Table 3: Patient Disposition

Parameter	Placebo	LCM 400mg/day	LCM 800mg/day	Moxi	Total
	n (%)				
Randomized	62	60	71	54	247
Randomized and treated	62 (100)	60 (100)	71 (100)	54 (100)	247 (100)
Completed trial	55 (88.7)	57 (95.0)	54 (76.1)	54 (100)	220 (89.1)
Prematurely discontinued	7 (11.3)	3 (5.0)	17 (23.9)	0	27 (10.9)
Reason for discontinuation					
Adverse event	0	0	2 (2.8)	0	2 (0.8)
Subject withdrew consent	4 (6.5)	1 (1.7)	11 (15.5)	0	16 (6.5)
Other	3 (4.8)	2 (3.3)	4 (5.6)	0	9 (3.6)

LCM = lacosamide; Moxi = moxifloxacin
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Randomized Set (RS): All randomized subjects were included in the RS.

Safety Set (SS) All randomized subjects who received at least 1 dose of trial medication were included in the SS.

Pharmacodynamic Set (PDS): All SS subjects who completed through Day 3 in the moxifloxacin group and through Day 6 in the lacosamide and placebo groups and had a sufficient H-12 data to calculate reliable estimates for the pharmacodynamic parameters were included in the PDS. Any subject with a major protocol deviation that would render the ECG data unreliable or render the data incomparable among subject groups was excluded from the PDS. The set of subjects that comprised the PDS was defined prior to unblinding. Subjects were replaced if they did not complete through Day 3 for subjects assigned to moxifloxacin or through Day 6 for subjects assigned to either placebo or lacosamide, including completion of the H-12 assessment on Day 3/6. Subjects who were replaced were excluded from the PDS and, therefore, were excluded from the primary analysis.

All randomized subjects received at least 1 dose of trial medication and therefore were included in the SS. Twenty-seven subjects discontinued from the trial prior to completing the dosing regimen and thus were not included in the PDS. An additional 6 subjects were missing H-12 ECG data at greater than 3 time points on primary ECG recording days; these subjects were classified as major protocol deviators and were excluded from the PDS.

Table 4 provides a summary of baseline demographics for the study patients by randomized group.

Table 4: Baseline Demographics

Parameter	Placebo N=62	LCM 400mg/day N=60	LCM 800mg/day N=71	Moxi N=54	All subjects N=247
Age (years)					
Mean (SD)	24.1 (6.1)	24.7 (6.4)	24.9 (6.7)	25.1 (7.3)	24.7 (6.6)
Min, Max	18-45	18-44	18-43	18-44	18-45
Sex					
Male (n[%])	30 (48.4)	27 (45.0)	28 (39.4)	27 (50.0)	112 (45.3)
Female (n[%])	32 (51.6)	33 (55.0)	43 (60.6)	27 (50.0)	135 (54.7)
Race					
White (n[%])	51 (82.3)	54 (90.0)	65 (91.5)	48 (88.9)	218 (88.3)
Black (n[%])	2 (3.2)	1 (1.7)	3 (4.2)	3 (5.6)	9 (3.6)
Asian (n[%])	2 (3.2)	3 (5.0)	1 (1.4)	2 (3.7)	8 (3.2)
Other (n[%])	7 (11.3)	2 (3.3)	2 (2.8)	1 (1.9)	12 (4.9)
Height (cm)					
Mean (SD)	171.6 (9.0)	170.3 (8.6)	170.0 (8.5)	172.0 (9.1)	170.9 (8.8)
Min, Max	150-191	150-191	152-188	152-193	150-193
Weight (kg)					
Mean (SD)	72.94 (11.89)	72.90 (12.09)	69.36 (11.85)	75.81 (13.04)	72.53 (12.33)
Min, Max	50.4-109.4	47.7-104.4	47.2-96.2	53.6-109.4	47.2-109.4
BMI (kg/m^2)					
Mean (SD)	24.70 (3.04)	25.05 (3.13)	23.91 (3.05)	25.52 (3.22)	24.74 (3.15)
Min, Max	19.0-32.0	19.7-31.4	18.9-31.0	19.0-32.0	18.9-32.0

BMI = body mass index; LCM = lacosamide; Max = maximum; Min = minimum; Moxi = moxifloxacin; SD = standard deviation; SS = Safety Set

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4.2.7.2 Statistical Analyses

4.2.7.2.1 Primary Analysis

The primary analysis was based on a non-inferiority comparison of each LACOSAMIDE group with placebo using 1-sided 95% confidence intervals (or, equivalently, the upper limits of 2-sided 90% confidence intervals) for maximum time-matched change from Baseline in QTcI (calculated by taking the maximum of all time-matched changes for each subject for each day).

