**SUPPORTING INFORMATION**

**TABLE S1**  
Baseline patient demographics and characteristics (3-month population)

|                     | Lacosamide (n = 210) | Carbamazepine (n = 221) | Total (n = 431) |
|---------------------|-----------------------|-------------------------|----------------|
| Age, mean (SD), years | 39.0 (16.4)           | 37.8 (15.8)             | 38.4 (16.1)    |
| <25 years, n (%)     | 52 (24.8)             | 58 (26.2)               | 110 (25.5)     |
| 25 to <45 years, n (%) | 86 (41.0)           | 87 (39.4)               | 173 (40.1)     |
| 45 to <65 years, n (%) | 52 (24.8)           | 63 (28.5)               | 115 (26.7)     |
| ≥65 years, n (%)     | 20 (9.5)              | 13 (5.9)                | 33 (7.7)       |
| Male, n (%)          | 118 (56.2)            | 128 (57.9)              | 246 (57.1)     |
| Weight, kg, mean (SD) | 70.8 (16.0)           | 72.3 (15.7)             | 71.5 (15.8)    |
| Body mass index, mean (SD), kg/m² | 24.4 (4.7)      | 24.9 (4.9)              | 24.7 (4.8)     |
| <25, n (%)           | 123 (58.6)            | 124 (56.1)              | 247 (57.3)     |
| 25 to <30, n (%)     | 63 (30.0)             | 73 (33.0)               | 136 (31.6)     |
| ≥30, n (%)           | 24 (11.4)             | 24 (10.9)               | 48 (11.1)      |

Comorbid endocrine disorders, metabolism and nutrition disorders, social circumstances, vascular disorders reported by ≥2% of total patients:

|                     | Lacosamide (n = 210) | Carbamazepine (n = 221) | Total (n = 431) |
|---------------------|-----------------------|-------------------------|----------------|
| Hypertension, n (%) | 31 (14.8)             | 41 (18.6)               | 72 (16.7)      |
| Postmenopause, n (%) | 12 (5.7)              | 11 (5.0)                | 23 (5.3)       |
| Hypercholesterolemia, n (%) | 7 (3.3)       | 11 (5.0)                | 18 (4.2)       |
| Obesity, n (%)      | 3 (1.4)               | 10 (4.5)                | 13 (3.0)       |
| Menopause, n (%)    | 3 (1.4)               | 10 (4.5)                | 13 (3.0)       |
| Hypothyroidism, n (%) | 3 (1.4)              | 8 (3.6)                 | 11 (2.6)       |
### Total cholesterol

| Patients with levels below upper limit of the reference range, n (%)<sup>a</sup> | 135 (64.6)<sup>c</sup> | 149 (67.4) | 284 (66.0)<sup>d</sup> |
| Patients with levels above upper limit of the reference range, n (%)<sup>b</sup> | 74 (35.4)<sup>c</sup> | 72 (32.6) | 146 (34.0)<sup>d</sup> |

### LDL-cholesterol

| Patients with levels below upper limit of the reference range, n (%)<sup>e</sup> | 154 (73.7)<sup>c</sup> | 176 (81.1)<sup>g</sup> | 330 (77.5)<sup>h</sup> |
| Patients with levels above upper limit of the reference range, n (%)<sup>f</sup> | 55 (26.3)<sup>c</sup> | 41 (18.9)<sup>g</sup> | 96 (22.5)<sup>h</sup> |

Abbreviations: LDL, low-density lipoprotein; SD, standard deviation.

<sup>a</sup>Total cholesterol levels ≤200 mg/dL.

<sup>b</sup>Total cholesterol levels >200 mg/dL.

<sup>c</sup>n = 209.

<sup>d</sup>n = 430.

<sup>e</sup>LDL-cholesterol levels ≤130 mg/dL.

<sup>f</sup>LDL-cholesterol levels >130 mg/dL.

<sup>g</sup>n = 217.

<sup>h</sup>n = 426.

