

Effects of Lacosamide, Pregabalin, and Tapentadol on Peripheral Nerve Excitability: A Randomized, Double-blind, Placebo-controlled, Crossover, Multicenter Trial in Healthy Subjects

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Lacosamide, pregabalin, and tapentadol are used to treat neuropathic pain syndromes like diabetic and small fiber neuropathy but with variable success among patients
- Determining whether antineuropathic analgesic agents reach the appropriate compartment at sufficient concentrations to affect the targeted sodium channels might be accomplished by specific peripheral nerve excitability testing

ABSTRACT

Background: Chronic pain is a leading cause of disability globally, with limited treatment options and frequent adverse effects. The IMI-PainCare-BioPain project aimed to enhance analgesic drug development by standardizing biomarkers. This study, IMI2-PainCare-BioPain-RCT1, evaluated the effects of lacosamide, pregabalin, and tapentadol on peripheral nerve excitability in healthy subjects through a randomized, double-blind, placebo-controlled crossover trial.

Methods: The study included 43 healthy participants aged 18 to 45 yr. Participants underwent four treatment periods during which they received single doses of lacosamide (200 mg), pregabalin (150 mg), tapentadol (100 mg), or placebo. High-frequency stimulation was applied to induce hyperalgesia. The two primary endpoints were changes in strength–duration time constant (SDTC) in large sensory and motor fibers between lacosamide and placebo periods at the first postdose timepoint compared to baseline (60 min). Other predefined endpoints included recovery cycle, threshold electrotonus (TEd), and S2 accommodation, as well as effects of pregabalin and tapentadol.

Results: Lacosamide statistically significantly reduced SDTC in large sensory fibers (mean reduction, 0.04; 95% CI, 0.01 to 0.08; $P = 0.012$) and in motor fibers (mean reduction, 0.04; 95% CI, 0.00 to 0.07; $P = 0.039$) but had no effect on small sensory fibers at the first timepoint compared to placebo. There were no effects of pregabalin and tapentadol on SDTC. Of other predefined endpoints, lacosamide produced statistically significant changes in subexcitability, S2 accommodation TEd(peak), and TEd40(Accom) in large sensory fibers. No statistically significant changes were observed in refractoriness, relative refractory period, or accommodation half-time at the first timepoint compared to placebo.

Conclusions: This study demonstrates that nerve excitability testing can detect pharmacodynamic effects on large myelinated fibers in healthy subjects. Lacosamide statistically significantly reduced peripheral nerve excitability, particularly in large sensory fibers.

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- One nerve excitability testing biomarker, the strength–duration time constant, can be used to sensitively detect changes in persistent sodium channel activity

What This Article Tells Us That Is New

- This single-dose, multinational, placebo-controlled, subject- and assessor-blind, randomized four-way crossover trial tested the ability of lacosamide (200 mg), pregabalin (150 mg), and tapentadol (100 mg) to block hyperalgesia induced by superficial electrical stimulation in healthy subjects ($n = 43$)
- Lacosamide, but not pregabalin and tapentadol, statistically reduced the strength–duration time constant in large sensory fibers compared to placebo
- Further studies with improved methodologies, larger data sets, and potentially alternative protocols may allow more sensitive testing of small fiber excitability and its modulation by drugs

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Abbreviations: **DMA**, dynamic mechanical allodynia; **EDT**, electrical detection threshold; **HFS**, high-frequency stimulation; **IMP**, investigational medicinal product; **MMRM**, mixed model for repeated measures; **NET**, nerve excitability testing; **PROM**, patient-reported outcome measure; **PROMIS**, Patient-Reported Outcomes Measurement Information System; **RCT**, randomized controlled trial; **RRP**, relative refractory period; **SAP**, statistical analysis plan; **SDTC**, strength–duration time constant; **Ted**, depolarizing threshold electrotonus; **TEh**, hyperpolarizing threshold electrotonus; **TRONDRT4B**, Trondheim Repeated Threshold Tracking Protocol for Small Fibers

Chronic pain is a leading cause of disability,¹ with treatments often inadequate and accompanied by adverse effects. Drug development for this condition is challenging, with few options available. Key challenges include determining whether the drug engages its target to produce desired effects and whether it reaches the appropriate compartment at sufficient concentrations for therapeutic efficacy.

IMI-PainCare-BioPain, an European Union-funded collaboration, aims to improve analgesic drug development through standardization and pharmacologic validation. It

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investigates biomarkers in the nociceptive system's various compartments (peripheral, spinal cord, and cerebral) to quantify drug exposure and target engagement, advancing novel analgesics for clinical trials. Four randomized controlled trials (RCTs) assessed the effect of three drugs thought to have actions on the brain (tapentadol), spinal cord (pregabalin), and the peripheral nervous system (lacosamide) in healthy subjects.^{2,3} This study, IMI2-PainCare-BioPain-RCT1, focused on the peripheral domain.

Lacosamide, pregabalin, and tapentadol treat neuropathic pain, which is pain caused by a lesion or disease of the somatosensory nervous system.^{4,5} Lacosamide stabilizes the slow-inactivated state of sodium channels⁶ and also binds to the fast-inactivated state with slower binding and unbinding kinetics.⁷ It is European Union–approved for epilepsy and has shown efficacy on pain-like behavior in neuropathic models.⁸ Despite inconsistent results in RCTs,^{9–14} lacosamide has shown efficacy in treating painful diabetic neuropathy^{10,12} and small fiber neuropathy caused by $\text{Na}_v1.7$ mutations.⁹ Single 200-mg doses in healthy subjects showed acceptable side effects.^{15,16} Pregabalin acts on $\alpha_2\delta$ subunits of voltage-gated calcium channels and is a first-line treatment for neuropathic pain,¹⁷ with European Union approval for peripheral and central neuropathic pain at daily doses of 150 to 600 mg. Single 300-mg doses have been studied in healthy subjects.^{18–21} Tapentadol is a strong opioid with effects also on the reuptake of noradrenaline. Tapentadol sustained release has been authorized in the European Union for the treatment of severe chronic pain in adults that is solely responsive to opioid analgesics, while tapentadol immediate release (in the form of film-coated tablets) is authorized for the alleviation of moderate to severe acute pain in adults that is solely responsive to opioid analgesics. Withdrawal trials showed some efficacy for painful diabetic polyneuropathy,^{22,23} with a 100-mg dose used as the maximum in healthy subjects.

