Detection and Adjustment for Participant Response Effects in a 2-Period, Randomized, Double-blind, Placebo-controlled Trial of Celecoxib Oral Solution for the Acute Treatment of Migraine

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Background

- Randomization is widely assumed to allow for unbiased estimates of treatment effects in clinical trials
- In multiple-attack migraine trials, even with re-randomization between attacks, the FDA requires registrational efficacy evidence be based exclusively on the first treated attack to avoid potential for "carryover effects," more appropriately referred to as "response tendencies"
- Therefore, multiple-attack migraine trials provide an opportunity to assess if/how response to the first treated attack influences response to the second treated attack even after re-randomization
- Multiple-attack migraine trials with re-randomization are ideal laboratories for testing statistical methods that overcome "response tendencies" that re-randomization cannot

Objective

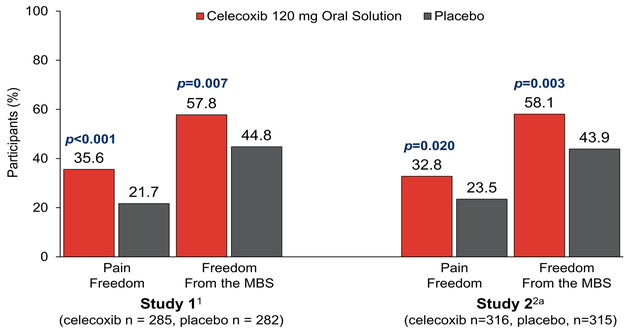
- Assess whether response tendencies influencing treatment response can be detected and, if detected, determine whether they can be adjusted for

Methods

Study Conduct

- This program consisted of two independent randomized, double-blind, placebo-controlled, multicenter, 2-attack phase 3 trials comparing celecoxib 120 mg oral solution (Elyxyb) — a liquid formulation of the cyclooxygenase-2-selective nonsteroidal anti-inflammatory drug indicated for the acute treatment of migraine — with placebo in the acute treatment of migraine[1,2]
- **Inclusion criteria:**
  - Adults aged 18-75 years (inclusive) with a 12-month history of episodic migraine and 2 to 8 migraine attacks per month and 14 or fewer headache days per month no medication overuse, and 48 hours of headache-free time between migraine attacks
- In both trials, a single dose of celecoxib 120 mg oral solution was shown to be more effective than placebo when treating the first attack (Figure 1)[1,2]
- **Design:**
  - As an alternative to a conventional cross-over trial, participants who remained eligible within 2 to 7 days of treating the first attack were re-randomized into a second double-blind period, during which they treated 1 migraine attack of any headache pain intensity (mild, moderate, or severe)
  - During the first double-blind period, participants used celecoxib oral solution 120 mg or placebo to treat a single migraine attack of moderate to severe headache pain intensity

Figure 1. Pain Freedom and Freedom From the Most Bothersome Symptom (MBS) at 2 Hours Postdose: Celecoxib 120 mg 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.

Post Hoc Analysis

- This analysis used data from the second of 2 phase 3 trials of celecoxib 120 mg oral solution versus placebo (NCT03009019)[2]
  - The coprimary efficacy endpoints were pain freedom and freedom from the most bothersome symptom (MBS) at 2 hours postdose
- Two logistic mixed-effects models were fit to the coprimary endpoints — one to detect whether response in the first double-blind period predicted response in the second double-blind period, and one attempting to adjust for the detected effect
  - **Detection:** outcome was 2nd double-blind period endpoints
    - Predictors:
      - Corresponding endpoint response from 1st double-blind period
      - Treatment (active vs placebo) in 1st double-blind period
      - Treatment (active vs placebo) in 2nd double-blind period
      - All 2-way interactions and the single 3-way interaction
      - Random effect for site
  - **Adjustment:** Outcome was treatment response in 1st and 2nd treatment periods analyzed as repeated measures within participant
    - Predictors:
      - Double-blind period (repeated measure)
      - Treatment (active vs placebo)
      - Double-blind period by treatment interaction
      - Random effect for both site and participant
- The percentage of the variance explained by participant response tendency was estimated by calculating the intraclass correlation coefficient (ICC) from the adjustment stage model

