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Randomized, Controlled Trial of Lasmiditan over Four Migraine Attacks: First Attack Findings

[1]Krikke-Workel J, [1]Krege JH, [2]Ashina M, [3]Smith T, [1]Lin Q, [1]Klise S, [1]Bragg S, [1]Doty EG, [1]Dowsett SA, [4]Reuter U*

[1]Eli Lilly and Company, Indianapolis, IN, USA; [2]Danish Headache Center and Dept Neurology, Rigshospitalet Glostrup, University of Copenhagen, Denmark; [3]StudyMetrix Research, St Peters, MO, USA; [4]Department of Neurology, Charité-Universitätsmedizin Berlin, Berlin, Germany

BACKGROUND

- Lasmiditan is a selective serotonin (5-HT_{1F}) receptor agonist (ditan), approved by the FDA for the acute treatment of migraine, with or without aura, in adults.[1]
- In Phase 3 single migraine attack studies (SAMURAI and SPARTAN), the percentage of patients achieving pain freedom and MBS freedom at 2 hours post dose was significantly greater among patients receiving lasmiditan at all doses compared to those receiving placebo.
- This Phase 3 placebo-controlled study (CENTURION) was designed to assess the efficacy, including first attack efficacy and consistency of response, and safety of lasmiditan in acute treatment of 4 migraine attacks with or without aura. *Trial Registration Number: NCT03670810*
- The primary endpoints were pain freedom at 2h (first attack) and pain freedom at 2h in at least 2 out of 3 attacks (consistency of effect).
- Here, we present the findings from analysis of the first attack data.

[1]REYVOW® (lasmiditan) tablets [package insert]. Eli Lilly and Company, Indianapolis, IN; 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211280s000lbl.pdf
[2]Kuca B et al. Lasmiditan is an effective acute treatment for migraine: A phase 3 randomized study. *Neurology* 2018; 91: e2222-e2232.
[3]Goadsby PJ et al. Phase 3 randomized, placebo-controlled, double-blind study of lasmiditan for acute treatment of migraine. *Brain* 2019; 142: 1894-1904.

RESULTS Efficacy Summary

- Overall trial summary - All primary and gated secondary endpoints were met (p<0.001 in all cases).
- Findings from the mITT population (excluding attacks of mild severity) were similar to those for the ITT population.
- First attack findings are shown in the adjacent table.
- For pain freedom at 2h, the therapeutic gain with lasmiditan (difference from PBO) was ~17% for LTN 100 and ~21% for LTN 200.

RESULTS First Attack Findings

	PBO (N=443)	LTN 100 (N=419)		LTN 200 (N=434)	
	n (%)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
Primary					
Pain freedom 2h*	37 (8.4)	108 (25.8)	3.8 (2.6, 5.7)	127 (29.3)	4.6 (3.1, 6.8)
Gated secondary					
Pain relief 2h	183 (41.3)	274 (65.4)	2.7 (2.1, 3.6)	283 (65.2)	2.7 (2.0, 3.5)
Pain relief 1h	130 (29.3)	204 (48.7)	2.3 (1.7, 3.1)	205 (47.2)	2.2 (1.6, 2.9)
Sustained pain freedom 24h	19 (4.3)	57 (13.6)	3.5 (2.1, 6.0)	75 (17.3)	4.7 (2.8, 7.9)
Sustained pain freedom 48h†	19 (4.3)	39 (9.3)	2.3 (1.3, 4.0)	67 (15.4)	4.1 (2.4, 6.9)
Pain freedom 1h†	9 (2.0)	25 (6.0)	3.1 (1.4, 6.7)	55 (12.7)	7.0 (3.4,14.4)
Pain freedom 2h, triptan insufficient responders	17 (8.8)	44 (24.0)	3.3 (1.8, 6.0)	52 (25.6)	3.6 (2.0, 6.4)
Disability free 2h	42 (9.5)	78 (18.6)	2.2 (1.5, 3.3)	86 (19.8)	2.5 (1.7, 3.7)
Other secondary					
MBS free 2h	111 (28.0)	152 (40.4)	1.7 (1.3, 2.4)	154 (39.0)	1.6 (1.2, 2.2)
Rescue medication use 2-24h	119 (29.3)	61 (19.6)	0.5 (0.3, 0.7)	59 (19.2)	0.4 (0.3, 0.6)
Much/V. much better PGIC, 2h	59 (13.3)	125 (29.8)	2.9 (2.0, 4.1)	130 (30.0)	3.0 (2.1, 4.3)

*For patients pain free at 2h, pain recurrence within 48h was reported for 41% assigned placebo; 36% LTN 100; and 28% LTN 200 p<0.001 for all gated endpoints; p≤0.001 for other secondary endpoints unless otherwise specified below
†not gated for LTN 100. p=0.004 for LTN 100 vs PBO in both cases

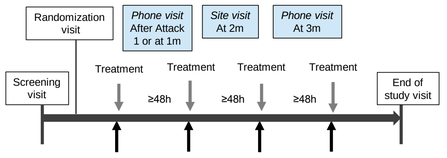
CONCLUSION

- Lasmiditan was superior to placebo for all gated endpoints and its overall safety and tolerability was generally consistent with that observed in previous Phase 3 lasmiditan studies. During the first attack, lasmiditan was superior to placebo for:
  - pain freedom beginning at 1h, with the effect sustained at 24 and 48h;
  - pain relief beginning at 30 mins (LTN 200);
  - Freedom from disability at 2h;
  - Pain freedom at 2h in triptan insufficient responders.
- These results confirm the early and sustained efficacy of lasmiditan.

