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Long-term cardiovascular safety of lasmiditan for the acute treatment of migraine for up to one year: Interim results of an open-label Phase 3 study (GLADIATOR)

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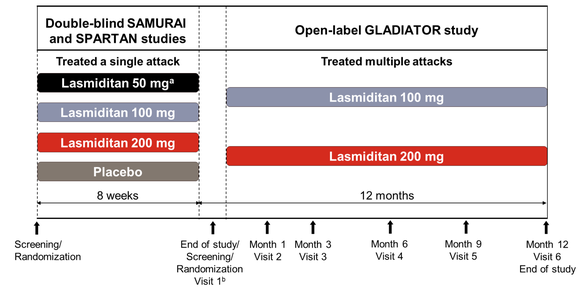
BACKGROUND AND OBJECTIVE

- Migraine is the second highest cause of disability worldwide[1]
- Triptans are considered the standard of care for the acute treatment of migraine, but are contraindicated in patients with certain types of cardiovascular (CV) disease due to vasoconstrictive effects mediated via serotonin (5-HT) 1B receptors[2]
- Lasmiditan is a selective 5-HT_{1F} receptor agonist that lacks the vasoconstrictive activity of some other acute treatments for migraine[3]
- Two previous studies of lasmiditan (SAMURAI and SPARTAN) for the acute treatment of a single migraine attack demonstrated that the drug is associated with a low incidence of CV treatment-emergent adverse events (TEAEs)[4,5]
  - In these studies, there was no difference in the frequency of CV TEAEs between subjects with and without CV risk factors[6]
- To assess the long-term CV safety of lasmiditan for the acute treatment of migraine for up to 1 year, interim data from the Phase 3 study GLADIATOR[7] were analyzed

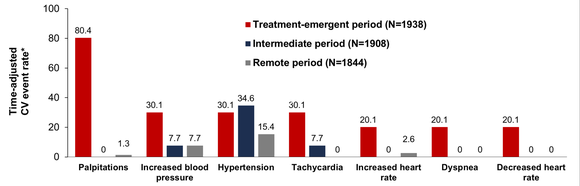
STUDY DESIGN



[a]Lasmiditan 50 mg was evaluated only in the SPARTAN study.
[b]The gap between SAMURAI/SPARTAN and GLADIATOR was generally up to 12 weeks.

KEY RESULT

Treatment-Related CV Events* in Three Time Periods Following Treatment with Lasmiditan 100 or 200 mg (Dose Data Pooled) in Patients (N=1978) with Migraine



*Time-adjusted CV event rate per 1000 patient-years of exposure = number of events x 1000 ÷ PTAR (in years). PTAR for treatment-emergent period was cumulative time in years of all treated migraines from when a patient started a dose to 48 hours after their last dose for the given migraine, or end of study, whichever came earlier; PTAR for intermediate period was cumulative time in years of all treated migraines from end of treatment-emergent period to 1 week later, or to first dose for next migraine, or end of study, whichever came earlier; PTAR for remote period was cumulative time in years of all treated migraines from end of intermediate period to first dose for next migraine, or end of study, whichever came earlier.
CV, cardiovascular; N, number of patients in the analysis population; n, number of events within each specific category;
PTAR, person-time at risk.

CONCLUSIONS

- In an interim analysis of the long-term GLADIATOR study, no vasoconstriction-related CV events occurred during the lasmiditan treatment-emergent period
- No CV safety concerns were identified during long-term use of lasmiditan in patients with CV risk factors
- No CV safety concerns were identified during long-term use of lasmiditan in elderly patients
- The CV safety of lasmiditan was generally consistent with data from single-attack studies

Strengths and Limitations

Strengths

- Large number of patients participated in the study
- Large proportion of patients with CV risk factors
- Patients were monitored for a prolonged period postdose to ensure no events were missed

Limitations

- Relatively small number of elderly patients
- No placebo control arm
- The impact of cumulative exposure to lasmiditan was not assessed