Results

- Of the 531 participants who completed the first treatment period, 491 (243 celecoxib oral solution, 248 placebo) were re-randomized into the second double-blind treatment period
- Among participants who achieved 2-hour pain freedom and 2-hour MBS freedom in the first double-blind treatment period, celecoxib oral solution was more effective than placebo for 2-hour pain freedom (70% vs 59%) and 2-hour MBS freedom (76% vs 69%) in the second double-blind treatment period
- Response in the first double-blind trial period was a significant predictor of response in the second double-blind trial period for pain freedom (odds ratio 6.71 [2.42, 18.56], p<0.001) and MBS freedom (odds ratio 4.95 [1.90, 12.89], p=0.001) at 2 hours postdose (Table 1)
- The ICC calculations indicated that 35% of the variance in 2-hour pain freedom response and 27% of the variance in 2-hour MBS freedom response for the second attack was explained by participant response tendency, thus confirming some carryover effect even with the re-randomization (Table 2)

Table 1. Detecting Participant Response Effects in the Second Double-Blind Treatment Period

	PAIN FREEDOM				FREEDOM FROM THE MBS			
Predictor	Estimated Odds Ratio	Lower	Upper	p-value	Estimated Odds Ratio	Lower	Upper	p-value
Main Effects								
2nd Treatment	2.20	1.09	4.41	**0.027***	1.80	0.71	4.56	0.217
1st Response	6.71	2.42	18.56	**<0.000***	4.95	1.90	12.89	**0.001***
1st Treatment	0.93	0.44	1.97	0.840	0.99	0.39	2.52	0.982
2-Way Interactions								
1st Treatment x 1st Response	0.77	0.20	2.97	0.707	1.11	0.27	4.55	0.880
1st Treatment x 2nd Treatment	1.01	0.36	2.79	0.990	0.92	0.23	3.73	0.910
1st Response x 2nd Treatment	1.26	0.29	5.59	0.758	0.91	0.23	3.65	0.891
3-Way Interactions								
1st Treatment x 1st Response x 2nd Treatment	0.48	0.07	3.22	0.454	1.01	0.14	7.32	0.995

Estimated random effects for site were converted to ICC values. The ICCs were 3.3% for pain freedom and 11.8% for freedom from the MBS. That is, site effects accounted for ~3.3% and ~11.8%, respectively, of the variance in the probability of achieving pain freedom and MBS freedom at 2 hours postdose. Bold, starred p-values indicate significant effects.

Table 2. Adjusting for Participant Response Effects in the Second Double-Blind Treatment Period

	PAIN FREEDOM				FREEDOM FROM THE MBS			
Predictor	Estimated Odds Ratio	Lower	Upper	p-value	Estimated Odds Ratio	Lower	Upper	p-value
Treatment	2.50	1.43	4.36	**0.001***	2.01	1.20	3.38	**0.008***
Double-blind period	1.83	1.08	3.11	**0.026***	1.36	0.83	2.24	0.221
Treatment x period interaction	1.03	0.49	2.17	0.935	0.89	0.43	1.87	0.765

ICCs estimated from the adjustment stage model indicated that participant response tendency explained 35% of the variance in response on 2-hour pain freedom and 27% of the response on 2-hour freedom from the MBS. Bold, starred p-values indicate significant effects.

Conclusions

- **In unadjusted models, participant response in the first double-blind trial period was a significant predictor of response in the second double-blind trial period, demonstrating the limitations of rerandomization**
- **In models adjusting for participant response tendencies using random effects, the effect of response tendency was not statistically significant and treatment with celecoxib 120 mg oral solution was restored as the significant driver of efficacy**
- **Randomization alone is insufficient in such complex disorders and trials, and additional methods are required to address these natural effects that occur in any clinical trial**
- **This finding has implications for the interpretation of multiple-attack studies where treatment status is not changed**

Disclosures: RBL and SJT have received honoraria for research support and/or consulting from Scilex Holding Company, which owns the rights to celecoxib oral solution; DL is employed by Scilex Holding Company. Pharmaceuticals.

References: 1. *Headache*. 2020;60:58-70; 2. *J Pain Res*. 2021;14:2529-2542.