Pain Freedom With Celecoxib Oral Solution, Ubrogepant, and Rimegepant Through 4 Hours Postdose: Post Hoc Analysis in the Acute Treatment of Migraine

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Background

Celecoxib oral solution utilizes an innovative, engineered, patented microemulsion formulation

- Celecoxib oral solution (Elyxyb) is a liquid formulation of the cyclooxygenase-2-selective nonsteroidal anti-inflammatory drug indicated for the acute treatment of migraine
- The liquid formulation leads to short T_{max} of 42 minutes[1]
- The Self-Micro-Emulsifying Drug Delivery System (SMEDDS) increases solubility, dissolution rate, and bioavailability by:
  - Overcoming the hydrophobic property of celecoxib [2]
  - Forming a nanometer-sized microemulsion for enhanced bioavailability[3]
  - Increasing intestinal wall permeability[2]
  - May overcome GI stasis associated with migraine[4]
- In two Phase 3 multicenter, randomized, double-blind, placebo-controlled, clinical trials, a single dose of celecoxib 120 mg oral solution was shown to be effective in the acute treatment of migraine, as measured by the coprimary efficacy endpoints of freedom from pain and the most bothersome symptom at 2 hours postdose (Figure 1)[5,6]

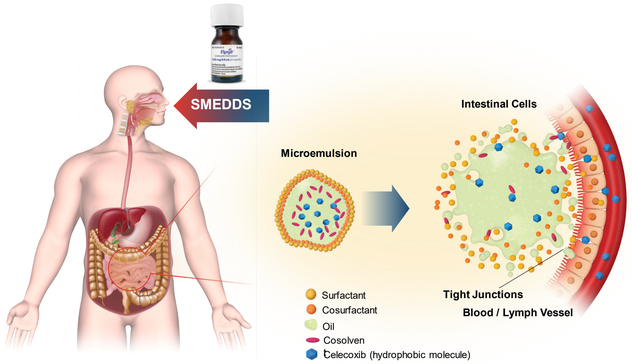
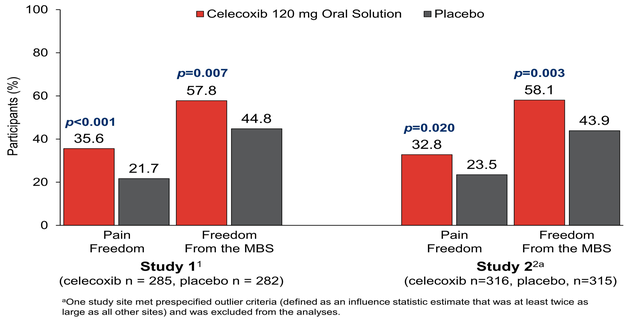


Figure 1. Pain Freedom and Freedom From the Most Bothersome Symptom at 2 Hours Postdose: Celecoxib Oral Solution Versus Placebo



[a]One study site met prespecified outlier criteria (defined as an influence statistic estimate that was at least twice as large as all other sites) and was excluded from the analyses.

Objective

- Use pooled data from 2 independent, randomized, double -blind, placebo-controlled, multicenter, 2-attack phase 3 trials of celecoxib 120 mg oral solution to compare the therapeutic gain (TG), number needed to treat (NNT), number needed to harm (NNH), and likelihood of being harmed or helped (LHH) for celecoxib 120 mg oral solution, ubrogepant 100 mg,[7] and rimegepant 75 mg[8] in the acute treatment of migraine pain over the first 4 hours postdose

Methods

- Proportions of participants who received active treatment or placebo and who reported pain freedom were computed at 15, 30, 45, 60, 90, 120, and 240 minutes postdose
- Outcomes compared based on placebo-subtracted data available
- Participants taking rescue medication after 120 minutes postdose were censored; even if achieving pain freedom at 240 minutes, their pain-free status was designated a failure
- One site was removed from analysis of Study 1 because it was an influential outlier (value 2x all other sites), as evaluated by the DFBETAs influence statistics

Data sources

- Celecoxib 120 mg oral solution:
  - Pooled Study 1 and Study 2
  - First double-blind period
- Ubrogepant 100 mg: ACHIEVE I[1]
- Rimegepant 75 mg: 302 Trial[2]
- Pain Free & TG Endpoint Times
  - Computed at 15, 30, 45, 60, 90, 120, and 240 minutes postdose
  - Celecoxib & rimegepant censored at 3 and 4 hours postdose for rescue medication; ubrogepant not censored (data not reported)
- NNT, NNH, LHH Endpoint Times:
  - 120 minutes postdose

Placebo-subtracted analysis[9,10]

- Therapeutic Gain (TG) = Active response – placebo response
- Number Needed to Treat (NNT) = 1/Therapeutic Gain
- Therapeutic Harm (TH) = Active Adverse Events (AEs) – placebo AEs
- Number Needed to Harm (NNH): Therapeutic Harm (TH within 48 hours postdose): Active any AE – Placebo any AE
- NNH: 1 / TH
- Likelihood of being harmed or helped (LLH) = NNH/NNT
  - For NNT, lower values = better efficacy
  - For NNH, higher values = better safety and tolerability
  - For LLH, higher values = good efficacy with few AEs

