Effect of Ubrogepant vs Placebo on Pain and the Most Bothersome Associated Symptom in the Acute Treatment of Migraine

BACKGROUND:

- Approximately one billion people are burdened by migraines worldwide. Migraines can negatively impact all aspects of life due to long lasting, debilitating symptoms (photophobia, phonophobia, nausea).
- While there are treatment options currently available some patients experience side effects, do not experience adequate relief. or have medical conditions (cardiovascular and gastrointestinal) that contraindicate their use.

OBJECTIVE:

- To compare efficacy and tolerability of ubrogepant and placebo for the treatment of acute migraine attacks.

METHODS

- **Design**: multisite, randomized, double-blind, placebo-controlled trial
- **Duration:** single attack (extended follow up)
- **Inclusion criteria:** 18-75 yo, history of migraine for at least 1 year consistent with ICHD-3-beta diagnosis criteria, experienced 2-8 migraine attacks w/ moderate to severe headache pain per month of the 3 months before screening, migraine onset before 50yo, history migraine lasting 4-72 hours if untreated/ unsuccessfully treated, episodes separated by at least 48 hours.
- **Exclusion criteria:** difficulty distinguishing migraine from tension-type or other type headache, diagnosis of chronic migraines by ICHD-3-beta, using treatment for migraines on 10 or more days a month for the previous 3 months, clinically significant hematologic, endocrine, cardiovascular, cerebrovascular, pulmonary, renal, hepatic, gastrointestinal, or neurologic disease; and a history of 15 or more headache days per month on average in the previous 6 months.
- 1686 participants were randomized (562 in 50mg group, 561 in 25mg group, 563 in placebo group) to receive a dose either 50mg ubrogepant, 25mg ubrogepant, or placebo within four hours of qualifying migraine onset (moderate to severe pain and at least one of the three symptoms (photophobia, phonophobia, nausea), had not taken any prohibited medication, had a new migraine, migraine was not already resolving.) An optional second dose could be taken 2-48 hours after the initial dose (treatments groups were randomized to receive a second dose of either ubrogepant or placebo, those is placebo group received a second dose of placebo.)
- **Primary measures:** pain freedom 2 hours after dose, and absence of most bothersome migraine-associated side effect (photophobia, phonophobia, nausea 2 hours after dose.
- **Secondary measures:** pain relief at 2 hours, sustained pain relief 2-24 hours, sustained pain freedom 2-24 hours, absence of each migraine-associated symptom (photophobia, phonophobia, nausea). Functional Disability Scale: ability to function normally, tolerability/safety.
- 85% power to detect a difference between ubrogepant doses (assuming equal effectiveness) and placebo for primary outcomes, and 60% power to detect differences in treatments for secondary outcome measures. Powers are calculated with a sample size of 550 participants per group.
- Data handling was modified intent to treat.

RESULTS

- 1465 received treatment. 488 in 50mg group, 478 in 25mg group, and 499 in placebo group.
- **Primary outcome measures:** percentage of pain freedom at two hours was significantly higher in both the 50mg (21.8%) and 25 mg groups (20.7%) compared to placebo (14.3%). Absolute difference between 50mg and placebo 7.5%, and between 25mg and placebo 6.4%. Percentage reported of absence of most bothersome symptom was significantly greater for the 50mg group (38.9%, absolute difference= 11.5%) compared to placebo (27.4%), but not the 25mg group (34.1%, absolute difference= 6.7%).
- **Secondary outcome measures:** pain relief achieved at 2 hours was 62.7% for the 50mg group, 60.5% for the 25mg group, and 48.2% for the placebo group. Pain relief achieved 2-24 hours was 36.7% for the 50mg group, 32.5% for the 25mg group, 21% for the placebo group. Sustained pain relief 2-24 hours 14.4% for 50mg group, 12.7% for the 25mg group, 8.2% for the placebo group. Absence of photophobia at 2 hours was 43.8% for the 50mg group, 39.3% for the 25mg group, and 35.5% for placebo. Absence of phonophobia at 2 hours was 54.1% for the 50mg group, 53.6% for the 25mg group, 46.3% for placebo. Absence of nausea at 2 hours was 71.3% for the 50mg group, 70.6% for 25mg group, 70% for placebo group.
- **Author's conclusion:** 50mg ubrogepant had significantly higher percentages for both pain freedom and absence of most bothersome symptom 2 hours after dose, while 25mg was only significant for pain freedom.

STRENGTHS

- Randomization being stratified based on response to triptans
- All medications were placed in the same blister packing, reducing the risk of unblinding.

LIMITATIONS

- Short study duration (only look at a single attack)
- Exclusion of people with cardiovascular and gastrointestinal contraindications to triptans and NSAIDs from the study
- Target sample sizes were to meet to reach calculated power to detect differences in treatment groups and placebo

CONCLUSIONS

- Ubrogepant 50mg has potential as a treatment option to for acute treatment of migraines, but due to the extensive inclusion/exclusion criteria it is difficult to extrapolate the results onto the rest of the migraine population.
- Ubrogepant may be a good option for patients who have contraindications to current treatment option, but high costs of the medication may limit its use.
- More randomized controlled trials, comparing ubrogepant to placebo and current treatments (triptans), are needed to determine the efficacy of ubrogepant and its place in practice.

Reference: Lipton RB, Dodick DW, Ailani J, et al. Effect of Ubrogepant vs Placebo on Pain and the Most Bothersome Associated Symptom in the Acute Treatment of Migraine: The ACHIEVE II Randomized Clinical Trial. *JAMA.* 2019;322(19):1887–1898. doi:10.1001/jama.2019.16711

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