SAMURAI Phase 3 Pivotal Trial Conducted Under SPA

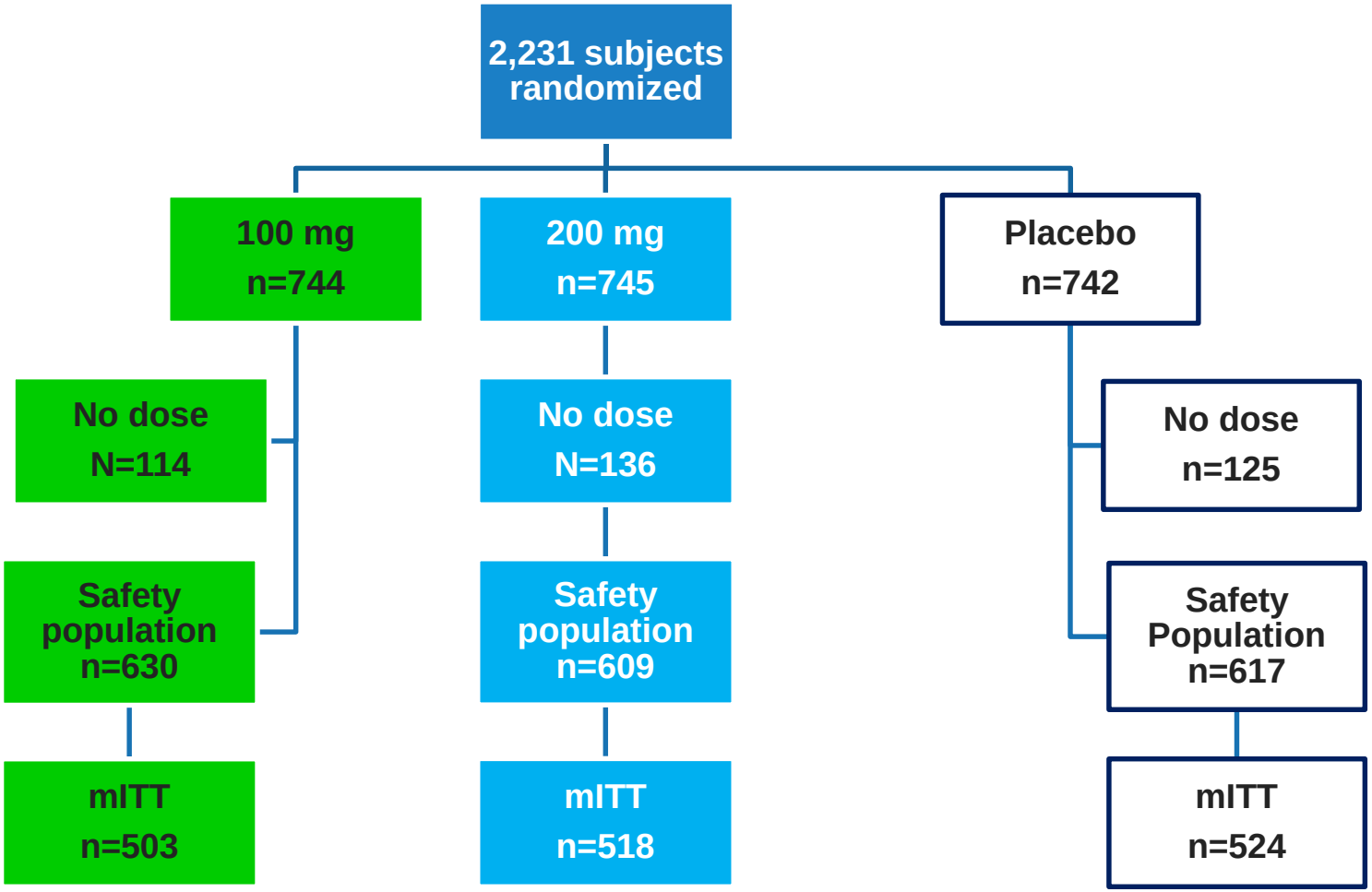
- 2,231 patients randomized: “All Comers”
  - 3 arms: lasmiditan 100 mg, 200 mg or placebo
  - All patients utilized electronic diaries
- Treatment: a **single migraine** with a **single dose** of lasmiditan or placebo; a second dose was permitted for rescue or recurrence
- Primary Endpoint: proportion of patients headache pain free at **two hours**
  - powered at > 90%
- Key Secondary Endpoint: proportion of patients MBS free at two hours
  - powered at > 80%
- SPA pre-specified analysis population – modified intent to treat (mITT)
  - All randomized subjects who used at least one dose of study drug to treat a qualifying migraine attack and had any post-dose assessments. Subjects were evaluated by the drug to which they were randomized
  - Qualifying migraine attack was defined as a migraine treated with study drug within four hours of onset

SAMURAI Population Breakdown

Population	Number	Notes
Randomized	2,231	
Randomization failures	(120)	
Never dosed	(255)	
Safety Population	1,856	Dosed with study drug
Did not record a single time point	(185)	
ITT	1,671	Dosed and recorded 1 time point
Dosed > 4 hours after start	(126)	
mITT	**1,545**	**Dosed a qualifying migraine**

Similar to other migraine clinical trials, ~ 30% of patients randomized in SAMURAI were not included in the mITT

SAMURAI – Analysis Populations By Dose



Similar pre-specified analysis populations (mITT) across all arms

mITT=Modified Intent To Treat

SAMURAI Demographics

Randomized Population

- 83.3% Female
- Mean age 41.6 years
- 74.4% Caucasian
- MIDAS score of 31
- 5.1 attacks per month
- 31.5% history of Aura
- 50% prior triptan users
- 10% opiate/barbiturate users
- 25.3% use of prophylactic migraine medication to reduce frequency of attacks

Cardiovascular Risk Factors	% of SAMURAI
Randomized Population	100%
Migraine + 1 Additional CVRF[1]	82%
BMI ≥ 30 kg/m^2	45%
Significant Family History CAD	34%
Former Smokers	16%
Current Smokers	16%
Hypertension	13%
Post-menopausal Women	12%
Male ≥ 40 years old	10%
Hyperlipidemia	5%
Hypercholesterolemia	5%
Type 2 Diabetes	1%