Hepatobiliary disorders were also evaluated; however, no preferred term was reported by ≥2% Total patients.
## TABLE S2
Percentage of patients on each dose level at 12 months and 3 months

| Patients (%) | LCM (n = 138) | CBZ (n = 133) | Total (n = 271) | LCM (n = 210) | CBZ (n = 221) | Total (n = 431) |
|--------------|---------------|---------------|----------------|---------------|---------------|----------------|
|              |               |               | 12-month population | 3-month population |
| Dose level 1 | 93.5          | 91.7          | 92.6           | 72.9          | 73.8          | 73.3           |
| Dose level 2 | 3.6           | 6.0           | 4.8            | 17.6          | 19.0          | 18.3           |
| Dose level 3 | 2.9           | 2.3           | 2.6            | 9.5           | 7.2           | 8.4            |

Abbreviations: CBZ, carbamazepine; LCM, lacosamide.

Lacosamide: dose level 1: 200 mg/d; dose level 2: 400 mg/d; dose level 3: 600 mg/d;
carbamazepine: dose level 1: 400 mg/d; dose level 2: 800 mg/d; dose level 3: 1200 mg/d.
# TABLE S3

Total cholesterol and LDL cholesterol at Baseline and 3 months and change from Baseline to 3 months (3-month population) in patients with baseline levels below or above the upper limit of the reference range

| Treatment | n     | Baseline, mean (SD) | 3-month treatmenta, mean (SD) | Analysis of covariance modelb | Change in lipid levels from Baseline at 3 months |
|-----------|-------|---------------------|-------------------------------|-------------------------------|----------------------------------------------|
|           |       |                     |                               |                               |                                              |
| Total cholesterol below upper limit of the reference range at Baselinec | | | | | |
| LCM, mg/dL | 135   | 168.1 (24.4) | 169.3 (28.2) | 135 | 1.8 (1.9) | < .001 |
| CBZ, mg/dL | 149   | 161.0 (26.3) | 179.4 (31.4)**** | 149 | 18.4 (1.8) |
| Total cholesterol above upper limit of the reference range at Baselined | | | | | |
| LCM, mg/dL | 74    | 227.1 (21.7) | 214.6 (30.2)**** | 74 | −11.3 (4.0) | < .001 |
| CBZ, mg/dL | 72    | 227.3 (20.3) | 248.1 (48.8)**** | 72 | 20.2 (4.0) |
| LDL cholesterol below upper limit of the reference range at Baselinee | | | | | |
| LCM, mg/dL | 154   | 96.1 (21.5) | 96.8 (25.6) | 154 | 1.1 (1.6) | < .001 |
| CBZ, mg/dL | 176   | 89.7 (23.9) | 101.1 (30.2)**** | 176 | 11.2 (1.5) |
| LDL cholesterol above upper limit of the reference range at Baselinef | | | | | |
| LCM, mg/dL | 55    | 147.7 (14.9) | 135.7 (21.8)**** | 55 | −11.0 (3.1) | < .001 |
| CBZ, mg/dL | 41    | 151.5 (14.0) | 168.2 (30.5)*** | 41 | 16.1 (3.7) |

Abbreviations: ANCOVA, analysis of covariance; CBZ, carbamazepine; LCM, lacosamide; LDL, low-density lipoprotein; LS, least squares; SD, standard deviation; SE, standard error.
The 3-month lipid levels included lipid values collected at 90 days (plus a 30-day window) of treatment during the Treatment period. The ANCOVA model included treatment as a main effect and age, sex, body mass index, and Baseline lipid level as covariates.

- Total cholesterol levels ≤200 mg/dL.
- Total cholesterol levels >200 mg/dL.
- LDL-cholesterol levels ≤130 mg/dL.
- LDL-cholesterol levels >130 mg/dL.

Within-treatment group comparison 3 months vs Baseline; paired t test

- ***P < .001.
- ****P < .0001.
FIGURE S1
Patients included in the 12-month lipid analysis (Safety Set)

Total patients N=886

Excluded
Patients not treated with LCM for at least 12 months n=145

Patients received least one dose of trial medication
LCM: N=444 CBZ: N=442

Excluded
Patients not treated with CBZ for at least 12 months n=152

Patients treated with trial medication for ≥12 months
LCM: n=299 CBZ: n=290

Excluded
Patients received lipid-modifying agents at Baseline and/or during the initial 12 months of LCM treatment n=46

Patients treated with trial medication for ≥12 months and did not receive lipid-modifying agents at Baseline and/or during the initial 12 months of treatment
LCM: n=253 CBZ: n=243

Excluded
Patients received lipid-modifying agents at Baseline and/or during the initial 12 months of CBZ treatment n=47