In the current study (RCT1), we hypothesized that lacosamide has an effect on peripheral measures of nerve excitability. Nerve excitability testing (NET) utilizes threshold-tracking protocols to provide information on membrane potential changes, membrane polarization, ion channel function, and ionic pump activity during impulse conduction at the site of stimulation.^{24–30} The strength–duration time constant (SDTC) was chosen as the primary endpoint due to its sensitivity to changes in persistent sodium channel activity, lacosamide's direct target. SDTC reflects the strength–duration relationship, making it an ideal biomarker for drug-induced nerve excitability changes.³¹ We used peripheral NET-derived biomarkers and evaluated the effect of lacosamide, pregabalin, tapentadol, and placebo on large and small sensory and motor fibers, aiming to advance analgesic development. Further objectives of IMI-BioPain include optimizing sensitivity to change for peripheral nerve excitability outcomes and

testing for clinical evidence for sodium channel block by pregabalin or tapentadol.

Materials and Methods

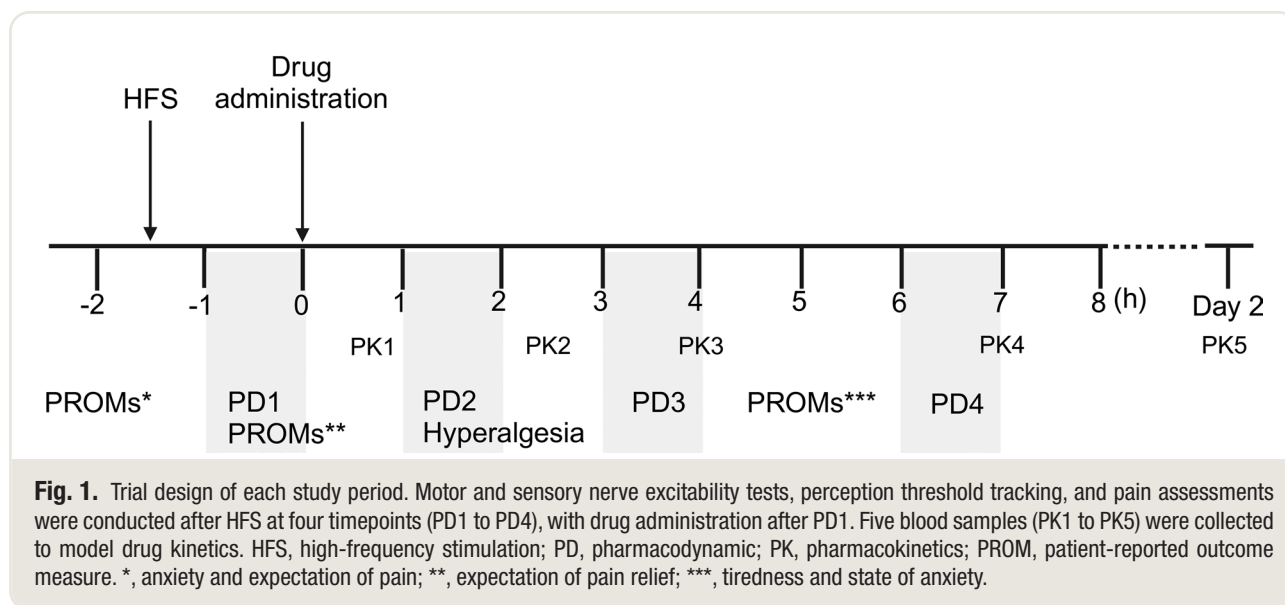
Study Design

IMI2-PainCare-BioPain-RCT1 was a single-dose, multinational, placebo-controlled, subject- and assessor-blind, randomized four-way crossover trial in healthy subjects to study the effect of lacosamide, pregabalin, and tapentadol on peripheral nerve excitability. The study was performed from July 2020 to February 2022 at four sites: Denmark (Danish Pain Research Center, Aarhus University, Aarhus), Belgium (Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels), Germany (Mannheim Center for Translational Neuroscience, University of Heidelberg, Mannheim), and Italy (Department of Human Neuroscience, Sapienza University, Rome). The study was approved by each local ethics committee and national competent authority and was registered with the European Union Clinical Trials Register on June 25, 2019 (EudraCT 2019-000942-36; principal investigator: Nanna B. Finnerup). The study was monitored by ConsulTech GmbH. All subjects gave written informed consent. Details of the methods are described in the published protocol.²

The study consisted of a screening visit and four study periods, during which pharmacodynamic testing comprising of NET was assessed before and at three timepoints after single doses of lacosamide, pregabalin, tapentadol, and placebo, separated by at least 1 week, as previously described.^{2,32} High-frequency stimulation (HFS) was applied on the left forearm to induce an area of hypersensitivity. Patient-reported outcome measures (PROMs) including subject anxiety, pain expectation, expectation of pain relief, and tiredness assessments were collected at each study period. Furthermore, five blood samples were taken to measure plasma drug levels for pharmacokinetics (fig. 1). During the screening visit, we collected PROMs including PROMIS Global-10, General Self-Efficacy, General Anxiety Disorder-7, Patient Health Questionnaire-9, and Pain Sensitivity, with comprehensive results presented separately.

Participants

Inclusion criteria included White subjects aged 18 to 45 yr with body mass index of 18 to 30 kg/m² and right-hand dominance. Exclusion criteria were abnormal electrocardiogram, vital signs and lab parameters for renal and hepatic function, alcohol consumption within the past 48 h, changes in physical exercise activities within the last week, pain within the past 4 days, sleep restriction within the last 3 days, and any drug taken within



the past 4 days, except for contraceptives (for full list, please see supplemental tables S1 and S2, <https://links.lww.com/ALN/E168>).