[1] Cardiovascular risk factor

Cardiovascular Conditions Present in Subjects Randomized in SAMURAI

arrhythmias, mitral valve disease, angina, atrial fibrillation, congestive heart failure, prior myocardial infarction, Raynaud's disease, deep vein thrombosis, ischemic stroke, cerebral infarction

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CAD=Coronary Artery Disease

Selection of the Most Bothersome Symptom

- During the attack, but pre-dosing, subjects were asked:
  - indicate the presence or absence of nausea, phonophobia or photophobia at the time of the attack
  - identify which associated symptom present was 'most bothersome'
- At each time point assessment, subjects were asked to indicate presence or absence of each associated symptom
- Endpoint was patient-centric and measured treatment effect

Selected MBS in SAMURAI	100 mg (n=469)	200 mg (n=481)	Placebo (n=488)
Nausea	115 (24.5%)	118 (24.5%)	115 (23.6%)
Phonophobia	117 (24.9%)	96 (20.0%)	104 (21.3%)
Photophobia	237 (50.5%)	267 (55.5%)	269 (55.1%)

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MBS=Most Bothersome Symptom

Efficacy Results

PRIMARY ENDPOINT	100 mg (n=503)	200 mg (n=518)	Placebo (n=524)
% of Subjects Pain Free[1] at 2h	28.2%	32.2%	15.3%
Odds ratio (95% CI)	2.2 (1.6 – 3.0)	2.6 (2.0 – 3.6)	
p value	< 0.001	< 0.001	

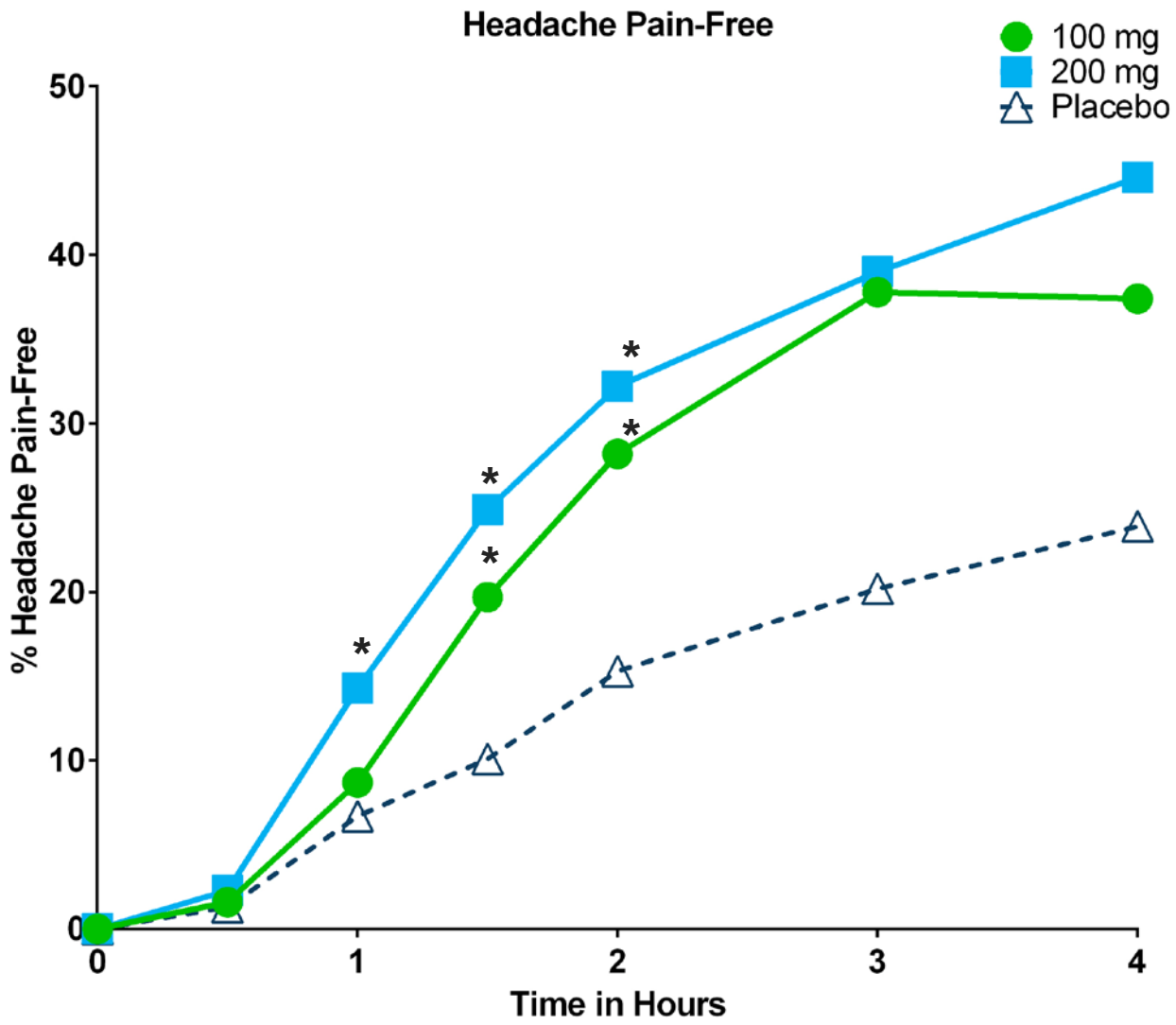
[1] Headache pain-free is as a reduction in headache severity from mild (1), moderate (2), or severe (3) at baseline to none (0) at the indicated assessment time

KEY SECONDARY ENDPOINT	100 mg (n=469)	200 mg (n=481)	Placebo (n=488)
% of Subjects MBS[2] Free at 2h	40.9%	40.7%	29.5%
Odds ratio (95% CI)	1.7 (1.3 – 2.2)	1.6 (1.3 – 2.1)	
p value	p < 0.001	p < 0.001	

[2] Most Bothersome Symptom of either nausea, phonophobia or photophobia

MBS=Most Bothersome Symptom

Headache Pain Freedom (mITT population)



