received funding under a research contract with Axsome Therapeutics to support the work and to provide publication support; medical writing assistance was provided by Gabrielle Dardis, PhD, and Madison Walker, MPH, of RTI Health Solutions.

Methods

- A fixed-effects Bayesian NMA was conducted for AXS-07 versus gepants (rimegepant, 75 mg; ubrogepant, 50 mg and 100 mg; zavegepant, 10 mg)
 - MOMENTUM for AXS-07¹⁰ and 7 placebo-controlled phase 3 trials of the comparator gepants¹¹⁻¹⁸ were included
 - The objective of MOMENTUM was to evaluate the efficacy and safety of AXS-07 in participants with inadequate response to previous acute treatments for migraine
 - Data for ubrogepant 50 mg and 100 mg were pooled
- Results were summarized with odds ratios and 95% credible intervals (CrIs). To determine which treatment was likely to be the most efficacious for each outcome, the surface under the cumulative ranking curve (SUCRA) and probability of each treatment being the most efficacious were calculated for each endpoint
- All endpoints were binomial and used a logit link within a fixed-effects generalized linear model
- Two evidence networks were available for 7 endpoints
 - Network 1: Pain relief at hour 2, sustained pain relief from 2-24 hours, pain freedom at hour 2, sustained pain freedom from 2-24 hours, absence of most bothersome symptoms (MBS) at hour 2, and ability to perform normal activities at hour 2
 - Network 2: Use of rescue medications from 2-24 hours

			Network	
Trial		Treatments	1	2
MOMENTUM (NCT0389600) ¹⁰	Placebo	AXS-07	✓	✓
Study 301 (NCT03235479) ¹¹	Placebo	Rimegepant 75 mg	✓	✓
Study 302 (NCT03237845) ¹²	Placebo	Rimegepant 75 mg	✓	✓
Study 303 (NCT03461757) ¹³	Placebo	Rimegepant 75 mg	✓	✓
ACHIEVE I (NCT02828020) ¹⁴	Placebo	Ubrogepant 50 mg Ubrogepant 100 mg	✓	-
ACHIEVE II (NCT02867709) ¹⁵	Placebo	Ubrogepant 50 mg	✓	-
ACHIEVE I and II ¹⁶	Placebo	Ubrogepant 50 mg	-	✓
NCT03872453 ¹⁷	Placebo	Zavegepant 10 mg	✓	✓
NCT04571060 ¹⁸	Placebo	Zavegepant 10 mg	✓	✓



Limitations

- Limitations inherent to fixed-effects Bayesian NMA methods must be considered, including the assumption of homogeneous effect sizes

Results

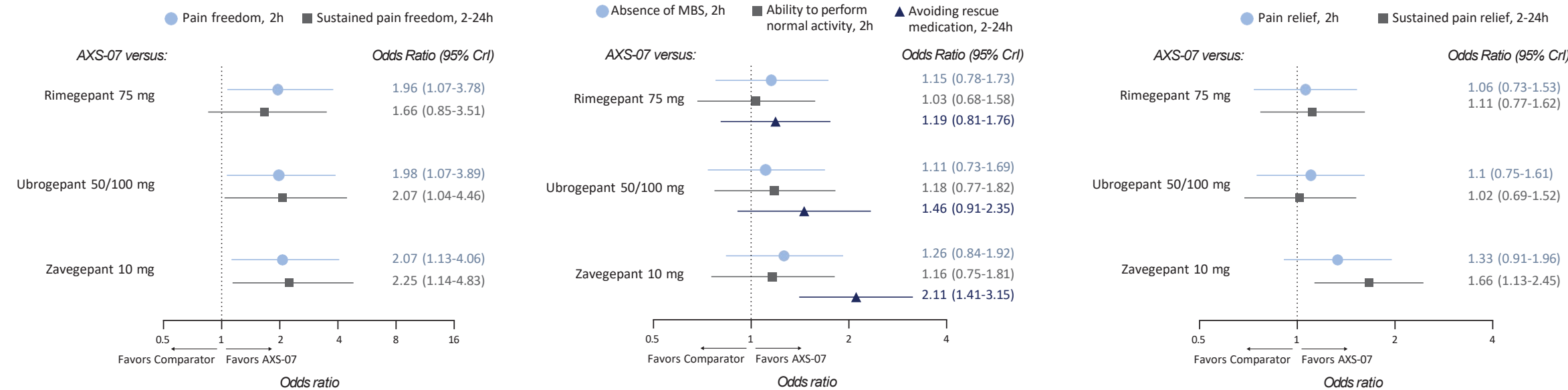
AXS-07 Versus Comparator Gepants

- Compared with rimegepant, ubrogepant, and zavegepant, participants treated with AXS-07 were more likely to experience:

