The Efficacy of Dihydroergotamine Versus Emerging Acute Migraine Medications

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Objectives

Rapid and consistent freedom from pain and associated symptoms without recurrence is defined as a main goal for the acute treatment of migraine per the AHS Consensus Statement (2018). The objective of this study was to evaluate how well several novel acute migraine treatment options match this goal.

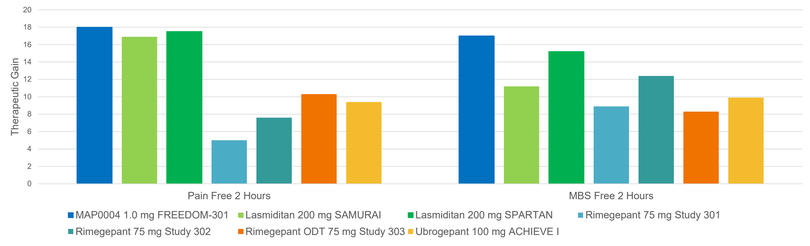
Methods

Efficacy data from Phase 3 studies with orally inhaled dihydroergotamine (DHE, MAP0004), lasmiditan 200 mg, rimegepant 75 mg, rimegepant ODT 75 mg and ubrogepant 100 mg were compared. Freedom from pain, photophobia, phonophobia, and nausea at 2 hours and sustained pain freedom from 2-24 hours were evaluated. The therapeutic gain (TG), defined as the difference in the proportion of responders between active medication and placebo, was used for the analysis of each endpoint. The data presented is the largest TG data for each endpoint achieved with each of the analyzed drugs. While the data is not from head-to-head clinical studies, the similarity in study designs, subject demographics, and statistical analyses allow for cross-trial comparisons. The MAP0004 MBS at 2 hours data was modelled on rimegepant and lasmiditan data using freedom from individual symptoms at 2 hours regardless of baseline status and frequency distribution of photophobia, phonophobia, and nausea.

Results

- **Oral pulmonary DHE and lasmiditan showed similar pain freedom at 2 hours while the gepants showed lower efficacy (Figure 1).**
  - ✓ Therapeutic gain for pain freedom at 2 hours was similar for MAP0004 and lasmiditan 200 mg (18% versus 17.5%) while rimegepant and ubrogepant were lower (range: 5-10.3%).
  - ✓ MAP0004 had the highest MBS freedom at 2 hours (17%) compared to lasmiditan (range: 11.2-15.2%), rimegepant (range: 8.3-12.4%), and ubrogepant (9.9%).

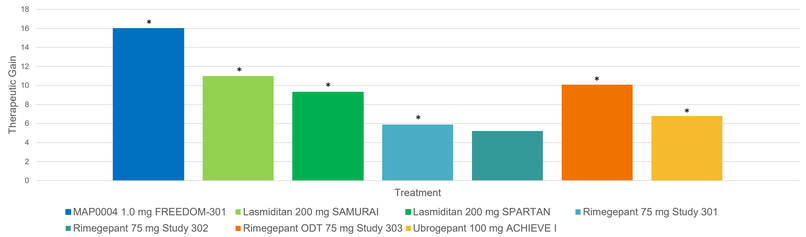
Figure 1. Therapeutic gain for pain and most bothersome symptom freedom at 2 hours



All data were statistically significant versus placebo.
The MAP0004 MBS value is modelled based on individual symptom data as MBS was not originally calculated.

- **Oral pulmonary DHE showed the highest therapeutic gain for sustained pain freedom from 2-24 hours (Figure 2)**
  - ✓ MAP0004 achieved the largest therapeutic gain for sustained pain freedom from 2-24 hours while the efficacy of the emerging treatments was similar (16% versus 5.2-11%).

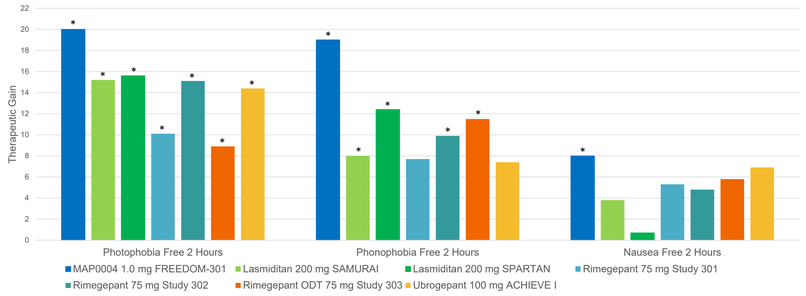
Figure 2. Therapeutic gain for sustained pain freedom from 2-24 hours



* = Statistically significant versus placebo.

- **Oral pulmonary DHE showed the largest freedom from photophobia and phonophobia and the only statistically significant effect for freedom from nausea (Figure 3)**
  - ✓ MAP0004 showed the largest therapeutic gain for freedom from photophobia (20% versus 8.9-15.6%) and freedom from phonophobia (19% versus 7.4-12.4%).
  - ✓ MAP0004 showed the only statistically significant effect for freedom from nausea among all products (8% versus 5.2-11%).

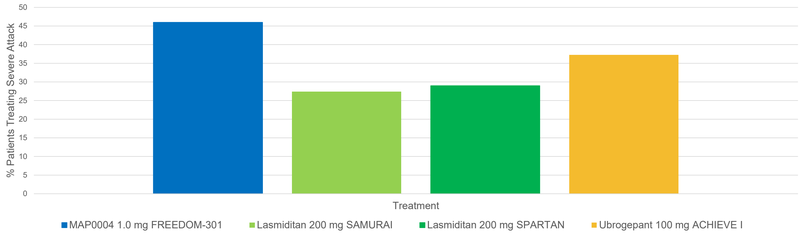
Figure 3. Therapeutic gain for freedom from photophobia, phonophobia, and nausea at 2 hours



* = Statistically significant versus placebo.

- **Oral pulmonary DHE outperformed the emerging treatments despite having higher % patients treating a severe attack and longer treatment window (Figure 4).**
  - ✓ The MAP0004 Phase 3 study showed a higher percentage of patients treating a severe attack than the emerging treatments (45-47% versus 26.2-37.1%).
  - ✓ The MAP0004 Phase 3 study allowed patients to treat a migraine more than 8 hours after onset while the emerging treatments were 4 hours or less.

Figure 4. % patients treating severe attack and treatment window from attack onset to treatment



Treatment	Window from Attack Onset to Treatment
MAP0004 1.0 mg FREEDOM-301	Allowed to treat more than 8 hours after onset (70% treated within 4 hours)
Lasmiditan 200 mg SAMURAI	Allowed to treat up to 4 hours after onset (1.1 hours mean)
Lasmiditan 200 mg SPARTAN	Allowed to treat up to 4 hours after onset (1.2 hours mean)
Ubrogepant 100 mg ACHIEVE I	Taken at time of qualifying migraine

Conclusions

- Orally inhaled DHE demonstrated superior anti-migraine efficacy compared to emerging treatments.
- DHE use has been limited by route of administration and/or performance of approved dosage forms.
- Newer investigational products, such as STS101 (intranasal DHE powder), that demonstrate C_{max} and drug exposure comparable to or greater than MAP0004, may overcome these limitations.
- A double-blind, randomized, placebo-controlled Phase 3 efficacy study with STS101 (EMERGE™) is ongoing to evaluate the product as an acute treatment for migraine (NCT 03901482).

References

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