* $p < 0.001$

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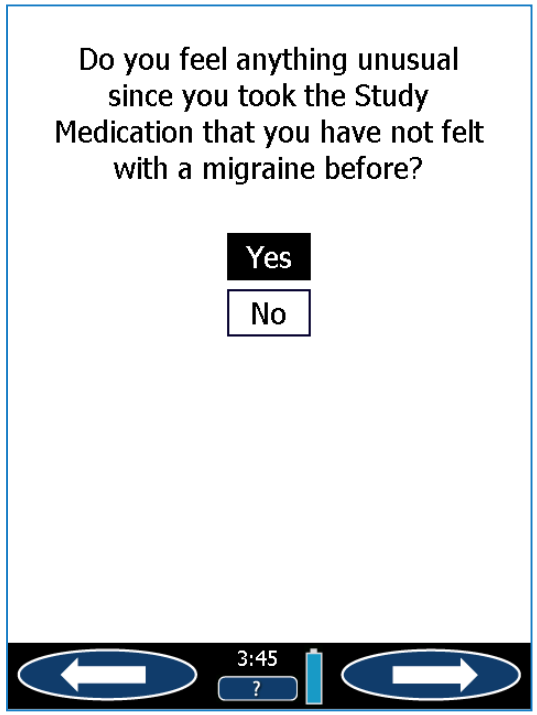
Treatment Emergent Adverse Events (TEAE)

- Lasmiditan was well tolerated
- Majority of TEAEs were nervous system disorders
- Majority of TEAEs were mild or moderate in severity
- There were no treatment-related Serious Adverse Events (SAEs)
- AEs were also captured before the migraine and then after migraine until end of study visit



Electronic diary screen capture

SAMURAI Treatment Emergent Adverse Events (TEAE)

TEAE[1]	100 mg (n=630)	200 mg (n=609)	Placebo (n=617)
Dizziness	75 (11.9%)	94 (15.4%)	19 (3.1%)
Paresthesia	36 (5.7%)	46 (7.6%)	13 (2.1%)
Somnolence	33 (5.2%)	32 (5.3%)	14 (2.3%)
Nausea	16 (2.5%)	29 (4.8%)	9 (1.5%)
Fatigue	24 (3.8%)	18 (3%)	1 (0.2%)
Lethargy	12 (1.9%)	14 (2.3%)	1 (0.2%)
Vertigo	6 (1%)	2 (0.3%)	0

[1] Percentages of patients who reported each particular TEAE within the safety population for each dose

- 91% of TEAEs were mild or moderate in severity in lasmiditan treated patients
- No SAEs in SAMURAI considered related to treatment

Lasmiditan was well tolerated in this large study, which includes 82% of patients with CVRF

CVRF=cardiovascular risk factors

No Significant Difference in Cardiovascular TEAEs

TEAE[1]	100 mg (n=630)	200 mg (n=609)	Placebo (n=617)	All Patients (n=1,856)
Palpitations	2 (0.3%)	4 (0.7%)	0	6 (0.3%)
Reasonably or possibly related	2 (0.3%)	3 (0.5%)	0	5 (0.3%)
Bradycardia	1 (0.2%)	0	1 (0.2%)	2 (0.1%)
Reasonably or possibly related	1 (0.2%)	0	0	1 (0.1%)
LV Hypertrophy	0	0	1 (0.2%)	1 (0.1%)
Reasonably or possibly related	0	0	0	0
Sinus bradycardia	0	1 (0.2%)	0	1 (0.1%)
Reasonably or possibly related	0	0	0	0
Tachycardia	1 (0.2%)	0	0	1 (0.1%)
Reasonably or possibly related	0	0	0	0

[1] All CV TEAEs were coded as mild or moderate

Secondary Endpoints

- Headache pain relief and time course
- Onset of action
- Most Bothersome symptom and time course
- Associated symptoms
- Use of a second dose of study drug
- Patient Global Impression of Change
- Summary of disability

Headache Pain Relief (ITT population)

SECONDARY ENDPOINT	100 mg (n=562)	200 mg (n=555)	Placebo (n=554)
% of Subjects Pain Relief at 2h	59.4%	59.5%	42.2%
Odds ratio (95% CI)	2.4 (1.8 – 3.1)	2.5 (1.9 – 3.3)	
p value	$p < 0.001$	$p < 0.001$	

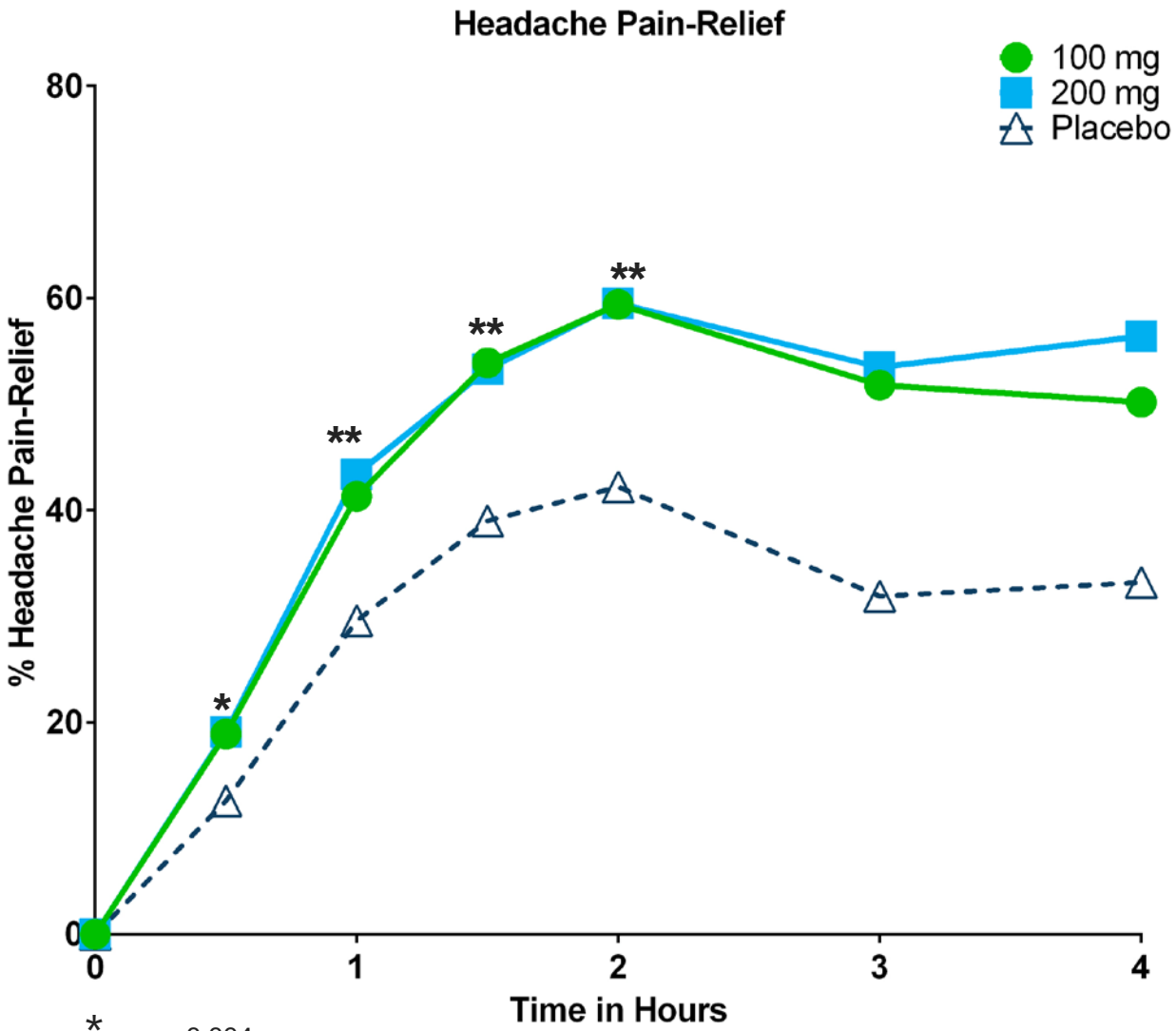
- Headache pain relief is defined as a reduction in headache severity from moderate (2) or severe (3) at baseline to mild (1) or none (0), or a reduction in headache severity from mild (1) at baseline to none (0), at the indicated assessment time
- P value, odds ratio, and confidence interval are from a two-sided test from a logistic regression model with treatment group and background use of medication to reduce the frequency of migraines as covariates