Confidence intervals were produced using an analysis of covariance (ANCOVA) model with effects for treatment and gender, and time-matched baseline QTcI as a covariate. Additionally, 2-sided confidence intervals for maximum time-matched change from baseline in QTcI were presented within each treatment group.

For ECG parameters, the baseline values were obtained from the H-12 assessment on Day -1. For time-matched changes, the baseline at each time point was the median of the 3 values obtained at each time point. The primary variable for this trial was the maximum time-matched change in QTcI from Baseline to Day 3 for the moxifloxacin group and Day 6 for the placebo and lacosamide groups. All analyses of the primary variable were based on data from the H-12 recorder. The primary analysis was based on a non-inferiority comparison of each lacosamide group with placebo using 1-sided 95% confidence intervals (or, equivalently, the upper limits of 2-sided 90% confidence intervals). Confidence intervals were produced using an ANCOVA model with effects for treatment and gender, and time-matched baseline QTcI as a covariate. The statistical model was fit with all 4 treatment groups; therefore, the estimate of the variance was a pooled estimate obtained from all 4 treatment groups. Time-matched baseline QTcI was the Baseline value from the time point on Day -1, which corresponds to the time point on Day 6 or Day 3 at which the maximum change occurs.

The sponsor also did a time averaged analysis. For time-averaged changes, the baseline value was obtained as follows: 1) the median of the 3 values at each time point on Day -1 was obtained, and 2) these 12 values were averaged to obtain the time-averaged baseline value.

The difference in the maximum time-matched change from Baseline in QTcI between the 400 mg/day lacosamide group and placebo was -4.3 and between the 800 mg/day lacosamide group and placebo was -6.3. In both cases, the upper limit of the 2-sided 90% CI (-0.5 and -2.5 for 400 mg/day lacosamide and 800 mg/day lacosamide, respectively) was below the 10 ms non-inferiority margin, thereby demonstrating that there is no relevant increase of QTcI caused by lacosamide. The sponsor claimed that assay sensitivity was demonstrated since the mean difference between moxifloxacin and placebo was 10.4 ms and the lower 95% confidence bound was >0, thereby showing a statistically significant effect over placebo. Results were similar for the SS and for males and females.

The statistical analysis of the maximum time-matched change on Day 6 (Day 3 for moxifloxacin) in QTcI is presented in the following table. The sponsor reported the 2-sided 90% confidence interval, as well as the 95% interval.

Table 5: Maximum* time-matched change on Day 6 (Day 3 for moxifloxacin) (PDS)

Treatment	n	Endpoint LSMean	Comparison	Treatment Difference (SE)	90% CI[a]	95% CI[a]
Placebo	54	20.9				
LCM 400mg/day	56	16.6	B – A	-4.3 (2.2)	-8.0, -0.5	-8.7, 0.2
LCM 800mg/day	52	14.6	C – A	-6.3 (2.3)	-10.0, -2.5	-10.8, -1.7
Moxi	52	31.3	D – A	10.4 (2.3)	6.6, 14.2	5.9, 14.9

Note: A = placebo, B = LCM 400mg/day, C = LCM 800mg/day, D = moxifloxacin
Note: p-values and confidence intervals are based on an ANCOVA model with effects for treatment and gender and time-matched Baseline QTcI as a covariate.
Note: Maximum time-matched change from Baseline to Day 3 for moxifloxacin group.
ANCOVA = analysis of covariance; CI = confidence interval of mean; LSMeans = least squares mean; LCM = lacosamide; Moxi = moxifloxacin; PDS = pharmacodynamic set; SE = standard error
a. Confidence intervals are for the treatment differences
*Mean of maximum over time within each individual subject

Table 6 and Table 7 give the results by hour on day 3 and day 6, respectively.