Interventions, Randomization, and Blinding

The investigational medicinal products (IMPs) used in the study were (1) lacosamide (Vimpat; UCB Pharma SA, Belgium) film-coated tablets (2×100 mg), (2) pregabalin (Lyrica; Pfizer, USA) capsules (2×75 mg), (3) tapentadol (Palexia; Grünenthal GmbH, Germany) immediate-release tablets (2×50 mg), and placebo capsules ($2 \times$ hard gelatin capsules filled with mannitol and colloidal silicon dioxide). The drugs were encapsulated and identical and were supplied by the pharmacy at the Heidelberg University Hospital.

Randomization was performed by the pharmacy.² The randomization process involved the use of four “four-period sequences” arranged in blocks, where each sequence was a random permutation of the four four-period sequences within a (basic) Latin square.³³ The basic Latin square was chosen randomly from a selection of the 24 available, see table 5.1 in Senn,³³ namely the Williams squares therein, with the constraint that each medication precedes each other medication once in this Latin square. The randomization was done by site. For each treatment period, a sealed decoding envelope was provided for each randomization number. Each envelope contained the identification of the IMP allocated to the respective subject.² The investigator, trial personnel, and subjects were blinded to the assignment of pregabalin, tapentadol, lacosamide, and placebo (double-blind procedure). The personnel analyzing plasma samples for pharmacokinetics analysis were unblinded during the analysis but submitted blinded data to the trial database.

Induction of Hyperalgesia Using HFS

We applied high-frequency electrical pulses to the skin of the left forearm using a multipin electrode (electrical painful stimulus P10; MRC Systems GmbH, Heidelberg, Germany) designed to selectively activate cutaneous nociceptors to induce a stable secondary hyperalgesia.^{34–36} We initially treated the skin with antiseptic and positioned the electrode on the left volar forearm, half-way distally from cubital fossa and along the midline. We then determined the electrical detection threshold (EDT) employing the Method of Limits. After the perception of the first stimulus with an increasing intensity of 0.05 mA, we administered up to six subsequent stimuli, acquiring three suprathreshold and three subthreshold values, from which we calculated the geometric mean to determine the definitive EDT. An electrical painful stimulus (electrical painful stimulus = EDT $\times$ 10) was applied to check whether it caused distal irradiation of pain or muscle contractions, and then repositioning of the electrode was necessary. The HFS with an intensity of EDT $\times$ 20 (1.5 mA lower and 8 mA higher cutoff) consisted of trains of 100-Hz pulses each lasting for 1 s with an interstimulus interval of 9 s and a pulse width of 2 ms. This sequence was repeated five times. The HFS protocol was delivered by DS5 isolated bipolar constant current stimulator (Digitimer Ltd., United Kingdom) and controlled by QtracS (written by H. Bostock, Institute of Neurology, University College London, London, United Kingdom). The subjects rated the painfulness of each stimulus by assigning a number between 0 and 100, where 0 was no pain and no “sharp,” “pricking,” “stinging,” or “burning” sensation, and 100 was the most intense pain imaginable.

Assessments

HFS-induced Hyperalgesia and Allodynia. The mapping of hyperalgesia and allodynia was performed on the left (sensitized) forearm using a 128-mN pin prick and a cotton swab.³⁷ The subjects were instructed to close their eyes and were asked to report if and when they felt the stimulus intensity change, such as becoming more intense or causing more pricking or stinging sensations. The stimuli were applied with a delay of up to 1.5 s to minimize priming and windup effects (supplemental fig. S1, <https://links.lww.com/ALN/E168>). The radius was calculated as the mean of the eight radii measured in millimeters.

Hyperalgesia testing and dynamic mechanical allodynia (DMA) assessments were conducted at both the control (nonsensitized) and test (sensitized) forearms. The control site referred to the contralateral location, mirroring the test site, and the test site was defined as within a minimum radius of 1 cm from the point where the multipin cathode of the electrode was positioned. To evaluate mechanical pain sensitivity, weighted pinprick stimuli of varying intensities (16, 64, and 256 mN) were administered, and the pain intensity was rated on a numerical rating scale ranging from 0 to 100. Three stimulus intensities were repeatedly applied in a randomized sequence at both sites. DMA was assessed using a cotton swab, cotton wisp, and soft brush interposed between pinprick stimuli. Three trials of each of the three innocuous stimuli were conducted at both sites. Participants were promptly asked to provide a numerical pain rating after each stimulus. Hyperalgesia was determined by calculating the geometric mean difference of the pain ratings obtained from the pinprick stimuli and DMA as the mean difference of innocuous stimuli between control and test sites.

Peripheral Nerve Excitability Using Threshold Tracking. During each pharmacodynamic session, the skin was cleansed, and the electrodes were positioned. Initially, perception threshold tracking was conducted on the right (nonsensitized) forearm. Subsequently, motor and sensory NETs were carried out on the right wrist. Last, perception threshold tracking was performed on the left (sensitized) forearm.