Onset of Action < 30 minutes

ITT population, n (%)	100 mg (N=562)	200 mg (N=555)	Placebo (N=554)
% of Subjects Headache Pain Relief at 30 minutes	106 (18.9%)	106 (19.1%)	70 (12.6%)
Odds ratio (95% CI)	1.6 (1.2 – 2.3)	1.7 (1.2 – 2.4)	
p value	p = 0.004	p = 0.002	

MBS recorded at baseline, n (%)	100 mg (N=469)	200 mg (N=481)	Placebo (N=488)
% of Subjects MBS Free at 30 minutes	59 (12.6%)	61 (12.7%)	38 (7.8%)
Odds ratio (95% CI)	1.7 (1.1 – 2.6)	1.7 (1.1 – 2.6)	
p value	p = 0.015	p = 0.013	

Headache Pain Relief Time Course (ITT population)



* p = 0.004

** p < 0.001

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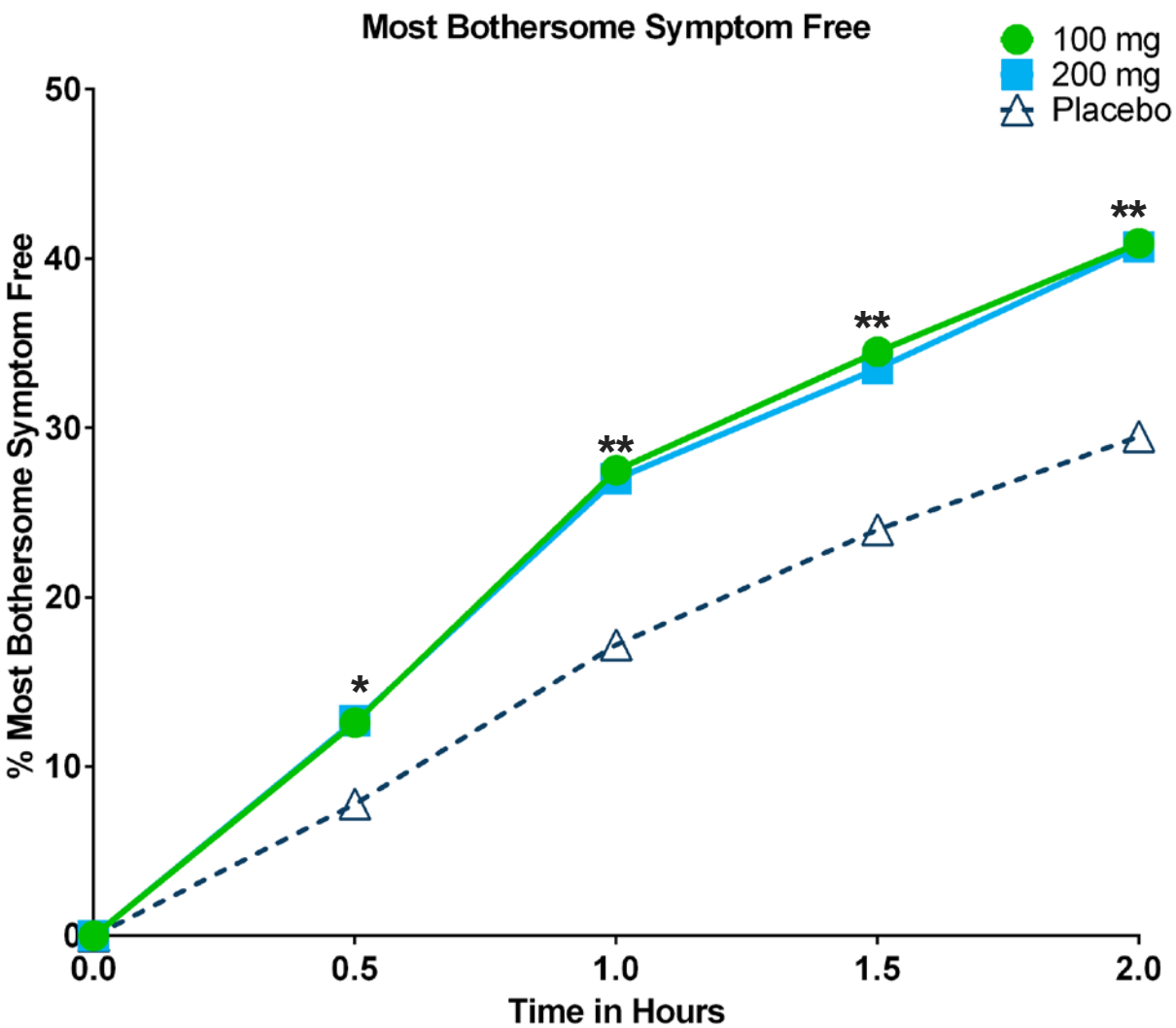
Most Bothersome Symptom Free Time Course (mITT population)



