ePoster #: 52

A close association of pain freedom with freedom from most bothersome symptom and from migraine-related functional disability in lasmiditan studies SAMURAI and SPARTAN

Li Shen Loo[1], Richard B Lipton[2], Stewart J Tepper (Presenter)[3], Raghavendra Vasudeva[1], Simin K Baygani[1], Eric M Pearlman[1], Paula M Hauck[1], John H Krege[1]

[1]Eli Lilly and Company, Indianapolis, IN, USA; [2]Department of Neurology, Albert Einstein College of Medicine, Bronx, NY, USA; [3]Geisel School of Medicine at Dartmouth, Hanover, NH, USA

OBJECTIVE

The objective of this investigation was to assess whether the outcomes of pain freedom or improvement to mild pain were associated with the outcomes of most bothersome symptom (MBS) freedom or functional disability freedom at 2 hours in pooled data from SAMURAI (NCT02439320) and SPARTAN (NCT02605174).

BACKGROUND

- Earlier trials on the acute treatment of migraine used pain relief at 2 hours as a primary efficacy outcome; pain freedom is now the primary measure of efficacy.[1-2]
- Freedom from pain at 2 hours after treatment is a clinically relevant endpoint and reflects patients' expectations.[2]

KEY RESULTS

Coexistence of Positive Outcome(s) With Pain Outcome at 2 Hours

Proportion with additional outcomes at 2 hours		Pain Freedom N=913	Improved to Mild Pain N=864	Continued Moderate/ Severe Pain N=1052
Number of outcomes	Outcome(s)			
1	MBS free, n (%)	839 (91.9)	388 (44.9)*	108 (10.3)*
	Functional disability free, n (%)	795 (87.1)	116 (13.4)*	12 (1.1)*
	PGIC (much better/very much better), n%	790 (86.5)	272 (31.5%)*	18 (1.7)*
2	Both MBS free and disability free, n (%)	763 (83.6)	93 (10.8)*	3 (0.3)[a]
3	MBS free, disability free, and PGIC (much better/very much better), n (%)	683 (74.8)	64 (7.4)*	2 (0.2)[a]
Neither MBS- nor disability freedom achieved, n (%)		42 (4.6)	453 (52.4)*	935 (88.9)*
Neither MBS free, disability free, nor PGIC (much better/very much better) achieved, n (%)		16 (1.8)	356 (41.2)*	925 (87.9)*

*p<0.001 vs group with pain freedom at 2 hours.
[a] p-values calculated if there were ≥10 patients in numerator and ≥ 10 in denominator.
Note: Data represent the total population (all treatment arms combined). p-values were generated from a two-sided test from a logistic regression model with study, pain response group and background use of medication to reduce the frequency of migraines as covariates. Firth's penalized likelihood approach was used to address issues of quasi-complete separation.

Proportion of Patients With Each Outcome Combination At 2 Hours Analyzed With the 2 by 2 Matrix

Odds Ratio = 35.5

		MBS Free: Yes	MBS Free: No
Pain Free	Yes	839 (28.4%)	74 (2.5%)
	No	496 (16.8%)	1550 (52.4%)

Odds Ratio = 64.0

		Disability Free: Yes	Disability Free: No
Pain Free	Yes	795 (26.9%)	118 (4.0%)
	No	195 (6.6%)	1851 (62.6%)

Odds Ratio = 1.0

		MBS Free: Yes	MBS Free: No
Improved to Mild Pain	Yes	388 (13.1%)	476 (16.1%)
	No	947 (32.0%)	1148 (38.8%)

Odds Ratio = 0.2

		Disability Free: Yes	Disability Free: No
Improved to Mild Pain	Yes	116 (3.9%)	748 (25.3%)
	No	874 (29.5%)	1221 (41.3%)

The odds of being MBS free was 35.5 for patients with pain freedom at 2h vs 1.0 for patients with mild pain.

The odds of being disability free was 64.0 for patients with pain freedom at 2h vs 0.2 for patients with mild pain.

Notes: The denominator is the total population (all treatment arms combined). Odds ratios were calculated using a Cochran-Mantel-Haenszel test with study as strata.

CONCLUSIONS

- **Pain freedom was frequently associated with MBS freedom and a return to normal activities**
- Majority of patients who were pain free were also MBS free and disability free
- Pain freedom was more closely related to all other outcomes (MBS freedom, functional disability freedom, PGIC (much better/very much better) than improvement to mild pain (p<0.001 for all outcomes)

Methods

- Post hoc analysis of patients from the modified intent-to-treat population[a] in SAMURAI and SPARTAN.
- All treatment arms (50mg [SPARTAN only], 100mg, 200mg lasmiditan and PBO) were pooled for these analyses.
- Baseline parameters for inclusion:
  - Moderate or severe pain
  - Self-identified most bothersome symptom (MBS = nausea, phonophobia, or photophobia)
  - Functional disability[c]
- Pain outcomes[b] defined as:
  - Pain freedom - reduction in pain severity to none
  - Improvement to mild pain – reduction in pain severity to mild pain
  - Continued moderate/severe pain- either remained at baseline pain level or moved bidirectionally between those 2 pain levels
- Coexistence of the following outcomes with pain freedom or improvement to mild pain were examined:
  - MBS freedom - absence of the self-identified MBS
  - Migraine-associated functional disability freedom
  - Patient Global Impression of Change