Table 6: Non-Inferiority Analysis of Time-Matched Change in QTcI (ms) by Day and Time - ANCOVA Model- Pharmacodynamic Set

Time Point	LS Means A	B	C	D	Treatment Difference B - A	C - A	D - A	90% Confidence Intervals B - A	C - A	D - A
Day 3										
1h	-5.7	-10.0	-10.5	5.7	-4.2	-4.8	11.5	(-8.4, -0.1)	(-9.0, -0.5)	(7.3, 15.7)
2h	-9.5	-10.4	-11.2	3.2	-0.9	-1.7	12.6	(-5.9, 4.1)	(-6.8, 3.3)	(7.6, 17.7)
3h	-1.2	-5.8	-5.5	11.1	-4.3	-4.4	12.2	(-8.9, 0.3)	(-9.0, 0.3)	(7.6, 16.9)
4h	2.8	-0.0	-3.7	16.2	-2.9	-6.7	14.2	(-6.7, 2.7)	(-10.5, -3.0)	(9.4, 19.1)
5h	-7.6	-10.3	-8.8	5.4	-2.6	-1.2	13.0	(-7.2, 1.9)	(-5.9, 3.5)	(8.3, 17.7)
6h	-5.1	-9.1	-15.1	1.8	-4.0	-10.0	6.9	(-9.1, 1.0)	(-15.2, -4.8)	(1.7, 12.0)
10h	-4.6	-8.8	-7.9	8.5	-0.8	-2.8	12.1	(-6.6, 5.3)	(-7.8, 1.3)	(6.6, 17.7)
12h	-10.2	-11.7	-12.4	-3.4	-1.5	-2.2	6.8	(-6.3, 3.2)	(-7.1, 2.7)	(1.9, 11.6)
14h	-5.4	-8.2	-9.8	1.2	-2.7	-4.3	6.6	(-7.2, 1.7)	(-8.9, 0.3)	(2.0, 11.2)
16h	-2.6	-7.2	-11.0	2.1	-4.6	-8.5	4.7	(-9.0, -0.2)	(-13.0, -4.0)	(0.2, 9.2)
18h	-1.6	-4.8	-10.1	7.8	-3.3	-8.6	9.3	(-6.9, 0.4)	(-12.2, -4.9)	(5.6, 13.0)
24h	3.2	-4.2	-2.3	8.9	-7.5	-5.5	0.7	(-12.1, -2.8)	(-10.2, -0.7)	(-4.1, 5.5)

Note: A = Placebo, B = LCM 400mg/day, C = LCM 800mg/day, D = Moxifloxacin
Note: Non-inferiority comparisons are based on the upper limits of 90% CIs for the difference between LCM groups and placebo using a non-inferiority bound of 10ms.
Note: Least squares means and confidence intervals are based on ANCOVA with effects for treatment, gender and time-matched Baseline value as a continuous covariate.
The ANCOVA model was fit separately at each time point.
Note: Only Day 3 and Day 6 are analyzed. Analysis for Day 6 is based on data from Day 3 for Moxifloxacin.

Table 7: Non-Inferiority Analysis of Time-Matched Change in QTcI (ms) by Day and Time - ANCOVA Model - Pharmacodynamic Set

Time Point	LS Means A	B	C	D	Treatment Difference B - A	C - A	D - A	90% Confidence Intervals B - A	C - A	D - A
Day 6										
1h	-2.8	-9.6	-10.8	5.8	-6.8	-8.0	8.6	(-11.6, -2.0)	(-12.8, -3.7)	(4.8, 12.9)
2h	3.0	-6.2	-4.9	3.1	-9.1	-7.9	0.1	(-13.6, -4.7)	(-12.4, -3.3)	(-4.4, 4.7)
3h	-2.8	-2.8	-8.0	11.0	0.2	-5.2	13.8	(-4.5, 5.0)	(-10.0, -0.4)	(9.0, 18.6)
4h	-8.7	-2.1	-6.1	16.2	1.6	-2.4	19.3	(-2.6, 5.8)	(-6.7, 1.9)	(15.5, 24.1)
5h	-9.3	-11.9	-11.9	5.4	-2.6	-2.6	14.7	(-7.5, 2.4)	(-7.6, 2.4)	(9.7, 19.7)
8h	-9.4	-10.3	-11.6	1.8	-0.9	-2.2	11.2	(-5.6, 3.8)	(-7.0, 2.6)	(6.4, 16.0)
10h	-0.8	-4.8	-5.4	8.6	-3.9	-7.5	9.4	(-8.8, 0.9)	(-12.5, -2.6)	(4.5, 14.4)
12h	-9.1	-9.2	-11.5	-3.4	-0.2	-2.5	5.7	(-4.9, 4.6)	(-7.3, 2.3)	(0.8, 10.5)
14h	-1.3	-3.6	-5.0	1.2	-2.4	-3.7	2.5	(-7.0, 2.2)	(-8.4, 1.0)	(-2.3, 7.2)
16h	-14.1	-17.2	-15.1	2.2	-3.2	-1.0	16.3	(-7.8, 1.4)	(-5.7, 3.7)	(11.6, 21.0)
18h	-2.2	-3.7	-9.8	7.8	-0.6	-6.7	11.0	(-4.8, 3.7)	(-11.0, -2.3)	(6.7, 15.3)
24h	1.9	-2.8	-4.8	8.9	-4.7	-6.7	2.0	(-10.1, 0.7)	(-12.1, -1.3)	(-3.5, 7.5)