* p = 0.015
** p < 0.001

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Associated Symptoms and Probability of Selecting as MBS (mITT population)

Baseline Symptoms, n (%)	100 mg (n=503)	200 mg (n=518)	Placebo (n=554)
Nausea	210 (41.7%)	232 (44.8%)	221 (42.2%)
Phonophobia	303 (60.2%)	322 (62.2%)	327 (62.4%)
Photophobia	386 (76.7%)	391 (75.5%)	416 (79.4%)
None	34 (6.8%)	37 (7.1%)	36 (6.9%)

MBS Selected	Selection Preference[1]
Nausea	52%
Phonophobia	33%
Photophobia	65%

[1] Selection preference expressed as a proportion of the number of patients who selected that baseline symptom as most bothersome versus the number of patients that had the baseline symptom

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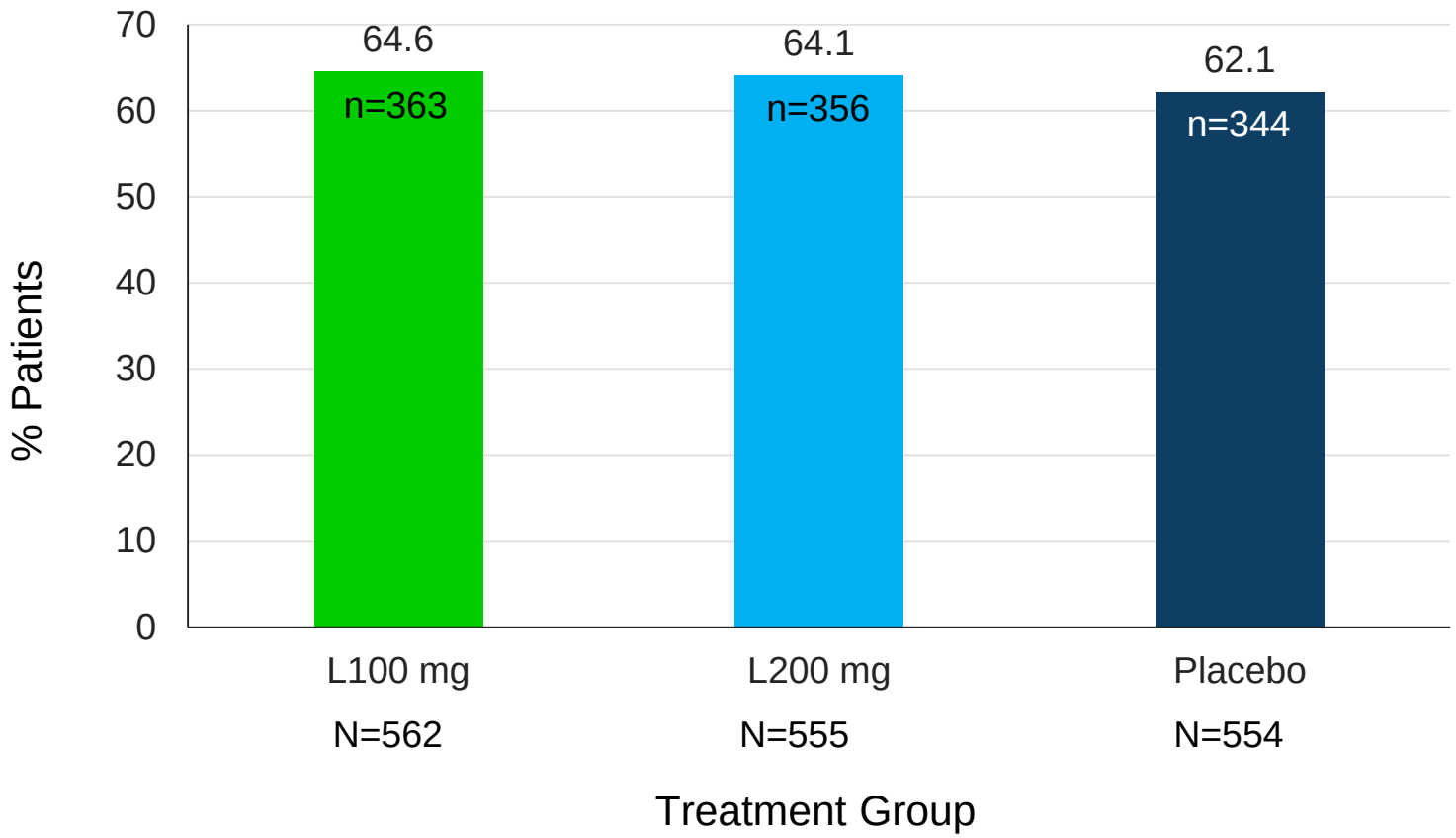
MBS=Most Bothersome Symptom

Proportion of Nausea-Free Subjects at Two Hours Post Dose (ITT population)