Motor and Sensory Nerve Excitability Tests. Motor and sensory NETs were performed on the median nerve in the right (nonsensitized) wrist using the QtracS computerized program (developed by the Institute of Neurology, University College London and distributed by Digitimer Ltd.), as previously described.² Modified shorter protocols, specifically Trondheim Motor Excitability Protocol (TRONDOLM) and Trondheim Sensory Excitability Protocol (TRONDOLS) for motor and sensory NET³⁸ respectively, were employed for this study. Numerous excitability parameters were evaluated, encompassing the following aspects: (1) analysis of the stimulus response curve to determine the amplitude of the target response, (2) measurement of the SDTC as an indicator of

passive membrane properties and nodal persistent Na⁺ conductance, (3) assessment of hyperpolarizing and depolarizing threshold electrotonus (TEh and TE_d) to gauge internodal conductance and membrane potential, and (4) examination of the recovery cycle of excitability, which evaluated the restoration of excitability subsequent to an action potential and provided insights into the function of nodal Na⁺ channels. Among these, SDTC was chosen as a primary endpoint due to its sensitivity to changes in persistent sodium channel activity, a key pharmacologic target of lacosamide. SDTC provides a direct measure of membrane properties and channel function with robust reliability. Rheobase was not prioritized due to its higher susceptibility to variability from factors such as stimulus intensity and skin resistance.³¹ This rationale aligns with findings from previous studies highlighting SDTC's robustness compared to rheobase in assessing pharmacologic effects.^{30,38}

Small Fiber Nerve Excitability Tests. To evaluate the excitability of small nerve fibers, the TRONDRT4B protocol controlled by QtracS was employed for conducting perception threshold tracking.³⁸ This was examined on both sensitized and nonsensitized forearms. The multipin MRC electrode (the same one used for HFS) was positioned on the skin. The perception threshold was estimated by progressively increasing the intensity of repeated stimulations until the subject perceived the stimulation, as indicated by a button press. Since the subject signaled when the stimulation was barely detectable, the sensations experienced were typically nonpainful. The TRONDRT4B protocol modulated stimulus current intensity and pulse width. Stimulus intensity was automatically adjusted in small steps (0.05 mA) to track perception thresholds, while pulse widths varied across seven predetermined durations (ranging from 0.1 to 1.0 ms). This approach allowed precise assessment of SDTC, calculated from the relationship between stimulus charge and duration as described by Weiss's law. Pia *et al.*³⁸ reported moderate retest reliability of the TRONDRT4B protocol for small sensory fibers, potentially contributing to data variability. To mitigate this, we applied strict quality thresholds, excluding recordings that failed predefined reliability criteria, ensuring robust analyses.

Rating of Pain Intensity and Unpleasantness. Participants rated the intensity of pain and unpleasantness experienced during each pharmacodynamic session using a numerical rating scale ranging from 0 to 100.

Pharmacokinetics. In each study period, four blood samples, each measuring 6 ml, were drawn on the day of drug dosing. Additionally, one blood sample was collected the following day in tubes containing K2-EDTA as an anticoagulant. All blood samples were centrifuged within 30 min after collection. Consequently, a total of 132 ml of blood was obtained

per subject over the four study periods. The collected plasma was promptly frozen at temperatures ranging from -20° to -80°C within 1 h of sampling. They remained frozen until being sent for analysis.

Welab conducted the bioanalysis using validated methods. A noncompartmental analysis was applied to the individual concentration-time profiles to estimate the pharmacokinetic parameters for lacosamide, pregabalin, and tapentadol. Drug levels at all sampling times were analyzed on samples collected from subjects who received an active treatment. Only a single timepoint sample, 150 min (2.5 h) or 240 min (4 h), was analyzed in subjects who received placebo. However, these placebo samples were analyzed for lacosamide, pregabalin, and tapentadol. Therefore, the bioanalytical facility was unblinded to analyze multiple timepoints from the specific active treatments and single timepoints from corresponding placebos. A total of 676 valid results for all three drugs were obtained from a total of 30 bioanalytical runs.

Patient-reported Outcome Measures (PROMs). Participants were asked to rate their tiredness on a scale of 0 to 100, where 0 indicated “very alert” and 100 indicated “very sleepy.” Anxiety was measured using the State-Trait Anxiety Inventory (Mind Garden, Inc., USA).³⁶ Both tiredness and anxiety were assessed 5 h after the administration of the IMP.

Adverse Events and Safety. The study thoroughly documented any potential adverse events through a comprehensive registration process. Adverse events were evaluated through open-ended questions during each interaction, including both visits and telephone calls. The severity of adverse events and the potential relationship between the treatment drug and the adverse event were categorized as unrelated, unlikely related, possibly related, or probably related. Severity was further classified as mild, moderate, or serious. The adverse events were categorized according to the MedDRA dictionary. Serious adverse events encompassed outcomes such as death, life-threatening situations, the need for hospitalization or extension of existing hospital stays, persistent or significant disability, or occurrences of congenital anomalies or birth defects.

Predefined Objectives and Outcomes

The study was designed with two primary and three key secondary objectives. The two primary objectives were to compare SDTC changes from baseline to the first pharmacodynamic postdose timepoint in (1) large sensory fibers and (2) large motor fibers between lacosamide and placebo periods. The three key secondary objectives were to compare SDTC changes in (1) large sensory fibers and (2) large motor fibers between pregabalin and/or tapentadol and placebo periods (first pharmacodynamic postdose

and (3) to compare SDTC changes in small sensory fibers between lacosamide and placebo periods (first pharmacodynamic postdose). We chose lacosamide as the primary drug because of its expected effects on the peripheral compartment assessed in RCT1.

The primary endpoints were the changes of the SDTC measured in large sensory and large motor fibers, both at the scheduled first pharmacodynamic postdose timepoint relative to their respective predose pharmacodynamic measurements (*i.e.*, the difference from the baseline to the postdose timepoint for each study period). The key secondary endpoint was the SDTC measurement in small sensory fibers, assessed at the planned first pharmacodynamic postdose timepoint, relative to the predose baseline measurement.

In addition, we evaluated sensitivity to change for other prespecified and exploratory endpoints (1) hyperpolarizing threshold electrotonus (TEh [90 to 100 ms], TEh [peak, -70%]) and S2 accommodation, and (2) recovery cycle of nerve excitability (refractoriness, 2.5 ms [%] and relative refractory period), compared to the baseline, while all other endpoints including depolarizing threshold electrotonus [TEd(peak), TEd(10–20ms), TEd(40–60ms), accommodation half time, TEd40(Accom), TEd20(peak), TEd20(10–20ms), subexcitability, and superexcitability] were exploratory. Timepoints later than PD2 were exploratory. SDTC changes in small sensory fibers for pregabalin and/or tapentadol compared to placebo were also included as exploratory endpoints. The primary analyses were lacosamide *versus* placebo and the change from baseline to first pharmacodynamic postdose timepoint.

