

# Sex/Gender Equity Considerations in Clinical Trials of Gepants for Migraine: A Systematic Review

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## INTRODUCTION



- Migraine, a common disabling neurovascular disorder, ranks second among the world's causes of disability, and first among young women.
- Compared to men, migraine is more severe in women: longer headaches, more migraine symptoms, more migraine-related disability, greater worsening with age, and greater burden of complications.
- Migraine attacks and changes in headaches are associated to hormonal contraception, pregnancy, and menopause in 70% of affected women (Faubion 2018).
- Compared to non-menstrual attacks, menstrual migraine attacks are more severe, longer-lasting, and less responsive to treatment, resulting in a significant reduction of the quality of life for women (Wang 2023; van Casteren 2021).
- Newer treatments target the calcitonin gene-related peptide (CGRP) pathway which interacts with sex hormone processes such as ovarian hormone fluctuations (Labastida-Ramírez 2019).
- Novel migraine treatments need to incorporate sex/gender considerations to improve the quality of life of people with migraine particularly women.

## OBJECTIVE

To evaluate sex/gender equity considerations in published trials of second-generation CGRP antagonists (gepants) for migraine.

## METHODS

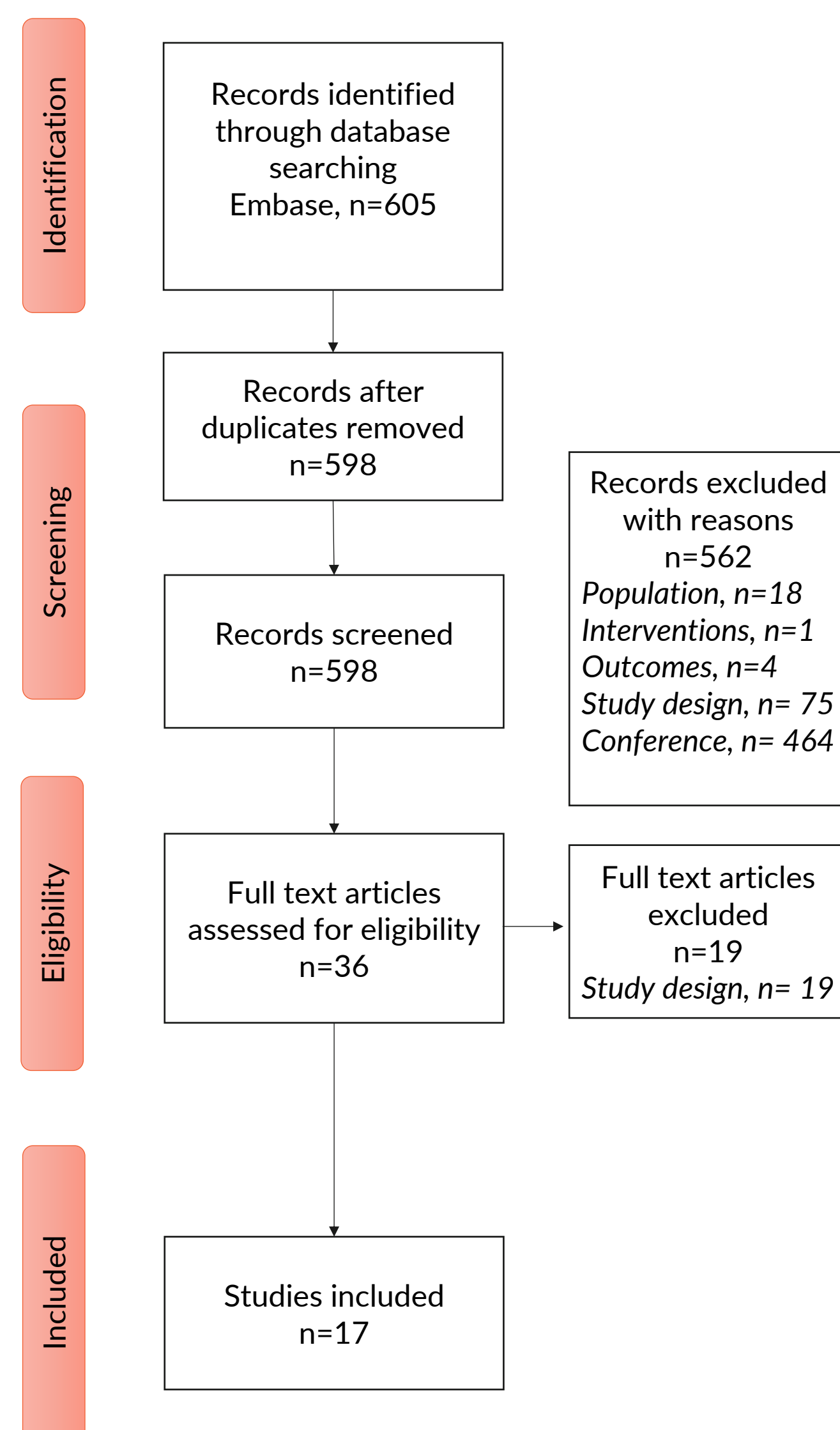
- Systematic review of primary trial publications reporting efficacy/safety of gepants for migraine.
- Data source: EMBASE (searched on 03 May 2024).