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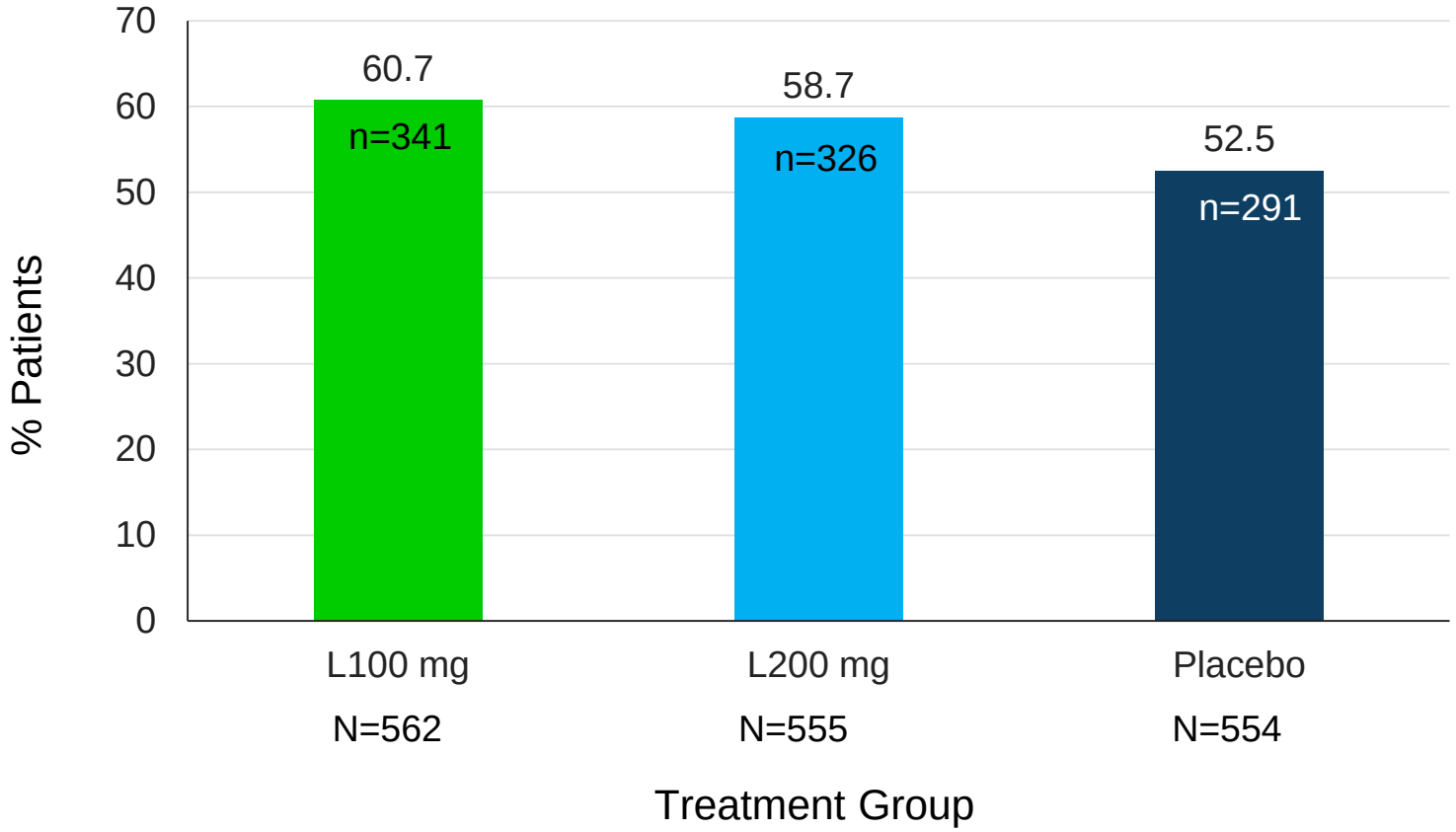
Proportion of Phonophobia-Free Subjects at Two Hours Post Dose (ITT population)



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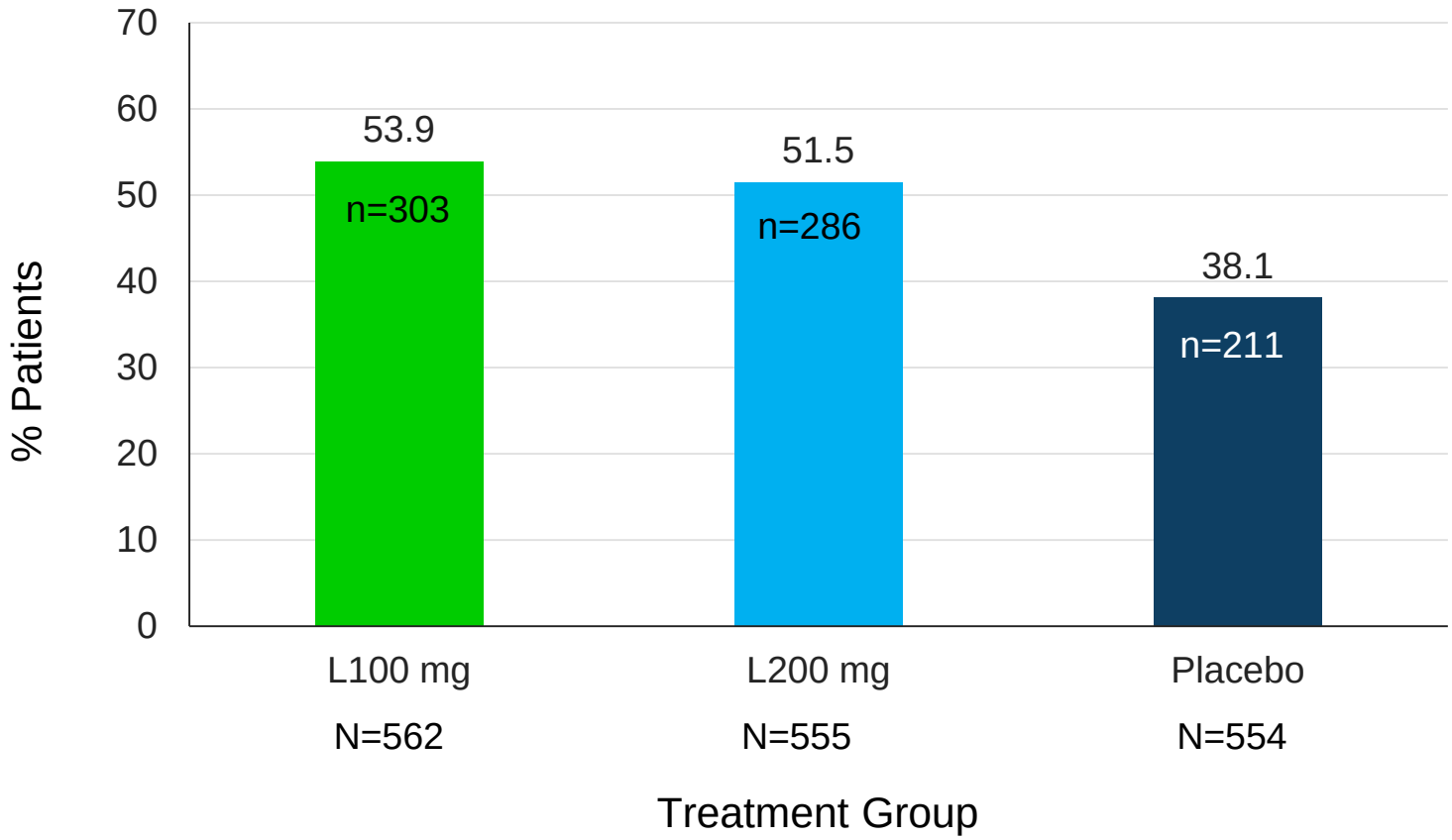
Proportion of Photophobia-Free Subjects at Two Hours Post Dose (ITT population)