Statistical Analysis

Sample Size. Research on the variability and effect sizes of excitability parameters has been conducted in various patient populations. Specifically, studies have examined amyotrophic lateral sclerosis patients treated with retigabine,³⁹ and patients with neuropathic pain and healthy controls treated with mexiletine.⁴⁰ These studies identified group differences of 0.04 to 0.06 ms in motor nerve excitability (0.416 *vs.* 0.458)^{39,40} and sensory nerve measures (0.54 *vs.* 0.60),⁴⁰ with standard deviations around 0.085, potentially reaching up to 0.10.^{39,40} In our primary analysis comparing lacosamide to placebo, we utilized a paired *t* test with a two-sided type I error of $\alpha/2 = 0.025$ and an assumed correlation of 0.5. The power analysis, conducted using STATA (StataCorp LCC, USA), indicated that a sample size yielding a power greater than 80% was reasonable. The study on large sensory fibers demonstrated significantly higher power compared to the study on motor fibers. Additionally, variations in expected standard deviations had minimal impact on power.² Considering the worst-case scenario, achieving a power of 0.80 would have necessitated 48 subjects. However, in the best-case scenario, 22 subjects

would have sufficed. To account for early dropouts, particularly during the initial phase, we planned to randomize a total of 60 subjects for entry into the treatment phase.

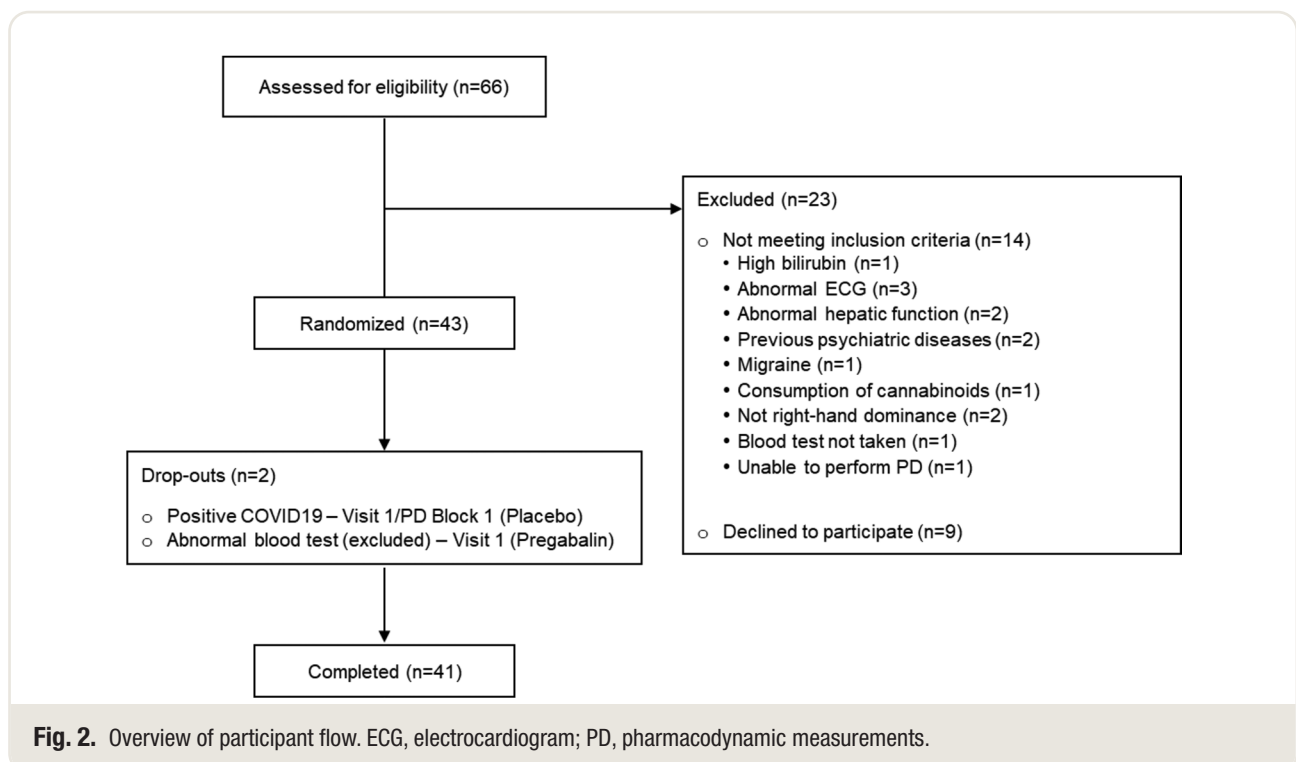
Statistical Methods. The confirmatory analyses adhered to the employed sequential multiple testing methods outlined by Bretz *et al.*⁴¹ Initially, the primary endpoints, SDTC of large sensory fibers and SDTC of motor fibers, were assessed for differences between the treatment groups, lacosamide and placebo. Lacosamide was chosen for its expected effects on the peripheral nervous system. The tests were conducted simultaneously, with the overall α divided equally between them, giving each test a type I error rate of $\alpha/2$. If significant differences were found in these tests, subsequent key secondary analyses were carried out using the α -levels carried over from the initial tests, following specified weights.²

Primary Analysis of Endpoints. The large sensory and motor fiber and small sensory fiber endpoint data, consisting of repeated measurements at the first pharmacodynamic timepoint postdose across the four periods, were analyzed using a mixed model for repeated measures (MMRM). Fixed effects in the model included baseline, treatment (four levels), timepoint (three levels), treatment by timepoint interaction along with period (four levels), and sequence to reflect the crossover design. The dependent variable in the model was the change from baseline. The variance-covariance structure for the repeated measure variable “period*timepoint” was chosen as first-order autoregressive (ar[1]).