[a] The modified intent-to-treat population includes all randomized patients who took at least one dose of study drug, who recorded any post-dose headache severity or symptom assessments, and who treated a migraine attack within 4 hours of onset.
[b] Unless otherwise noted, pain outcomes were assessed at 2 hours post-dose.
[c] Functional disability was assessed with the question "How much is your migraine interfering with your normal activities". Response options were "not at all", "mild interference", "marked interference", "need complete bed rest". Functional disability freedom was defined as having "Not at all" recorded at 2 hours.
MBS= most bothersome symptom, PBO= Placebo

Results

Patient Baseline Demographics Across the Different Pain Outcome Categories at 2 Hours

Parameter	Pain Freedom N=913	Improved to Mild Pain N=864	Continued Moderate/ Severe Pain N=1052
Age, mean (SD)	41.9 (12.9)	41.8 (12.1)	42.6 (11.8)
Female, n (%)	780 (85.4)	745 (86.2)	885 (84.1)
White, n (%)	711 (78.0)	734 (85.0)	908 (86.3)
Body Mass Index, mean (SD)	30.3 (7.8)	30.4 (10.6)	29.9 (7.8)
Family history of Coronary Artery Disease, n (%)	277 (30.3)	251 (29.1)	346 (32.9)
Duration of migraine history years, mean (SD)	17.2 (12.6)	19.0 (12.8)	20.0 (12.8)
Average migraine attacks/month in past 3 months, mean (SD)	5.1 (1.6)	5.2 (1.9)	5.4 (2.1)
Use of migraine preventive medication[a], n (%)	155 (17.0)	186 (21.5)	252 (24.0)

[a] Based on the question 'Is the subject currently using medications to reduce the frequency of migraine episodes?' asked during randomization.
Notes: Pain response groups are patients with pain freedom, mild pain, or continued moderate or severe pain at 2h. Data represent the total population (all treatment arms combined).

Baseline Migraine Characteristics Across the Different Pain Outcome Categories at 2 Hours

Migraine Baseline Characteristic	Pain Freedom N=913	Improved to Mild Pain N=864	Continued Moderate/ Severe Pain N=1052
Time to dosing hours, mean (SD)	1.0 (1.7)	1.29 (1.69)	1.25 (1.56)
Pain severity, n (%)			
Severe	230 (25.2)	170 (19.7)	390 (37.1)
Moderate	683 (74.8)	694 (80.3)	662 (62.9)
Migraine-associated symptoms, n (%)			
Photophobia	726 (79.5)	713 (82.5)	903 (85.8)
Phonophobia	600 (65.7)	576 (66.7)	740 (70.3)
Nausea	384 (42.1)	395 (45.7)	556 (52.9)
Migraine-related functional disability[a], n (%)			
Need complete bedrest	131 (14.3)	112 (13.0)	245 (23.3)
Marked interference	489 (53.6)	521 (60.3)	612 (58.2)
Mild interference	293 (32.1)	231 (26.7)	195 (18.5)

[a] Functional disability was assessed with the question "How much is your migraine interfering with your normal activities". Response options were "not at all", "mild interference", "marked interference", "need complete bed rest". Patients who recorded "Not at all" at time of dosing were excluded from the analysis.
Notes: Pain response groups are patients with pain freedom, mild pain, or continued moderate or severe pain at 2h. Data represent the total population (all treatment arms combined).

Disclosures

Richard B. Lipton has received research support from the National Institute of Health, serves on the editorial board of Neurology (unpaid) and Cephalalgia and as senior advisor to Headache (unpaid), has received support from the Migraine Research Foundation and the National Headache Foundation, has received research grants from Allergan, Amgen, Dr. Reddy's Laboratories, and Novartis, and serves as consultant, advisory board member or has received honoraria from Alder, Allergan, Amgen, Autonomic Technologies, Avanir, Biohaven, Boston Scientific, CoLucid, Dr. Reddy's Laboratories, electroCore, Eli Lilly and Company, eNeura Therapeutics, GlaxoSmithKline, Merck, Novartis, Teva, and Vedanta, has received royalties from Wolff's Headache (8th Edition, Oxford Press University, 2009) and Informa, and holds stock options in eNeura Therapeutics and Biohaven Pharmaceuticals.
Stewart Tepper - Grants for research (no personal compensation): Alder, Allergan, Amgen, Dr. Reddy's, ElectroCore, Eli Lilly, eNeura, Neurolief, Novartis, Scion Neurostim, Teva, Zosano; Consultant and/or Advisory Boards: Acorda, Alder, Alexsa, Allergan, Alphasights, Amgen, Aperture Venture Partners, Aralez Pharmaceuticals Canada, Axsome Therapeutics, BioDelivery Sciences International, Biohaven, Charleston Labs, Decision Resources, DeepBench, Dr. Reddy's, ElectroCore, Eli Lilly, eNeura, Equinox, ExpertConnect, GLG, GSK, Guidepoint Global, Impel, M3 Global Research, Magellan Rx Management, Marcia Berenson Connected Research and Consulting, Medicxi, Navigant Consulting, Neurolief, Nordic BioTech, Novartis, Pfizer, Reckner Healthcare, Relevale, Satsuma, Scion Neurostim, Slingshot Insights, Sorrento, Spherix Global Insights, Sudler and Hennessey, Teva, Theranica, Thought Leader Select, Trinity Partners, XOC, Zosano. Royalties: Springer. Salary: Dartmouth-Hitchcock Medical Center, American Headache Society. Li Shen Loo, Raghavendra Vasudeva, Simin K Baygani, Eric M Pearlman, Paula M Hauck, and John H Krege are employees and minor stockholders of Eli Lilly and Company.
Previously presented at the online platform of AHS (2020) American Headache Society - 62nd Annual Scientific Meeting; Jun 13, 2020.

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