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Use of a Second Dose of Study Drug (Safety Population)

- A second dose of study drug was allowed after two hours for rescue or recurrence

	100 mg (n=630)	200 mg (n=609)	Placebo (n=617)
Second Dose Taken (active or placebo)	289	236	401
Utilization Rate of Second Dose[1]	46%	39%	65%

[1] Utilization rate expressed as proportion of subjects who took any second dose of study drug in a treatment group to the safety population of the same treatment group

Subjects treated with lasmiditan were less likely to utilize a second dose

Efficacy of Second Dose of Study Drug (ITT population)

- Subjects were randomized to receive 2:1 lasmiditan to placebo for second dose, unless original dose was placebo

SECONDARY ENDPOINT	100 mg/ 100 mg (n=139)	100 mg/ Placebo (n=62)	200 mg/ 200 mg (n=109)	200 mg/ Placebo (n=52)	Placebo/ Placebo (n=319)
% of Subjects Pain Free at 2h **after Rescue Dose**	29.0%	12.9%	26.6%	23.1%	16.9%
Odds ratio (95% CI)	2.2 (1.4 – 3.6)		2.0 (1.2 – 3.3)		
p value	$p < 0.001$	n.s.	$p < 0.012$	n.s.	

- The number of subjects who took a second dose of study drug for **recurrence** was very small (53 out of 1,671) with no significant difference between five treatment groups

Lasmiditan was effective as a second dose rescue medication

TEAE Following Second Dose of Study Drug (Safety population)

TEAE, n (%)	100 mg/ 100 mg (n=203)	100 mg/ Placebo (n=86)	200 mg/ 200mg (n=159)	200 mg/ Placebo (n=79)	Placebo/ Placebo (n=401)
Dizziness	5 (2.5%)	7 (8.1%)	12 (7.5%)	9 (11.4%)	6 (1.5%)
Somnolence	7 (3.4%)	2 (2.3%)	1 (0.6%)	1 (1.3%)	3 (0.7%)
Paresthesia	3 (1.5%)	2 (2.3%)	0	1 (1.3%)	6 (1.5%)
Fatigue	5 (2.5%)	1 (1.2%)	2 (1.3%)	1 (1.3%)	2 (0.5%)
Nausea	3 (1.5%)	1 (1.2%)	1 (0.6%)	2 (2.5%)	3 (0.7%)
Vomiting	2 (1.0)	0	1 (0.6%)	1 (1.3%)	3 (0.7%)
Muscular Weakness	3 (1.5%)	0	0	0	0
Asthenia	0	0	1 (0.6%)	2 (2.5%)	1 (0.2%)
Tachycardia	0	1 (1.2%)	0	0	0
Palpitations	1 (0.5%)	0	0	0	0

A second dose of lasmiditan was well tolerated

Patient Global Impression of Change (ITT population)

SECONDARY ENDPOINT	100 mg (n=562)	200 mg (n=555)	Placebo (n=554)
PGIC 2 hours post-dose, n (%)			
Very Much Better	54 (9.6%)	57 (10.3%)	34 (6.1%)
Much Better	155 (27.6%)	153 (27.6%)	87 (15.7%)
A Little Better	153 (27.2%)	143 (25.8%)	159 (28.7%)
No Change	83 (14.8%)	60 (10.8%)	146 (26.4%)
A Little Worse	16 (2.8%)	31 (5.6%)	28 (5.1%)
Much Worse	8 (1.4%)	13 (2.3%)	14 (2.5%)
Very Much Worse	8 (1.4%)	5 (0.9%)	3 (0.5%)
Missing	85 (15.1%)	93 (16.8%)	83 (15.0%)
p value	$p < 0.001$	$p < 0.001$	

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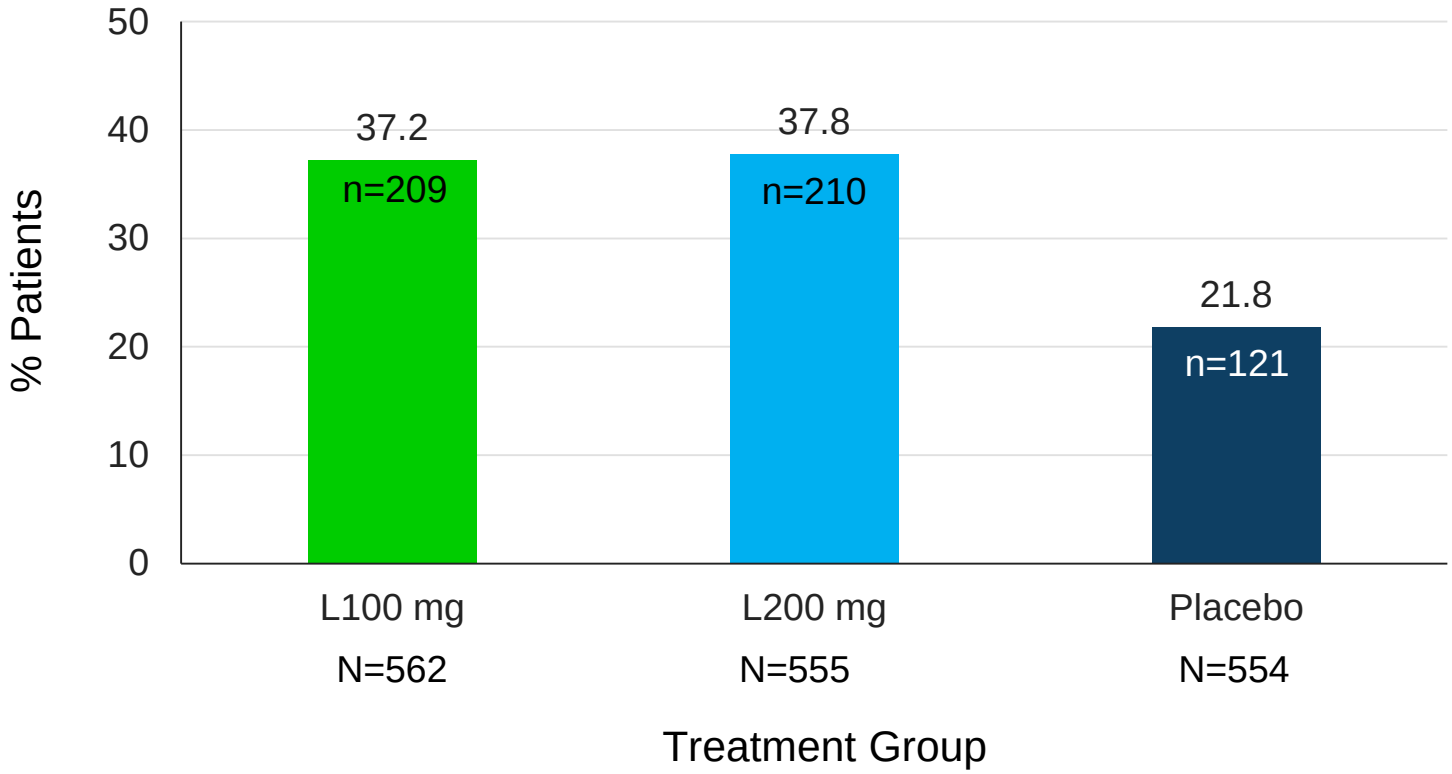
PGIC=Patient Global Impression of Change