Results

Participants

- In the population analyzed for efficacy (N=1695), 601 participants were treated with celecoxib 120 mg oral solution, 557 with ubrogepant 100 mg, and 537 with rimegepant 75 mg
- The demographics and baseline characteristics of the celecoxib, ubrogepant, and rimegepant trial populations were comparable, with most participants (>75%) self-identifying as female and white and having a mean BMI >25 kg/m^2

Efficacy

- At all postbaseline timepoints through 4 hours postdose, participants who were treated with celecoxib 120 mg oral solution we re more likely to report pain freedom than participants who received ubrogepant 100 mg or rimegepant 75 mg (Figure 2)
- When the treatments were compared using therapeutic gain (Figure 3), participants who received celecoxib 120 mg oral solution were more likely to be pain free than participants who received ubrogepant 100 mg or rimegepant 75 mg from 60 minutes postdose through 3 hours postdose
- Celecoxib oral solution provided a greater likelihood of being helped or and lower likelihood of being harmed than rimegepant or ubrogepant (Table 1)

Figure 2. Celecoxib Oral Solution, Ubrogepant, and Rimegepant for Pain Freedom Through 4 Hours Postdose

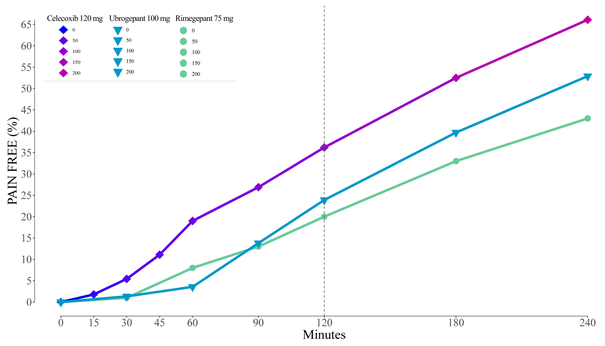


Figure 3. Celecoxib Oral Solution, Ubrogepant, and Rimegepant for Pain Freedom Through 4 Hours Postdose — Therapeutic Gain

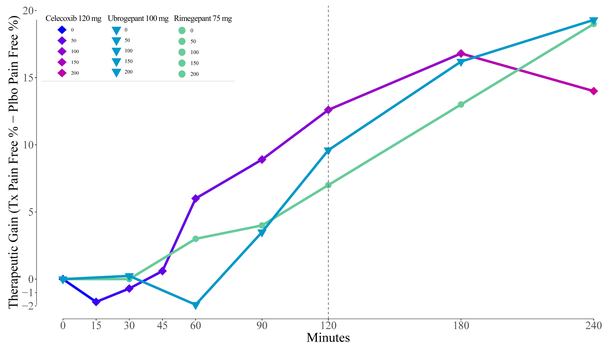


Table 1. NNT, NNH, LHH for Celecoxib Oral Solution, Ubrogepant, and Rimegepant Through 4 Hours Postdose

	NNT[c]	NNH[d]	LHH[e]
Celecoxib oral solution 120 mg[a]	8	38	4.75
Rimegepant 75 mg	14	34	2.43
Ubrogepant 100 mg[b]	10	29	2.90

NNT, number needed to treat; NNH, number needed to harm; LHH, likelihood of being helped or harmed.
[a]Estimated pooling Studies 1 and 2 and omitting one identified influential outlying site (609)
[b]Estimated pooling reported data from ACHIEVE I and II
[c]Estimated at 2 hours postdose
[d]Estimated from any adverse event reported within 48 hours of dosing
[e]Estimated as (1 / NNT) / (1 / NNH)

Conclusions

- **With celecoxib 120 mg oral solution:**
  - **Pain-free rates from 60 minutes through 3 hours postdose were higher than ubrogepant 100 mg and rimegepant 75 mg**
  - **NNT was lower, while NNH and LHH were higher, than with ubrogepant 100 mg and rimegepant 75 mg**
- **The design of SMEDDS liquid formulation of celecoxib oral solution (Elyxyb) may be linked to rapid onset due to its accelerated T_{max} = 42 minutes with good tolerability**
- **To achieve pain freedom with celecoxib oral solution, fewer patients may need to be treated, and may they have less likelihood of being harmed, than with ubrogepant 100 mg and rimegepant 75 mg**

Disclosures: SJT and DS have received honoraria for research support and/or consulting from Scilex Holding Company, manufacturer of celecoxib oral solution; EKC and DL are employed by Scilex Holding Company, manufacturer of celecoxib oral solution.

References: 1. *Clin Drug Investig*. 2017;37(10):937-946; 2. *Int Sch Res Notices*. 2014;2014:964051; 3. *Front Pharmacol*. 2019;10:459; 4. *Cephalalgia*. 2013;33(6):408-415; 5. *Headache*. 220;60:58-70; 6. *J Pain Res*. 2021;14:2529-2542; 7. *N Engl J Med*. 2019; 381:2230-2241; 8. *N Engl J Med*. 2019;381(2):142-149; 9. *Cephalalgia*. 2019;39:608-616; 10. *Cephalalgia*. 2021;41:851-864.