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Comparative Efficacy of Symbravo® Versus Gepants for Acute Treatment of Migraine: A Network Meta-Analysis

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Key Objective

To compare the efficacy of Symbravo® (formerly AXS-07; 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 treatment[1]
  - 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 Symbravo
  - Symbravo, consisting of 20 mg MoSEIC™ (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 adults[9]

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 Symbravo 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 Symbravo 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 Symbravo was likely to be better than gepants for relieving pain and other migraine symptoms

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Disclosures

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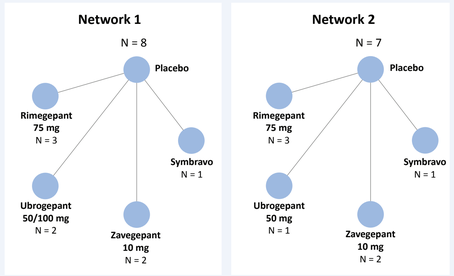
Methods

- A fixed-effects Bayesian NMA was conducted for Symbravo versus gepants (rimegepant, 75 mg; ubrogepant, 50 mg and 100 mg; zavegepant, 10 mg)
  - MOMENTUM for Symbravo[10] and 7 placebo-controlled phase 3 trials of the comparator gepants[11-18] were included
    - The objective of MOMENTUM was to evaluate the efficacy and safety of Symbravo 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

Trial		Treatments	Network 1	Network 2
MOMENTUM (NCT0389600)[10]	Placebo	Symbravo	✓	✓
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	✓	✓



Notes: Network 1 endpoints: Pain relief at 2h and sustained pain relief from 2-24h, pain freedom at 2h and sustained pain freedom from 2-24h, absence of MBS at 2h, and ability to perform normal activity at 2h.

Network 2 endpoint: Use of rescue medication from 2-24h.

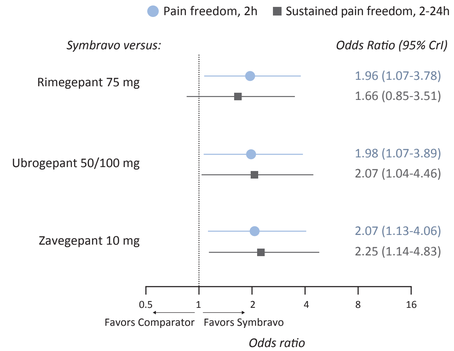
Limitations

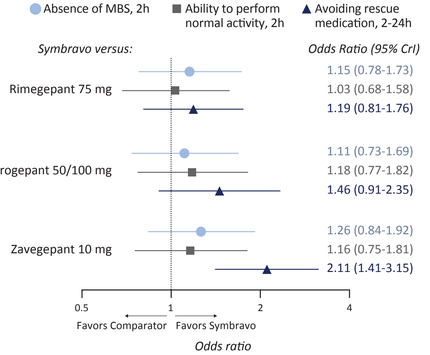
- Limitations inherent to fixed-effects Bayesian NMA methods must be considered, including the assumption of homogeneous effect sizes

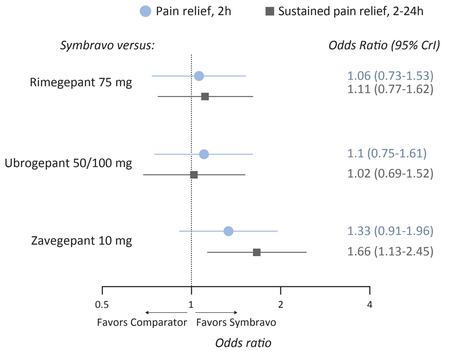
Results

Symbravo Versus Comparator Gepants

- **Compared with rimegepant, ubrogepant, and zavegepant, participants treated with Symbravo were <u>more likely to experience:</u>**
  - 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 freedom 2h-24h







CrI = credible interval; MBS = most bothersome symptoms.

Probability of Being the Most Efficacious Treatment

Endpoint	Symbravo Rank	Symbravo Probability most efficacious	Symbravo SUCRA	Rimegepant 75 mg Rank	Rimegepant 75 mg Probability most efficacious	Rimegepant 75 mg SUCRA	Ubrogepant 50/100 mg Rank	Ubrogepant 50/100 mg Probability most efficacious	Ubrogepant 50/100 mg SUCRA	Zavegepant 10 mg Rank	Zavegepant 10 mg Probability most efficacious	Zavegepant 10 mg 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.

[a] Symbravo 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, Symbravo had the greatest probability of being the most efficacious treatment compared with gepants

Safety and Tolerability Per Label

Adverse event	Symbravo[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.

[a] Adverse events for ubrogepant were calculated assuming a 50/50 distribution between doses.

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

Conclusions

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