Abbreviations: AE, adverse event; MBS, most bothersome symptom; PGIC, Patient Global Impression of Change; PF, pain freedom; PR, pain relief; LTN, lasmiditan; PBO, placebo

Disclosures: JKW, JHK, MA, TS, QL, SK, SB, EGD, SAD are full-time employees and minor stockholders at Eli Lilly and Company. MA is a consultant, speaker or scientific advisor for Allergan, Amgen, Alder, Eli Lilly and Company, Lundbeck, Novartis, and Teva, primary investigator for Alder, Amgen, Eli Lilly and Company, Novartis and Teva trials; he has no ownership interest and does not own stocks of any pharmaceutical company; he serves as associate editor of Cephalalgia, Headache, and Journal of Headache and Pain; he is the President of the International Headache Society. TS reports financial relationships with Alder-Lundbeck, Allergan, Amgen, Biohaven, Charleston Labs, Electrocore, Impel, Eli Lilly and Company, Novartis Novo Nordisk, Satsuma, Theranica, United Health Group, and Vorso Technologies. UR has received speaker fees and honorarium for consulting from Abbvie, Amgen, Allergan, Co-Lucid, Eli Lilly and Company, Medscape, Novartis, StreaMedUp, and TEVA Pharma; he serves as associated editor of the Journal of Headache and Pain and Frontiers in Neurology and Board Member of the European Headache Federation.

Study Design and Methods



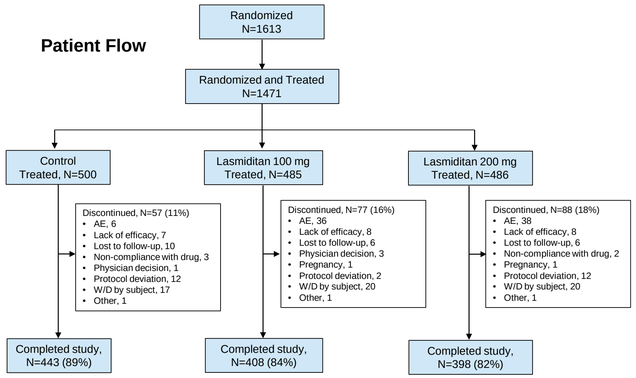
Randomized 1:1:1 to:	Attack 1	Attack 2	Attack 3	Attack 4
LTN 100 (N=539)	LTN 100	LTN 100	LTN 100	LTN 100
LTN 200 (N=536)	LTN 200	LTN 200	LTN 200	LTN 200
Control (N=538)	PBO	PBO	LTN 50	PBO
	PBO	PBO	PBO	LTN 50

Rescue/Recurrence
No second dose of study medication, but patients were permitted to use their own unexcluded medication

- The study had a modified parallel design enabling a comparison of the consistency of effect of two doses of lasmiditan to placebo.
- Patient population: A history of disabling migraine (MIDAS] score ≥11) for at least 1 year; migraine onset before age 50; 3-8 migraine attacks/ m but <15 headache days/m during the past 3m.
- Patients to record response to study drug at 0.5, 1, 2, 4, 6, 24, and 48h post dose using e-diary.
- Statistical testing used a logistic regression model and graphical multiplicity methodology to preserve overall type I error at 1-sided alpha level of 0.025 for the primary and gated secondary endpoints.
- *Safety population* = patients who take at least 1 dose of study drug;
- *Intention to treat (ITT) population* = patients who treated a migraine attack (mild, moderate or severe) and had any pain severity assessment ≤ 2h post dose;
- *Modified ITT (mITT)* = patients who treated a migraine attack of at least moderate severity and had any pain severity assessment ≤ 2h post dose.

Results

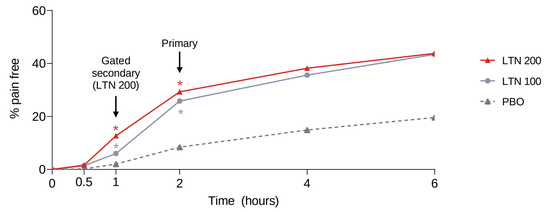
Patient Flow

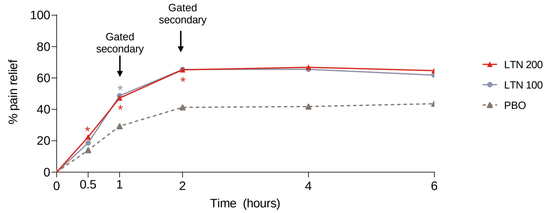


Baseline Characteristics

- Mean age 41 years; 84% female; 76% from Europe, 12% N. America, 12% Asia.
- Migraine history duration 12.9 years, MIDAS mean score 31.9.

Pain Freedom And Pain Relief over Time (First Attack)





*p<0.01 vs PBO. p<0.001 for all gated endpoints
Statistical testing not performed at timepoints after 2h

Safety Findings

- Across the study, the incidence of treatment emergent serious AEs was similar across treatment groups - control, n=2 (0.4%) (both after treatment with PBO); LTN 100, n=1 (0.2%), LTN 200, n=2 (0.4%); there were no major CV events consistent with ischemia.
- The most frequent treatment emergent AEs (TEAEs) with lasmiditan in the first attack (≥2% in either dose group) are shown below:

First Attack Findings	PBO (N=500)	LTN 100 (N=485)	LTN 200 (N=486)
% patients with ≥1 TEAE	22.4	53.0	61.1
- Dizziness	4.6	22.3	26.5
- Paresthesia	1.8	8.0	12.8
- Fatigue	1.8	7.6	9.5
- Nausea	3.8	6.4	10.1
- Vertigo	0.2	4.9	6.8
- Somnolence	1.4	4.1	7.6
- Hypoesthesia	0.6	3.7	1.9
- Muscular weakness	0.4	3.3	4.5
- Asthenia	0.2	2.9	4.7
- Feeling abnormal	0	1.6	2.7

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