Note: A = Placebo, B = LCM 400mg/day, C = LCM 800mg/day, D = Moxifloxacin
Note: Non-inferiority comparisons are based on the upper limits of 90% CIs for the difference between LCM groups and placebo using a non-inferiority bound of 10ms.
Note: Least squares means and confidence intervals are based on ANCOVA with effects for treatment, gender and time-matched Baseline value as a continuous covariate.
The ANCOVA model was fit separately at each time point.
Note: Only Day 3 and Day 6 are analyzed. Analysis for Day 6 is based on data from Day 3 for Moxifloxacin.

4.2.7.2.2 Categorical Analysis

A summary of the number of absolute and change from Baseline outliers in QTcI by day and time is presented in the following table.

Table 8: Summary of subjects with a new onset QTcI outlier value during the Treatment Phase (Pharmacodynamic Set)

Parameter	Placebo N=54	LCM 400mg/day N=56	LCM 800mg/day N=52	Moxi N=52
	n (%)			
QTcI				
450ms to <480ms	4 (7.4)	3 (5.4)	1 (1.9)	8 (15.4)
480ms to <500ms	0	0	0	0
≥500ms	0	0	0	0
QTcI				
Increase of 30 to <60ms	20 (37.0)	15 (26.8)	10 (19.2)	28 (53.8)
Increase of ≥60ms	1 (1.9)	0	0	4 (7.7)

LCM = lacosamide; Moxi = moxifloxacin; PDS = pharmacodynamic set

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There were no ECGs with a QTcI of 480 ms or greater at any post-Baseline time point that were not present at Baseline. The percentage of subjects with new onset values for QTcI of ≥ 450ms was 7, 5, 2, and 15 in the placebo, 400 mg/day lacosamide, 800 mg/day lacosamide, and moxifloxacin groups, respectively. One subject in the placebo group and 4 subjects in the moxifloxacin group had changes from baseline of ≥ 60ms in QTcI. No subject in either lacosamide group had a change from baseline in QTcI that was 60 ms or greater at any time point during the trial. The percentage of subjects with increases in QTcI that were 30 to 60 ms was higher in the moxifloxacin group and placebo groups, 54% and 37%, respectively, compared with 27% and 19% in the 400 mg/day and 800 mg/day lacosamide groups, respectively. The corresponding percentages with QTcI increases between 30 and 60 ms in the all randomized set were 56, 32, 25, 19, for Moxifloxacin, placebo, 400 mg/day lacosamide and 800 mg/day lacosamide, respectively.

4.2.7.3 Safety Analysis

No subject died. 1 subject had an SAE, a spontaneous abortion 9 days following her last dose of 800 mg of lacosamide. 1 subject had a 2 minute episode of syncope about 12 hours after being administered 800 mg of lacosamide on day 4; the sponsor reports no ECG being available at the time of occurrence.

27 subjects failed to complete the study (see Table 3); 15 of these were in the lacosamide 800 mg treatment group, 3 in the lacosamide 400 mg treatment group, 7 in the placebo group, and none in the moxifloxacin group. The reasons are as follows:

- 2 subjects (both in the 800 mg lacosamide treatment group and both female) were withdrawn due to AEs; 1 for neck pain and the other for hematemesis due to Mallory-Weiss tear.
- 8 additional female subjects in the 800 mg qd lacosamide treatment group and 1 female in the 400 mg qd group withdrew consent while experiencing AEs. All of these were related to some combination of dizziness, nausea and vomiting. The sponsor does not report any abnormalities or ECG for any of these subjects.
- 3 subjects in the 800 mg qd lacosamide treatment group and 4 subjects in the placebo group withdrew consent without ongoing AEs

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