### Eligibility criteria

Patients	Adults (>18 years) with episodic or chronic migraine
Interventions	Gepants <ul style="list-style-type: none"> <li>Atogepant</li> <li>Rimegepant</li> <li>Ubrogepant</li> <li>Zavegepant</li> </ul>
Outcomes	<ul style="list-style-type: none"> <li>Recruitment: proportion of women participants</li> <li>Sex of the first author</li> <li>Sample size</li> <li>Eligibility: inclusion/exclusion of pregnancy, contraception</li> <li>Data analysis: disaggregation of primary/secondary outcomes by sex, effect of hormone replacement therapy (HRT) and menstrual cycle</li> <li>Discussion of sex/gender implications</li> </ul>
Study design	Randomised controlled trials (randomized phase only [phase II and III])*
Date	No restrictions

\*Post hoc analyses were considered secondary sources of information and were examined separately if the main variable or other variables not included in primary publication were analysed from a gender perspective

### Study selection flowchart



## RESULTS

- We identified 17 unique trials:
  - rimegepant (6 RCTs),
  - atogepant (5 RCTs),
  - ubrogepant (4 RCTs),
  - zavegepant (2 RCTs).
- Sample sizes ranged from 313 to 1,727 patients.
- Trials were published from 2014 to 2024.
- Mean ages ranged from 36 to 43 years.
- 14/17 trials were in USA samples only.

## REFERENCES

Ailani 2021. N Engl J Med. 10.1056/NEJMoa2035908.  
Ashina 2023. Headache. 10.1111/head.14691.  
Croop 2019. Lancet. 10.1016/S0140-6736(19)31606-X.  
Croop 2021. Lancet. 10.1016/S0140-6736(20)32544-7.  
Croop 2022. Headache. 10.1111/head.14389.  
Dodick 2023. Lancet. 10.1016/S0140-6736(23)01683-5.