Methods

- GLADIATOR (NCT02565186)[7] was a Phase 3, randomized, open-label study of lasmiditan as the first treatment for migraine attacks occurring during a period of up to 1 year in patients who previously participated in SAMURAI (NCT02439320)[4] and SPARTAN (NCT02605174)[5]
- In GLADIATOR, patients were randomized 1:1 to open-label lasmiditan 100 or 200 mg to treat a migraine attack within 4 hours of the onset of moderate or severe pain
- SAMURAI and SPARTAN were Phase 3, randomized, double-blind, controlled studies of lasmiditan for the treatment of a single migraine attack in adults (aged ≥18 years) who:
  - Met International Classification of Headache Disorders, 2nd edition criteria for migraine with or without aura[8]
  - Had at least moderate migraine disability, defined as a Migraine Disability Assessment score (MIDAS) of ≥11
  - Had episodic migraine, defined as 3–8 migraine attacks/month and <15 headache days/month
- In addition, SAMURAI and SPARTAN allowed enrollment of patients with CV risk factors (e.g., hypertension, hypercholesterolemia, smoking, obesity, diabetes), and SPARTAN also permitted patients with coronary artery disease, arrhythmia, and uncontrolled hypertension
- If needed, a second dose of lasmiditan could be taken within 2–24 hours of the first dose in all studies
- Patients completed a daily electronic patient-reported outcome (ePRO) diary
  - If a patient recorded in their ePRO diary not feeling well or feeling something unusual after taking lasmiditan, the study site called the patient to determine whether an adverse event (AE) had occurred
  - AEs were coded using Standardized Medical Dictionary for Regulatory Activities (MedDRA) version 21.0, and CV AEs were identified using Standardized MedDRA Queries (SMQs)
  - The investigator assessed whether an AE was related to lasmiditan treatment
- Treatment-related CV event rates (incident and recurrent events) were calculated for three time periods, as it is possible some CV events were not reported as treatment emergent or were identified at a later date:
  - Treatment-emergent period (<48 hours postdose: from when a patient started a dose to 48 hours after their last dose for the given migraine, or end of study, whichever came earlier)
  - Intermediate period (48 hours to 1 week postdose; from end of treatment-emergent period to 1 week later, or to first dose for next migraine, or end of study, whichever came earlier)
  - Remote period (>1 week postdose; from end of intermediate period to first dose for next migraine, or end of study, whichever came earlier)
- TEAEs were defined as those occurring or worsening within 48 hours of the first study drug dose, regardless of whether a second dose was taken
- CV events occurring beyond 48 hours of dosing were also analyzed to determine whether such events increased in the treatment-emergent or intermediate periods compared with the remote period
- All vasoconstrictor-related likely CV events were also investigated
- Analyses were performed on the safety population, which consisted of all randomized patients who used ≥1 dose of lasmiditan (interim data cut-off 6 March 2018)
  - Time-adjusted CV event rates per 1000 patient-years of exposure were analysed overall, according to the number of baseline CV risk factors, and for elderly (aged ≥65 years) and non-elderly (<65 years) patients

Results

- At data cut-off, 1978 patients had received ≥1 dose of lasmiditan:
  - 963 received lasmiditan 100 mg
  - 1015 received lasmiditan 200 mg
- A total of 19,058 migraine attacks had been treated
- Median duration in the study was 288 days
- As expected, treatment-related CV events (e.g. palpitations, tachycardia) were more frequent in the treatment-emergent period than in the intermediate and remote periods
- No vasoconstriction-related CV events (e.g. angina) occurred in the treatment-emergent period, and such events were rarely observed in general:
  - The absolute number of each event ranged from 1 to 3, all in the remote period, limiting clinical interpretation

Table 1. CV Risk Factors at Baseline by Lasmiditan Dose

Characteristic	Lasmiditan 100 mg (N=963)	Lasmiditan 200 mg (N=1015)	All patients (N=1978)
CVRFs per ACC/AHA recommended variables[a], n (%)			
Age >40 years	533 (55.3)	595 (58.6)	1128 (57.0)
Current smoker	133 (13.8)	128 (12.6)	261 (13.2)
High total cholesterol (≥240 mg/dL)	77 (8.0)	103 (10.1)	180 (9.1)
Low HDL cholesterol (<40 mg/dL in men, <50 mg/dL in women)	336 (34.9)	357 (35.2)	693 (35.0)
High blood pressure (SBP ≥140 mmHg) and/or medical history of hypertension	79 (8.2)	69 (6.8)	148 (7.5)
Medical history of diabetes mellitus	0	0	0
Number of CVRFs, n (%)			
≥1	763 (79.2)	835 (82.3)	1598 (80.8)
≥2	308 (32.0)	342 (33.7)	650 (32.9)
≥3	76 (7.9)	73 (7.2)	149 (7.5)
≥4	11 (1.1)	2 (0.2)	13 (0.7)
≥5	0	0	0
Other risk factors of potential interest, n (%)			
Myocardial infarction	4 (0.4)	3 (0.3)	7 (0.4)
CAD	1 (0.1)	5 (0.5)	6 (0.3)
Unstable angina	3 (0.3)	4 (0.4)	7 (0.4)

[a]ACC/AHA guideline-recommended variables for CV risk assessment in adults without diagnosed disease.[9]
ACC, American College of Cardiology; AHA, American Heart Association; CAD, coronary artery disease; CV, cardiovascular; CVRF, cardiovascular risk factor; HDL, high-density lipoprotein; N, total number of patients in each group; n, number of patients with risk factor; SBP, systolic blood pressure.