After fitting the MMRM, robust estimates of least squares means and their differences between the lacosamide and placebo treatments were obtained by specifying appropriate contrasts for the comparisons. The estimate, along with the corresponding 95% CI and *P* value, is provided. The method for testing the primary endpoints, comparing the other treatment groups (pregabalin and tapentadol) with placebo, mirrored the model specifications used in the primary analysis. The method for testing other endpoints was identical to the specifications outlined in the primary analysis.

Additional Analyses. Several additional secondary analyses were conducted, including primary endpoint parameter extraction, functional biomarker analysis, PROMs item analysis, complex hierarchical modeling, and variance and effect size estimation for candidate endpoints for future clinical trials. Demographic and baseline characteristics were summarized using descriptive statistics. Biomarker response repeatability was assessed using Bland and Altman’s statistics.⁴² The mixed-effect model accounted for missing data.

Interpretation of Effect Sizes. Cohen’s *d* effect sizes were calculated based on the least squares mean differences obtained from the MMRM to classify and interpret the observed effects. We considered effect sizes minimal if Cohen’s *d* values are 0.2 or lower, indicating trivial effects unlikely to be



clinically relevant. Moderate effect sizes, ranging from 0.3 to 0.5, suggest some clinical significance. Large effect sizes are defined as Cohen's *d* values above 0.5, reflecting substantial differences likely to be clinically important.⁴³

This approach aligns with the predefined statistical analysis plan (SAP), ensuring consistency in evaluating treatment effects while accurately reflecting the crossover design of the study. The SAP did not specify additional analyses for carryover effects, as the study was not powered to detect such effects or higher-order interactions, and the model assumes their absence. Carryover effects were minimized by a 1-week washout period and the short elimination half-lives of the drugs (13 h for lacosamide, 6 h for pregabalin, and 4 h for tapentadol) and were confirmed by the absence of measurable drug concentrations at subsequent visits. Consequently, the model assumes the absence of carryover effects, consistent with the SAP and study design.

Results

Participants

A total of 66 individuals were screened for participation of which 43 met the inclusion and exclusion criteria. Two dropped out, and thus 41 completed the study (fig. 2). The 43 participants included in the data analysis ranged in age from 18 to 42 yr, and 49% were women (table 1).

HFS-induced Hyperalgesia and Allodynia

The detection threshold for superficial electrical nociceptive stimulation was reproducible across the four visits with mean $\pm$ SD HFS intensity of 2.5 ± 1.3 mA. Pain scores for HFS train 1 to 5 increased slightly from 45.6 ± 19.1 to 48.8 ± 19.3 , 50.1 ± 19.3 , 50.1 ± 19.4 , and 50.2 ± 19.8 , respectively. The HFS intensity and pain scores by treatment groups are presented in supplemental tables S3 and S4 (<https://links.lww.com/ALN/E168>). All participants showed areas of hyperalgesia and allodynia. The radius of pinprick hyperalgesia after medication was approximately 20 mm. The area of DMA was small, and

the intensity was very low (less than 1/100) in most participants; this precluded detailed analysis due to a floor effect (supplemental tables S5 and S6, <https://links.lww.com/ALN/E168>).

Pharmacodynamics

Primary and Key Secondary Objectives. Lacosamide statistically significantly reduced SDTC in large sensory fibers compared to placebo at the first postdose period (PD2) compared to baseline (PD1) (-0.044 ; 95% CI, -0.077 to -0.010 ; $P = 0.012$; Cohen's $d = -0.54$). The reduction in SDTC became more pronounced at later postdose periods (PD3 and PD4), with a greater reduction in SDTC observed at PD3 (-0.07 ; 95% CI, -0.11 to -0.04 ; $P < 0.001$; Cohen's $d = -0.88$), which persisted at PD4 (-0.08 ; 95% CI, -0.11 to -0.04 ; $P < 0.001$; Cohen's $d = -0.97$). These results suggest that lacosamide progressively decreases nerve excitability in large sensory fibers over time, likely due to its slower pharmacokinetic profile. In large motor fibers, lacosamide caused a smaller reduction in SDTC (-0.037 ; 95% CI, -0.072 to 0.002 ; $P = 0.039$; Cohen's $d = -0.45$), although this did not reach the preset statistical significance threshold of $P < 0.025$ (table 2; figs. 3 and 4). Additionally, lacosamide did not statistically significantly affect SDTC levels in small sensory fibers, either in the sensitized or in the nonsensitized arm, at the first postdose period (PD2) compared to baseline (PD1) (fig. 5; supplemental figure S2, <https://links.lww.com/ALN/E168>; supplemental table S7, <https://links.lww.com/ALN/E168>). However, these results may have been influenced by missing data, primarily caused by poor-quality recordings that did not meet reliability thresholds. The missing data were evenly distributed across treatment groups and did not vary systematically between the sensitized and nonsensitized arms. The relatively small number of reliable recordings ($N = 31$ across PD1 to PD4 for both arms) may have further affected reproducibility and reduced statistical power.

No statistically significant changes in SDTC were observed in large sensory or motor fibers with either pregabalin or tapentadol treatment compared to placebo at PD2, and this lack of effect remained consistent across the later timepoints (PD3 and PD4) (table 2; figs. 3 and 4). While the primary focus of this study was on SDTC due to its established reliability and sensitivity as a biomarker of nerve excitability, we also evaluated rheobase as part of the nerve excitability parameters. No statistically significant or consistent drug effects were observed on rheobase across treatment groups (data not shown), which supports the prioritization of SDTC for assessing pharmacodynamic effects.