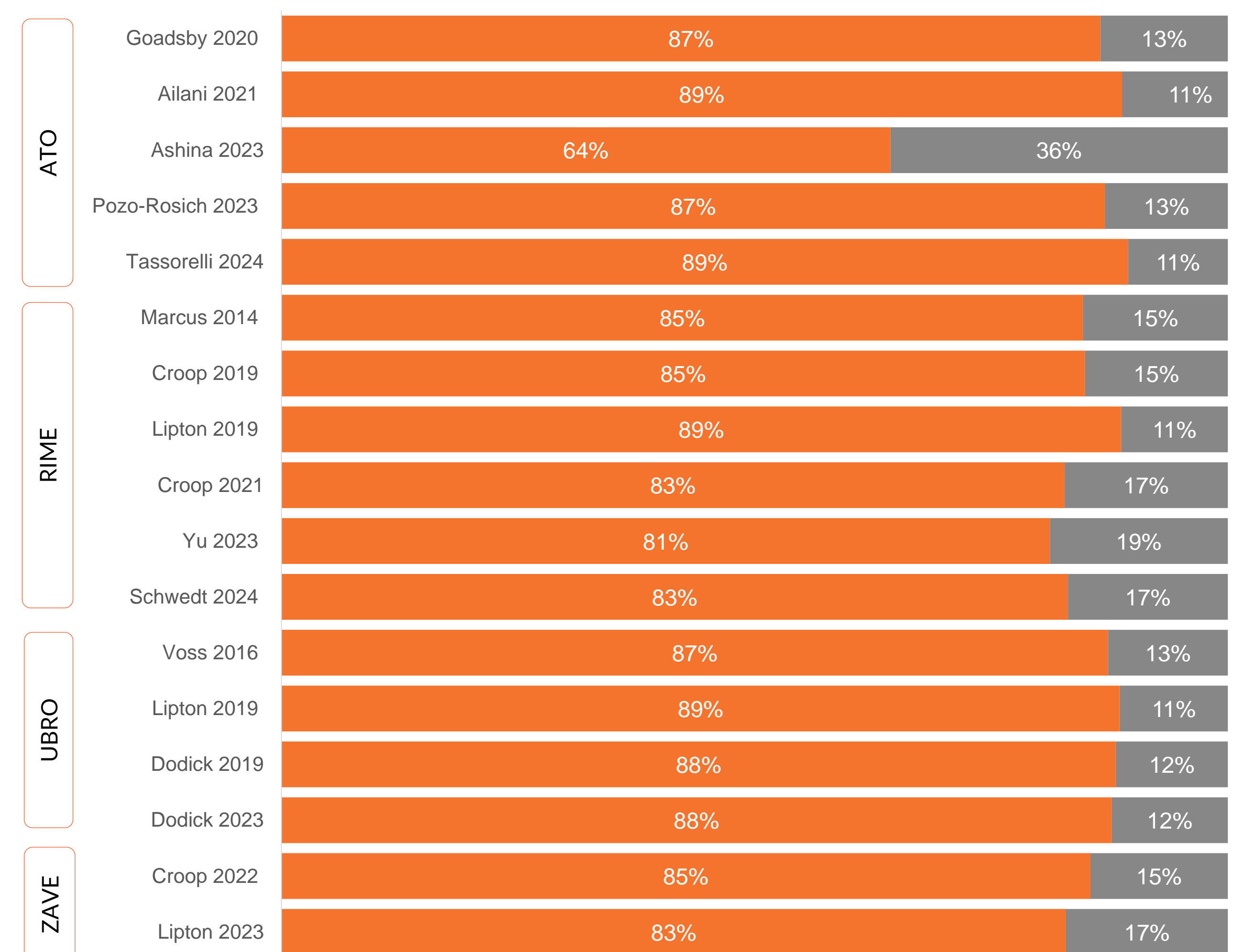
Dodick 2019. N Engl J Med. 10.1056/NEJMoa1813049.  
Faubion 2018. Mayo Clin Proc. 10.1016/j.mayocp.2017.11.027.  
Goatsby 2020. Lancet Neurol. 10.1016/S1474-4422(20)30234-9.  
Labastida-Ramírez 2019. Cephalalgia. 10.1177/0333102417739584.  
Lipton 2023. Lancet Neurol. 10.1016/S1474-4422(22)00517-8.  
Lipton 2019. N Engl J Med. 10.1056/NEJMoa1811090.

Lipton 2019. JAMA. 10.1001/jama.2019.16711.  
Marcus 2014. Cephalalgia. 10.1177/0333102413500727.  
Pozo-Rosich 2023. Lancet. 10.1016/S0140-6736(23)02236-5.  
Schwedt 2024. Neurol Ther. 10.1007/s40120-023-00562-w.  
Steiner 2020. J Headache Pain. 10.1186/s10194-020-01208-0.  
Tassorelli 2024. Lancet Neurol. 10.1016/S1474-4422(24)00025-5.

van Casteren 2021. Neurology. 10.1212/WNL.00000000000012723.  
Vetvik 2017. Lancet Neurol. 10.1016/S1474-4422(16)30293-9.  
Voss 2016. Cephalalgia. 10.1177/0333102416653233.  
Wang 2023. J Neurol. 10.1007/s00415-022-11477-1.  
Yu 2023. Lancet Neurol. 10.1016/S1474-4422(23)00126-6.



