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Safety Findings from CENTURION, a Phase 3 Consistency Study of Lasmiditan for the Acute Treatment of Migraine

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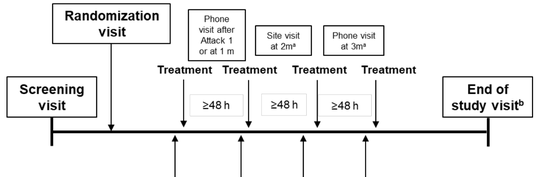
BACKGROUND AND OBJECTIVE

- Lasmiditan is a selective 5-HT_{1F} receptor agonist, approved by the FDA for the acute treatment of migraine, with or without aura, in adults[1]
- Common treatment emergent adverse events (TEAEs) reported during Phase 3, single attack studies of lasmiditan include dizziness, paresthesia, somnolence, fatigue, nausea, muscular weakness, and hypoesthesia[2,3]
- The objective of this study was to present safety findings from the placebo-controlled, double-blind Phase 3 study of lasmiditan treatment across four migraine attacks (CENTURION, Clintrials.gov registration number: NCT03670810)

STUDY DESIGN



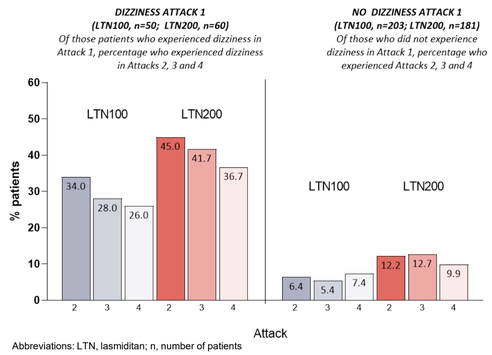
Randomized 1:1:1→	Attack 1	Attack 2	Attack 3	Attack 4
LTN 100 (N=539)	LTN 100	LTN 100	LTN 100	LTN 100
LTN 200 (N=536)	LTN 200	LTN 200	LTN 200	LTN 200
Control (N=538) *Randomized 1:1→*	PBO	PBO	LTN 50	PBO
	PBO	PBO	PBO	LTN 50

Abbreviations: LTN, lasmiditan; PBO, placebo; m, month
[a]Visits at 2 and 3 months applicable where patients had not already treated 4 attacks before these timepoints
[b]End of study visit occurred at 7 days after treating the last migraine attack or at 4 months after randomization

- Safety analyses presented here were conducted for patients who took ≥1 dose of study drug and using only patients who treated 4 attacks during the double-blind period

KEY RESULT

Figure 1. Incidence of Dizziness Across Attacks



Abbreviations: LTN, lasmiditan; n, number of patients

CONCLUSIONS

- In this blinded, controlled, multiple-attack study, lasmiditan was associated with generally mild or moderate central nervous system-related TEAEs of short duration
- TEAEs tended to decrease in frequency across the four attacks
- There were no new safety findings compared with previous single attack studies

Adverse Event Findings

Table 1: Adverse Event Summary over the Course of the Study

OVERALL	PBO (N=500)	LTN 100 (N=485)	LTN 200 (N=486)
Attacks treated	*≤3*	*≤4*	*≤4*
Deaths	0	0	0
Serious AE[a], n (%)	7 (1.4)	7 (1.4)	8 (1.6)
Study discontinuation due to AE[b], n (%)	6 (1.2)	36 (7.4)	38 (7.8)
% reporting ≥1 TEAE (1st attack only)	22.4	53.0	61.1

3rd/4th ATTACK	Control Group (N=500)	
	PBO	LTN 50[c]
Attacks treated	*3rd or 4th*	*3rd or 4th*
% reporting common TEAE[d]		
- Dizziness	2.6	5.6
- Paresthesia	1.5	1.1
- Fatigue	0.8	2.3

[a]Of the serious AEs, 5 were considered treatment emergent: PBO=2 (liver disorder, suicidal ideation); LTN100=1 (asthma); LTN200=2 (hemiplegic migraine and serotonin syndrome [met Hunter and Sternbach criteria])
[b]Dizziness most common TEAE leading to discontinuation
[c]No deaths, serious AEs, or AEs leading to discontinuation with LTN 50
[d]Common TEAE – reported in >2% of LTN group

Abbreviations: AE, adverse event; LTN, lasmiditan; PBO, placebo; TEAE, treatment-emergent AE

TEAE Findings Across Attacks

Table 2: Incidence, Onset, and Duration of Dizziness with Lasmiditan (100mg and 200mg Doses Pooled) by Attack