Other Prespecified Objectives. Lacosamide, pregabalin, and tapentadol did not produce statistically significant changes in TEh (90 to 100 ms) in either large sensory or motor

Table 1. Demographics and Baseline Characteristics

Characteristic	Mean $\pm$ SD	Range
Age, yr	25.4 ± 4.5	18–42
Weight, kg	70.1 ± 12.1	48–98
Height, cm	173.6 ± 11.1	150–198
Body mass index, kg/m ²	23.1 ± 2.1	18.6–29.4
Edinburgh handedness test score (right hand dominance)	92.0 ± 11.4	60–100
Systolic blood pressure, mmHg	119.1 ± 10.5	98–135
Diastolic blood pressure, mmHg	77.4 ± 9.0	51–90
Respiratory rate, breaths/min	14.3 ± 2.4	10–20

N = 43 (21 women and 22 men).

Table 2. Comparison of Treatment Effects on SDTC (ms) for Large Sensory and Motor Nerve Fibers

Measure	Lacosamide (N = 41)	Pregabalin (N = 42)	Tapentadol (N = 41)	Placebo (N = 42)
Large sensory fibers				
Baseline (PD1)				
Mean $\pm$ SD	0.60 $\pm$ 0.11	0.59 $\pm$ 0.10	0.59 $\pm$ 0.10	0.58 $\pm$ 0.11
Range	0.33 to 0.82	0.39 to 0.89	0.37 to 0.95	0.32 to 0.85
Time 1 (PD2)				
Mean $\pm$ SD	0.58 $\pm$ 0.11	0.64 $\pm$ 0.11	0.59 $\pm$ 0.08	0.61 $\pm$ 0.11
Difference from baseline, mean $\pm$ SD	-0.01 $\pm$ 0.08	0.05 $\pm$ 0.08	0.01 $\pm$ 0.09	0.04 $\pm$ 0.09
Difference <i>versus</i> placebo				
LS mean $\pm$ SE	-0.04 $\pm$ 0.02	0.02 $\pm$ 0.02	-0.02 $\pm$ 0.02	
95% CI	-0.08 to -0.01	-0.02 to 0.05	-0.05 to 0.02	
P value	0.012	0.32	0.27	
Cohen's <i>d</i>	-0.54	0.21	-0.24	
Time 2 (PD3)				
Mean $\pm$ SD	0.58 $\pm$ 0.11	0.62 $\pm$ 0.12	0.61 $\pm$ 0.12	0.65 $\pm$ 0.12
Difference from baseline, mean $\pm$ SD	-0.01 $\pm$ 0.08	0.04 $\pm$ 0.10	0.03 $\pm$ 0.11	0.07 $\pm$ 0.11
Difference <i>versus</i> placebo				
LS mean $\pm$ SE	-0.07 $\pm$ 0.02	-0.02 $\pm$ 0.02	-0.03 $\pm$ 0.02	
95% CI	-0.11 to -0.04	-0.05 to 0.02	-0.06 to 0.01	
P value	< 0.001	0.30	0.18	
Cohen's <i>d</i>	-0.88	-0.23	-0.31	
Time 3 (PD4)				
Mean $\pm$ SD	0.56 $\pm$ 0.11	0.61 $\pm$ 0.12	0.59 $\pm$ 0.10	0.63 $\pm$ 0.12
Difference from baseline, mean $\pm$ SD	-0.03 $\pm$ 0.09	0.02 $\pm$ 0.07	0.01 $\pm$ 0.09	0.05 $\pm$ 0.13
Difference <i>versus</i> placebo				
LS mean $\pm$ SE	-0.08 $\pm$ 0.02	-0.02 $\pm$ 0.02	-0.04 $\pm$ 0.02	
95% CI	-0.11 to -0.04	-0.06 to 0.01	-0.07 to -0.00	
P value	< 0.001	0.17	0.041	
Cohen's <i>d</i>	-0.97	-0.3	-0.44	
Large motor fibers				
Baseline (PD1)				
Mean $\pm$ SD	0.46 $\pm$ 0.10	0.45 $\pm$ 0.09	0.44 $\pm$ 0.08	0.44 $\pm$ 0.09
Range	0.34 to 0.70	0.32 to 0.70	0.27 to 0.71	0.29 to 0.72
Time 1 (PD2)				
Mean $\pm$ SD	0.47 $\pm$ 0.09	0.48 $\pm$ 0.11	0.46 $\pm$ 0.08	0.49 $\pm$ 0.12
Difference from baseline, mean $\pm$ SD	0.01 $\pm$ 0.07	0.02 $\pm$ 0.09	0.02 $\pm$ 0.08	0.05 $\pm$ 0.08
Difference <i>versus</i> placebo				
LS mean $\pm$ SE	-0.04 $\pm$ 0.02	-0.02 $\pm$ 0.02	-0.03 $\pm$ 0.02	
95% CI	-0.07 to 0.00	-0.06 to 0.01	-0.06 to 0.01	
P value	0.039	0.19	0.17	
Cohen's <i>d</i>	-0.45	-0.28	-0.30	
Time 2 (PD3)				
Mean $\pm$ SD	0.49 $\pm$ 0.12	0.48 $\pm$ 0.11	0.47 $\pm$ 0.11	0.51 $\pm$ 0.11
Difference from baseline, mean $\pm$ SD	0.03 $\pm$ 0.11	0.03 $\pm$ 0.08	0.03 $\pm$ 0.10	0.07 $\pm$ 0.09
Difference <i>versus</i> placebo				
LS mean $\pm$ SE	-0.04 $\pm$ 0.02	-0.04 $\pm$ 0.02	-0.04 $\pm$ 0.02	
95% CI	-0.07 to -0.00	-0.07 to 0.00	-0.08 to -0.00	
P value	0.045	0.06	0.034	
Cohen's <i>d</i>	-0.44	-0.43	-0.47	
Time 3 (PD4)				
Mean $\pm$ SD	0.48 $\pm$ 0.10	0.47 $\pm$ 0.11	0.46 $\pm$ 0.10	0.48 $\pm$ 0.08
Difference from baseline, mean $\pm$ SD	0.02 $\pm$ 0.09	0.02 $\pm$ 0.09	0.02 $\pm$ 0.10	0.03 $\pm$ 0.10
Difference <i>versus</i> placebo				
LS mean $\pm$ SE	-0.01 $\pm$ 0.02	-0.01 $\pm$ 0.02	-0.02 $\pm$ 0.02	
95% CI	-0.04 to 0.03	-0.05 to 0.02	-0.05 to 0.02	
P value	0.66	0.44	0.41	
Cohen's <i>d</i>	-0.1	-0.17	-0.18	

LS mean $\pm$ SE, 95% CI, and P value represent the results from a MMRM with change from baseline in SDTC of large sensory and motor fibers as the dependent variable, baseline, treatment, period, timepoint, and treatment by timepoint interaction as fixed factors as a covariate.