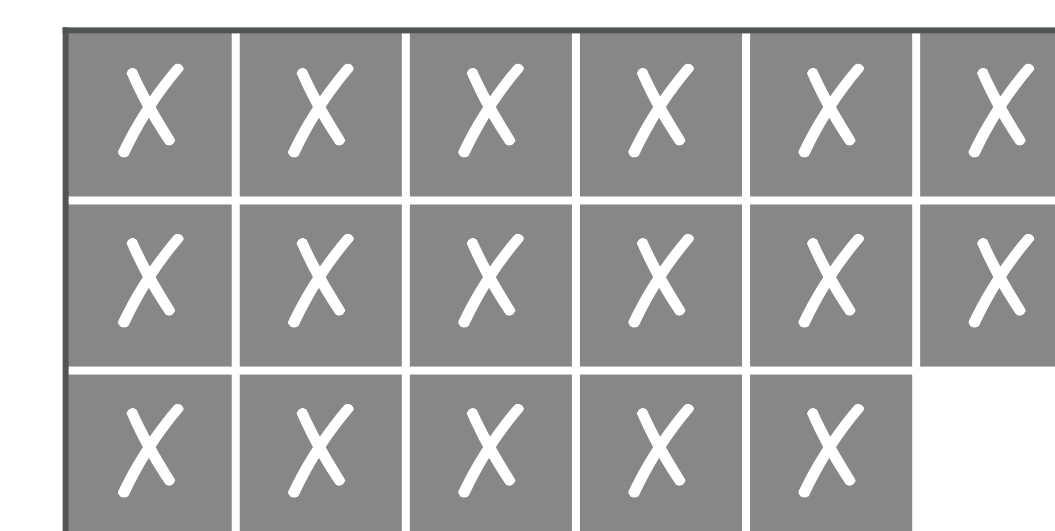
### Sex distribution across gepants clinical trials



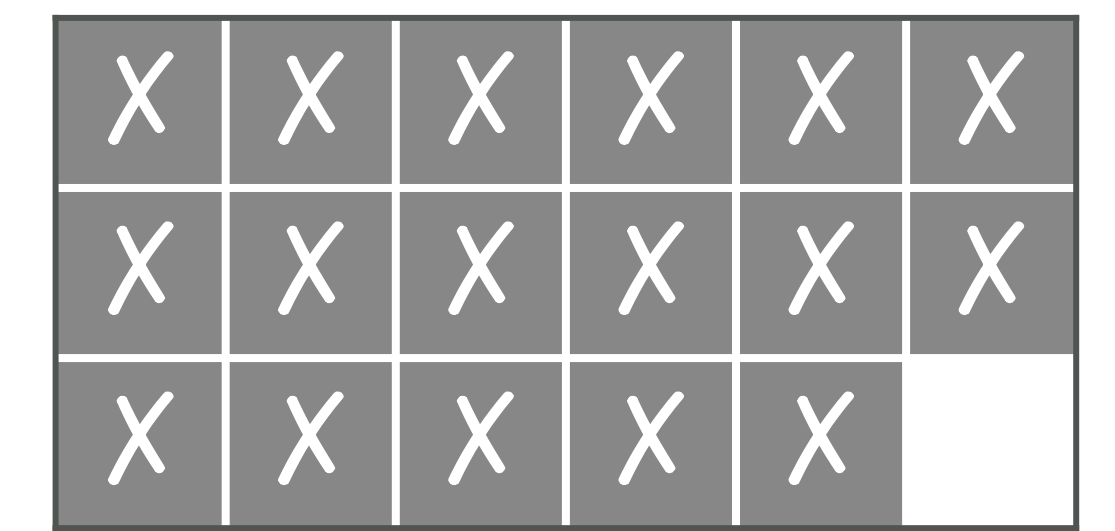
- 16/17 trials recruited >80% women participants, reflecting migraine's sex distribution.