Dizziness with LTN[a] across Attacks	No. of patients (%)[b]		Onset[c] median [Q1-Q3]), hrs		Duration (median [Q1-Q3]), hrs	
Attacks treated:	≥ 1	4 attacks	≥ 1	4 attacks	≥ 1	4 attacks
Attack 1	212 (21.8)	100 (20.2)	0.7 (0.4-1.2)	0.7 (0.4-1.3)	2.5 (1.0-5.8)	1.8 (1.0-3.9)
Attack 2	124 (15.3)	71 (14.4)	0.7 (0.4-1.0)	0.7 (0.4-1.2)	3.0 (1.2-6.0)	2.0 (1.0-4.5)
Attack 3	87 (13.6)	69 (14.0)	0.5 (0.4-1.0)	0.5 (0.4-1.1)	2.0 (1.0-4.7)	2.0 (1.0-4.0)
Attack 4	62 (12.6)	62 (12.6)	0.7 (0.5-1.0)	0.7 (0.5-1.0)	1.8 (1.0-3.2)	1.8 (1.0-3.2)

[a]Data are pooled from LTN100 and LTN200 dose groups; [b]Only patients with onset time recorded; [c]Time to onset was calculated as the difference between TEAE start time and the indicated dosing time
Abbreviations: hrs, hours; LTN, lasmiditan; PBO, placebo; TEAE, treatment-emergent adverse event

- For Dizziness:
  - Incidence decreased across attacks
  - Duration generally similar across attacks
  - Onset similar across attacks (0.5-0.7 hours)
  - In the placebo group, the number of patients experiencing dizziness was lower, with onset and tendency toward reduction across attacks
- Findings generally similar for other common TEAEs

Severity of Common TEAEs

Figure 2. Severity of Common TEAEs (1st attack)

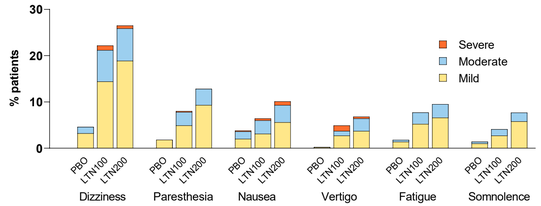
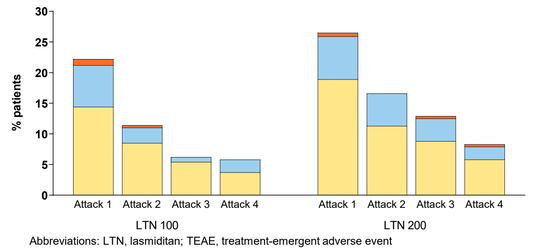


Figure 3. Severity of Dizziness by Attack



Abbreviations: LTN, lasmiditan; TEAE, treatment-emergent adverse event

- Findings generally similar for other common TEAEs

Other Safety Findings of Interest

- Serotonin syndrome was reported for two lasmiditan-treated patients* after taking lasmiditan; it was not reported for any placebo-treated patients
- No meaningful differences in suicidal ideation were observed across treatment groups (control group,1.5%; lasmiditan 100mg, 1.1%; lasmiditan 200mg, 0.9%); no patient reported suicidal behavior or self-injury without suicidal intent
- Motor vehicle accidents (patient as driver) after taking a dose of study drug included: n=1 (placebo), n=1 (lasmiditan 100mg), and n=1 (lasmiditan 200mg); there were no moving violations/citations after taking study drug
- Few injuries were reported over the course of the study (n=8 with lasmiditan, n=0 with placebo) The eight events with lasmiditan were limb injury (n=2), epicondylitis, fall, joint dislocation, ligament sprain, muscle rupture and rib fracture; no patient had multiple events

*One case was reported as serious (met Sternbach and Hunter's criteria). The patient had a history of depression and anxiety. Shortly after taking lasmiditan 200 mg to treat a migraine attack, the patient experienced CNS symptoms along with sweating and increased temperature. Concomitant medications included desogestrel and metoclopramide for migraine prophylaxis, and naratriptan and ibuprofen for acute treatment of attacks. The patient was hospitalized and treated with lorazepam 1 mg; symptoms and neurological examination normalized the next day and patient was discharged. There was one non-serious TEAE of serotonin syndrome reported, which did not meet criteria for serotonin syndrome

References: 1. REYVOW® (lasmiditan) tablets [package insert]. Eli Lilly and Company, Indianapolis, IN; 2019. http://pi.lilly.com/us/reyvow-uspi.pdf 2. Ashina, M et al. Cephalalgia 2021; 41(3): 294-304. 3. Krege, JH et al. Cephalalgia 2019; 39: 957-966

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