Lasmiditan had a Positive Patient Global Impression of Change

Proportion of Patients With Patient Global Impression of Change of 'Much' or 'Very Much' Better at Two Hours Post-Dose ITT Population



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Summary of Disability Associated with Migraine (ITT population)

SECONDARY ENDPOINT	100 mg (n=562)	200 mg (n=555)	Placebo (n=554)
Disability 2 hours post-dose, n (%)			
Not At All (0)	181 (32.2%)	180 (32.4%)	119 (21.5%)
Mild Interference (1)	137 (24.4%)	115 (20.7%)	156 (28.2%)
Marked Interference (2)	95 (16.9%)	92 (16.6%)	122 (22.0%)
Completely, Needs Bed Rest (3)	64 (11.4%)	75 (13.5%)	74 (13.4%)
p value	$p < 0.001$	$p < 0.001$	

Lasmiditan reduced disability related to migraine compared to placebo

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Summary

- Successful study – achieved both primary and key secondary endpoints with statistical significance
  - Significantly more patients dosed with lasmiditan experienced freedom from headache pain and headache pain relief at two hours than those dosed with placebo
  - Significant treatment effect on patient-centric MBS endpoint
  - Lasmiditan was effective when taken as a rescue dose
  - Patients dosed with lasmiditan had a favorable Patient Global Impression of Change and a reduction in migraine related disability compared to patients dosed with placebo
- Patient demographics reflect a population with a severe disability associated with migraine and a significant proportion with CV risk factors and conditions
- Lasmiditan was well tolerated both on the first and second dose

GLADIATOR Phase 3 Long-Term Open Label Trial

- Anticipate ~2,580 patients randomized to either lasmiditan 100 mg or 200 mg
  - Treatment: up to 8 migraine attacks per month for 12 months
  - Primary Endpoint:
    - The proportion of patients and the proportion of attacks associated with any adverse event and with specific adverse events.
  - Secondary Endpoint:
    - The proportion of migraine attacks treated with lasmiditan 100 mg and with lasmiditan 200 mg which respond at 2 hours, calculated for each 3 month period.
- Open at all sites involved in SAMURAI and enrolling in SPARTAN

GLADIATOR is expected to provide for >15,000 patient exposures to lasmiditan at time of NDA

Treatment

- Subjects stratified (yes or no) for use of concomitant medication that reduce frequency of migraines (preventative or prophylactics) (same stratification from ‘parent’ study)
- Subjects will be allowed to treat all acute migraine attacks of moderate or severe intensity for up to 1 year.
- The attack is to be treated within 4 hours of onset and headache should be of moderate or severe intensity.
- Any aura symptoms have resolved.
- FIRST treatment for new migraine attack. No prior analgesic or acute migraine treatment taken to treat current attack.
- Second dose provided for rescue/recurrence

Enrollment Update

Enrollment	Lasmiditan 100 mg	Lasmiditan 200 mg	Grand Total
Active	395	456	851
Early Discontinuation	163	141	304
Randomized Total	558	597	1,155
Retention Rate	71%	76%	74%

Retention rate of > 70% across both dose groups in long-term study

Large Safety Database Emerging

Subjects who dosed in respective arm	Lasmiditan 100mg (n=473)	Lasmiditan 200mg (n=465)	Grand Total (n=938)
Count of a first dose taken	2849	2614	5463
Count of a second dose taken	1257	869	2126
% of patients taking second dose	44%	33%	39%
Total number of doses reported	**4106**	**3483**	**7589**

Second dose frequency similar to SAMURAI

TEAEs by Dose

Adverse Events, n (events)	Lasmiditan 100mg	Lasmiditan 200mg	All Subjects n (events)
Dizziness	36 (48)	40 (67)	76 (115)
Lethargy/heavy	7 (15)	1 (2)	8 (17)
Numbness	2 (2)	8 (12)	10 (14)
Sleepiness/Somnolence	15 (21)	18 (39)	33 (60)
Tingling	14 (16)	10 (17)	24 (33)
Vertigo	4 (4)	5 (7)	9 (11)
Weakness	7 (11)	11 (24)	18 (35)

No SAEs related to treatment and no CV TEAEs reported

Discontinuations

	100 mg	200 mg	Total (%)
Discontinuations	163	141	304
Data to date	113	100	213
Adverse Events	40	43	39%
Subject request	54	29	39%
Lost to follow up	8	8	8%
Non-compliance with protocol	7	8	7%
Sponsor request	2	5	3%
Investigator request	2	4	3%
Pregnancy	0	3	1%
Percentage of Discontinuation	53%	47%	

Low discontinuation rate is driven by AEs and subject request

Conclusions

- GLADIATOR is a comprehensive long-term open label study of lasmiditan for the acute treatment of migraine
- Study requires continuous engagement of patient with e-diaries
- Retention rate is encouraging at >70%
- AEs are predicted by SAMURAI and are manageable