### Sex/gender equity considerations in clinical trial design and analysis of gepants

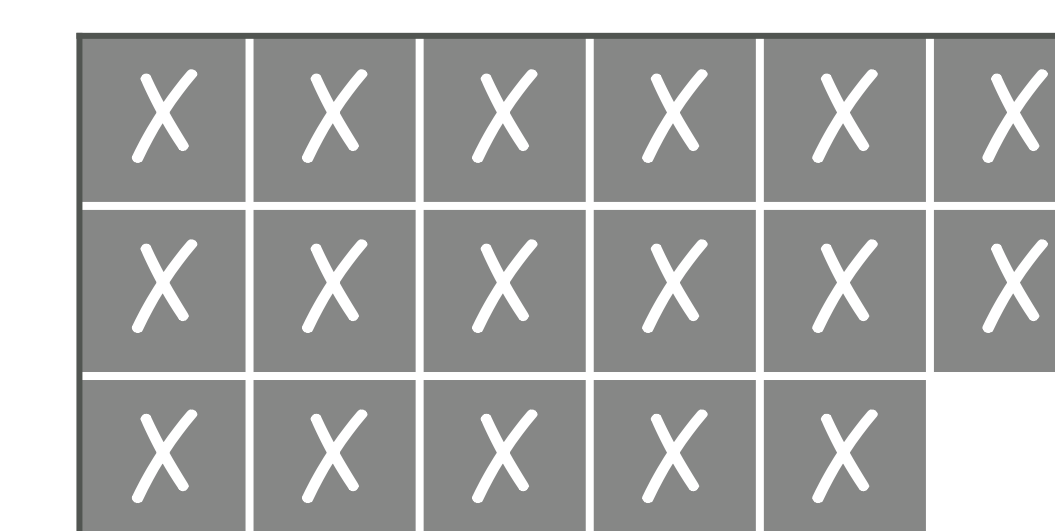
#### Disaggregated primary outcomes by sex



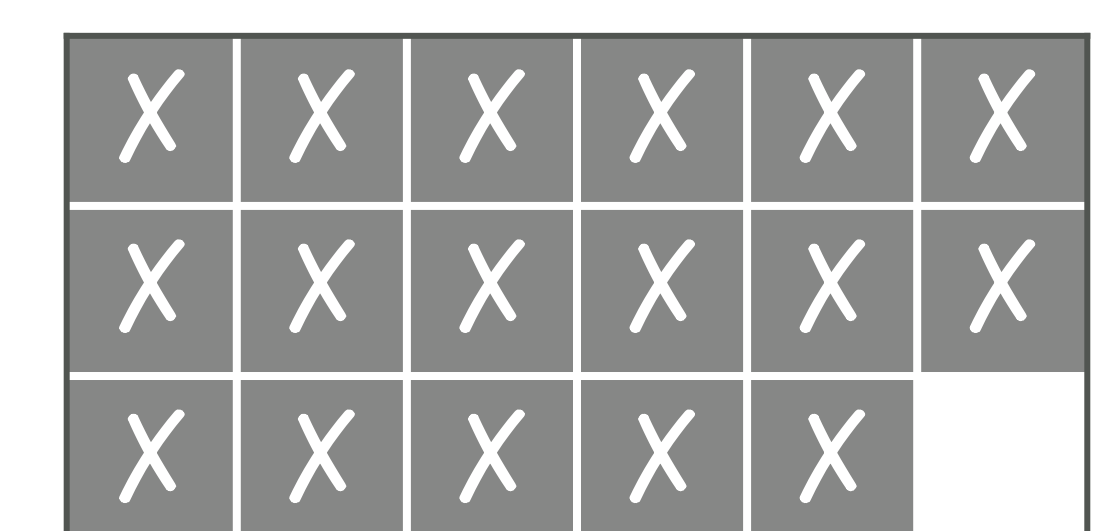
#### Disaggregated secondary outcomes by sex



#### Considered DDI with HRT or contraceptives



#### Considered impact of menstrual cycle



DDI: Drug-drug interaction, HRT: Hormone replacement therapy

- 13/17 trials explicitly specified pregnancy as an exclusion criterion, therefore less is known about the impact of gepants for this underrepresented subgroup of women.
- 6/17 trials mandated the use of contraception, however, none considered DDI with contraceptives.
- 14/17 trials did not consider the potential implications of gepants treatment on fertility intentions.
- Only 1 post-hoc study reported safety profile by sex.

## CONCLUSION

- Despite the well-established gendered nature of migraine and high proportions of women recruited, gepants trials for migraine often failed to incorporate sex/gender health equity considerations in study design, conduct, analysis, and reporting.
- This oversight may affect the health technology assessment process leading to potential biases and further inequities in health care recommendations and policies.
- Future studies should take a priori consideration of relevant aspects of sex/gender to improve quality of life of migraine patients especially women.