Table 2. Treatment-Related CV Events* in Three Time Periods Following Treatment with Lasmiditan 100 or 200 mg (Dose Data Pooled) in Patients with Migraine: Subgroup Analyses by Number of Baseline CV Risk Factors

CV event and number of CVRFs	Treatment-emergent period (N=1938)		Intermediate period (N=1908)		Remote period (N=1844)	
	n	Time-adjusted event rate per 1000 PYE*	n	Time-adjusted event rate per 1000 PYE*	n	Time-adjusted event rate per 1000 PYE*
Palpitations						
None	3	180.8	0	0	0	0
≥1	5	60.3	0	0	1	1.6
≥2	3	88.5	0	0	0	0
≥3	2	246.1	0	0	0	0
≥4	0	0	0	0	0	0
Increased blood pressure						
None	0	0	1	22.8	1	7.0
≥1	3	36.2	1	4.6	5	7.9
≥2	1	29.5	0	0	0	0
≥3	1	123.0	0	0	0	0
≥4	0	0	0	0	0	0
Palpitations						
None	3	180.8	0	0	0	0
≥1	5	60.3	0	0	1	1.6
≥2	3	88.5	0	0	0	0
≥3	2	246.1	0	0	0	0
≥4	0	0	0	0	0	0
Increased blood pressure						
None	0	0	1	22.8	1	7.0
≥1	3	36.2	1	4.6	5	7.9
≥2	1	29.5	0	0	0	0
≥3	1	123.0	0	0	0	0
≥4	0	0	0	0	0	0
Hypertension						
None	0	0	0	0	0	0
≥1	3	36.2	9	41.6	12	18.9
≥2	2	59.0	5	57.2	6	22.8
≥3	1	123.0	2	97.0	1	17.4
≥4	0	0	1	728.9	0	0
Tachycardia						
None	0	0	0	0	0	0
≥1	3	36.2	2	9.2	0	0
≥2	1	29.5	0	0	0	0
≥3	0	0	0	0	0	0
≥4	0	0	0	0	0	0
Dyspnea						
None	0	0	0	0	0	0
≥1	2	24.1	0	0	0	0
≥2	2	59.0	0	0	0	0
≥3	1	123.0	0	0	0	0
≥4	0	0	0	0	0	0
Decreased heart rate						
None	0	0	0	0	0	0
≥1	2	24.1	0	0	0	0
≥2	2	59.0	0	0	0	0
≥3	0	0	0	0	0	0
≥4	0	0	0	0	0	0
Increased heart rate						
None	0	0	0	0	0	0
≥1	2	24.1	0	0	2	3.1
≥2	1	29.5	0	0	0	0
≥3	0	0	0	0	0	0
≥4	0	0	0	0	0	0

*Time-adjusted CV event rate per 1000 PYE = number of events x 1000 ÷ PTAR (in years). PTAR for treatment-emergent period was cumulative time in years of all treated migraines from when a patient started a dose to 48 hours after their last dose for the given migraine, or end of study, whichever came earlier; PTAR for intermediate period was cumulative time in years of all treated migraines from end of treatment-emergent period to 1 week later, or to first dose for next migraine, or end of study, whichever came earlier; PTAR for remote period was cumulative time in years of all treated migraines from end of intermediate period to first dose for next migraine, or end of study, whichever came earlier.
CV, cardiovascular; CVRF, cardiovascular risk factor; N, number of patients in the analysis population; n, number of events within each specific category; PTAR, person-time at risk; PYE, patient-years of exposure.

CV Safety According to Baseline CV Risk Factors

- Consistent with single-attack studies, no CV safety concerns were identified during long-term use of lasmiditan in patients with CV risk factors
- Of the 24 patients with likely CV events, all but 2 had at least 1 CV risk factor; none were elderly
- Consistent with the overall population, treatment-related CV events were more frequent in the treatment-emergent than intermediate and remote periods, regardless of the number of CV risk factors
- Of 6 vasoconstriction-related likely CV events (angina [n=3], ischemic stroke [n=1], cerebral infarction [n=1], hypertensive crisis [n=1]), all occurred in the remote period, and the majority in patients with CV risk factors (5 in patients with ≥2 CV risk factors, 1 [angina] in a patient with no CV risk factors)
  - None were considered by the investigator to be treatment-related

CV Safety in the Elderly

- For the 77 elderly patients included in these analyses (4% of study population), no CV safety concerns were identified during long-term use of lasmiditan
  - No treatment-related CV events occurred in the elderly during the treatment-emergent and intermediate periods
  - Two treatment-related CV events (hypertension and supraventricular tachycardia) occurred during the remote period
  - No vasoconstriction-related CV events occurred in the elderly in any of the three time periods

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