Excluded
Patients did not provide blood samples under fasted conditions at Baseline and at 12 months n=115

Patients Analyzed for lipid levels
LCM: N=138 CBZ: N=133

CBZ, carbamazepine; LCM, lacosamide.
FIGURE S2
Patients included in the 3-month lipid analysis (Safety Set)

CBZ, carbamazepine; LCM, lacosamide.
Supporting information: changes in lipids levels at 3 months
At 3 months, mean lipid levels at Baseline were generally similar between patients randomized to LCM and CBZ (Figure S1). Three-month LCM monotherapy did not increase the mean levels of TC, LDL-C, non-HDL-C, HDL-C, and TGs. Increases in the mean levels of TC, LDL-C, non-HDL-C, and TGs were observed after 3-month CBZ monotherapy.

On applying the ANCOVA model for change in lipid levels from Baseline to 3 months a numerical difference was observed between LCM and CBZ for change in TC, LDL-C, non-HDL-C, HDL-C ($P < .001$ for each) and TGs ($P = .043$) levels.

FIGURE S3
Least squares mean change in lipids levels from Baseline at 3 months (ANCOVA), lipid levels at Baseline and 3 months (3-month population)

The ANCOVA model included treatment as a main effect and age, sex, body mass index, and Baseline lipid level as covariates. $n = 217$ for CBZ.

Table includes within treatment group comparison 3-month vs Baseline, paired $t$ test; $P$ values were based on means of observed values (unadjusted): LCM: Total cholesterol $P > .05$; LDL cholesterol $P > .05$; non-HDL-cholesterol $P > .05$; HDL cholesterol $P > .05$; triglycerides $P > .05$.

CBZ: Total cholesterol $P < .0001$; LDL cholesterol $P < .0001$; non-HDL-cholesterol $P < .0001$; HDL cholesterol $P < .0001$; triglycerides $P > .05$.

ANCOVA, analysis of covariance; CBZ, carbamazepine; HDL, high-density lipoprotein; LCM, lacosamide; LDL, low-density lipoprotein; LS, least squares; SD, standard deviation
Supporting information: patients with TC and LDL-C levels above the upper limit of the reference range at Baseline and 3 months

In patients on LCM monotherapy, the proportion with TC or LDL-C levels above the upper limit of the reference range was similar at Baseline and at 3 months (Figure S4). In patients on CBZ monotherapy, the proportion with TC or LDL-C levels above the upper limit of the reference range was higher at 3 months compared with Baseline.

**FIGURE S4**

Proportion of patients with total cholesterol and/or LDL cholesterol levels above the upper limit of the reference range at Baseline and 3 months (3-month population)

Reference ranges for total cholesterol: normal was 130-200 mg/dL, high was >200 mg/dL; Reference ranges for LDL cholesterol: under 18 years of age, normal was 0-110 mg/dL, high was >110 mg/dL; age 18 years and older, normal was 0-130 mg/dL, high was >130 mg/dL. CBZ, carbamazepine; LCM, lacosamide; LDL, low-density lipoprotein
Supporting information: proportion of patients with specified increase in lipid level between Baseline and 3 months
For TC, LDL-C, and non-HDL-C, the proportion of patients with a ≥20 or ≥40 mg/dL increase between Baseline and 3 months was higher in patients on CBZ than in those on LCM monotherapy (Figure S5).

FIGURE S5
Proportion of patients with a ≥20 or ≥40 mg/dL increase in total cholesterol, LDL cholesterol, and non-HDL cholesterol levels from Baseline at 3 months (3-month population)

\[ \text{≥20 mg/dL increase} \]
\[ \begin{align*}
\text{Total cholesterol} & : P < .0001 \\
\text{LDL} & : P < .0001 \\
\text{Non-HDL} & : P < .0001
\end{align*} \]

\[ \text{≥40 mg/dL increase} \]
\[ \begin{align*}
\text{Total cholesterol} & : P < .0001 \\
\text{LDL} & : P = .0002 \\
\text{Non-HDL} & : P < .0001
\end{align*} \]

\[ P\text{-values are from the Fisher's exact test; }^{a}n = 217 \text{ for CBZ.} \]

CBZ, carbamazepine; HDL, high-density lipoprotein; LCM, lacosamide; LDL, low-density lipoprotein; TC, total cholesterol.