- Pain freedom at 2h
- Sustained pain freedom 2h-24h

- Absence of MBS at 2h
- Ability to perform normal activity at 2h
- Avoidance of rescue medications 2h-24h

- Pain relief at 2h
- Sustained pain relief 2h-24h



CrI = credible interval; MBS = most bothersome symptoms.

Probability of Being the Most Efficacious Treatment

Endpoint	AXS-07			Rimegepant 75 mg			Ubrogepant 50/100 mg			Zavegepant 10 mg		
	Rank	Probability most efficacious	SUCRA	Rank	Probability most efficacious	SUCRA	Rank	Probability most efficacious	SUCRA	Rank	Probability most efficacious	SUCRA
Pain relief at 2h	1	0.565	0.810	2	0.268	0.748	3	0.164	0.654	4	0.003	0.288
Pain relief from 2-24h	1	0.502	0.811	3	0.093	0.631	2	0.406	0.807	4	0.000	0.251
Pain freedom at 2h	1	0.976	0.991	3	0.009	0.550	2	0.011	0.524	4	0.005	0.436
Pain freedom from 2-24h	1	0.927	0.976	2	0.064	0.724	3	0.007	0.451	4	0.002	0.349
Absence of MBS at 2h	1	0.632	0.827	3	0.106	0.595	2	0.235	0.696	4	0.027	0.382
Ability to perform normal activity at 2h ^a	1 ^a	0.525	0.769	1 ^a	0.358	0.783	4	0.046	0.456	3	0.071	0.491
Rescue medication use from 2-24h	1	0.80	0.940	2	0.17	0.764	3	0.03	0.540	4	0.00	0.251

Note: Treatment rankings were determined using SUCRA calculations, a common method employed in NMAs for calculating the probability of a treatment being the most efficacious, where the area under the cumulative ranking curve for each treatment represents its likelihood of being ranked highest.
^aAXS-07 had the highest probability of being the most efficacious treatment, whereas rimegepant had the greatest SUCRA value. SUCRA reflects how consistently a treatment performs across all possible ranks (1st, 2nd, 3rd, etc.), whereas the probability of most efficacious treatment only considers the times when the treatment is ranked first.

- For each endpoint assessed, AXS-07 had the greatest probability of being the most efficacious treatment compared with gepants

Safety and Tolerability Per Label

Adverse event	AXS-07 ¹⁰ (N = 581)	Rimegepant 75 mg ¹³ (N = 632)	Ubrogepant 50/100 mg ^{16,a} (N = 1439)	Zavegepant 10 mg ¹⁸ (N = 1023)
Dizziness	2%	-	-	-
Somnolence	2%	-	3%	-
Nausea	-	2%	3%	4%
Vomiting	-	-	-	2%
Dry mouth	-	-	1%	-
Taste disorders	-	-	-	18%
Nasal discomfort	-	-	-	3%

Note: Adverse event incidence is based on each drug's respective prescribing information. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. If the incidence is listed as <1%, then the model assumes 0%. For adverse event incidence not listed in the prescribing information, a "—" is listed. No drug prescribing information included malaise/fatigue, paresthesia, asthenia, diarrhea, dyspepsia, chest discomfort/chest pain, neck/throat/jaw pain, stiffness, rhinitis, application site reaction, other pain, pressure/tightness/heaviness, warm/cold sensations, muscle weakness, or vertigo.

^aAdverse events for ubrogepant were calculated assuming a 50/50 distribution between doses.

- AXS-07, rimegepant, ubrogepant, and zavegepant each have demonstrated favorable safety profiles, with varying treatment-emergent adverse events

Conclusions

- The NMA favors AXS-07 over the comparator gepants—rimegepant, ubrogepant, and zavegepant—in terms of its impact on the symptoms of migraine
- This analysis finds AXS-07 to be significantly more effective than gepants in achieving pain freedom 2h after administration, as well as sustained pain freedom from 2-24h
- AXS-07 offers a promising therapeutic alternative for patients with inadequate response to prior treatments