LS, least squares; MMRM, mixed model for repeated measures; SDTC, strength-duration time constant; SE, standard error.

fibers at any timepoint. In large sensory fibers, lacosamide was associated with nonsignificant increases in TEh (90 to 100 ms) (Cohen's *d* = 0.07 to 0.20; *P* = 0.40–0.76), while

changes in motor fibers were also not statistically significant (Cohen's *d* = 0.36; *P* = 0.11 at PD2). Pregabalin was associated with nonsignificant reductions in TEh

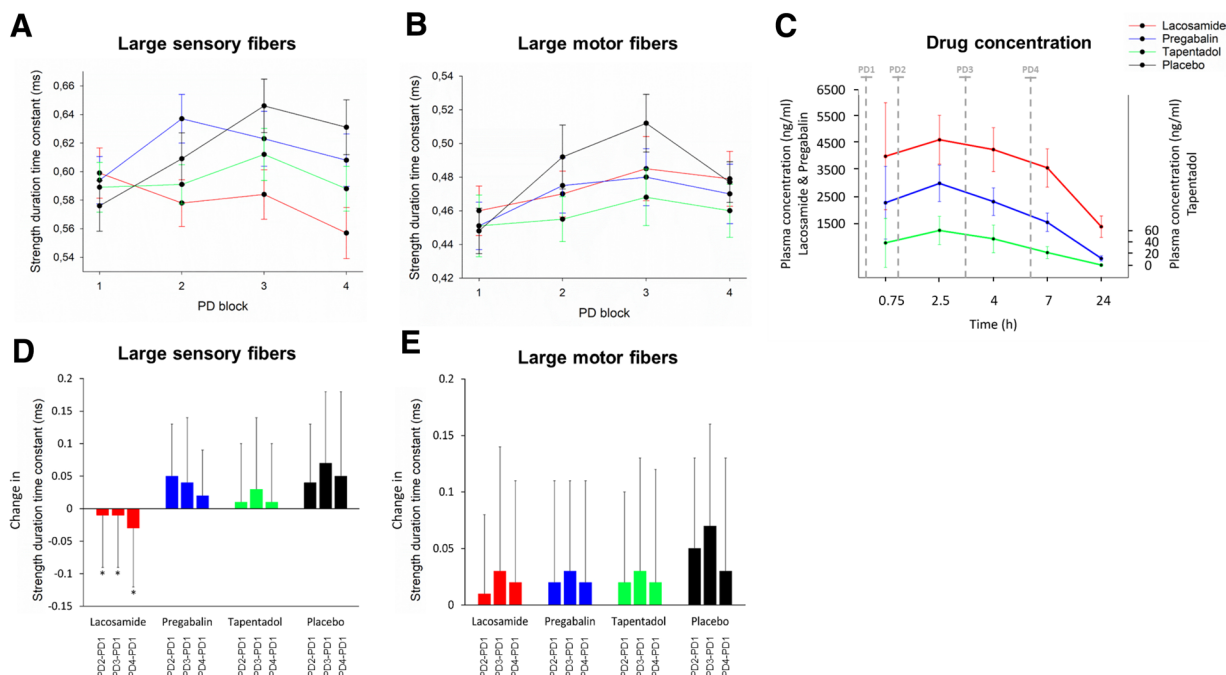


Fig. 3. Strength-duration time constant (SDTC; ms) and plasma concentration levels (ng/ml) for lacosamide (red), pregabalin (blue), tapentadol (green), and placebo (black) across PD1 to PD4. (A, B) Mean ($\pm$ SD) SDTC in large sensory (A) and motor (B) fibers measured at four PD sessions; PD1 (–1 h), PD2 (1 h), PD3 (3 h), and PD4 (6 h), with time relative to dose. (C) Plasma concentrations (mean $\pm$ SD) of lacosamide, pregabalin, and tapentadol at different timepoints (0.75, 2.5, 4, 7, and 24 h) postadministration. The timepoints for pharmacokinetic (PK) measurements do not align perfectly with the PD blocks (see fig. 1). (D, E) The change in SDTC from baseline (PD1) in large sensory (D) and motor (E) fibers is shown for each drug and placebo condition across PD blocks 2 to 4, with statistically significant reductions observed for lacosamide (*, $P < 0.025$) compared to placebo in large sensory fibers. PD, pharmacodynamic.

(90 to 100 ms) in sensory fibers at early postdose periods (Cohen's $d = 0.33$ to 0.34 ; $P = 0.14$), with further attenuation at PD4 ($P = 0.54$). Motor fiber TEh (90 to 100 ms) values after pregabalin remained statistically unchanged across all timepoints. Tapentadol did not induce any statistically significant alterations in TEh (90 to 100 ms) in either fiber type (see supplemental table S8, <https://links.lww.com/ALN/E168>).

For TEh (peak, –70%), lacosamide was associated with increases in large sensory fibers over time, although statistical significance was not consistently achieved (Cohen's $d = 0.33$ to 0.57 ; $P = 0.02$ to 0.14). Pregabalin was associated with nonsignificant reductions in TEh (peak, –70%) values (Cohen's $d = 0.42$ to 0.05 ; $P = 0.05$ to 0.85), which declined further by PD4. Tapentadol did not produce statistically significant changes in sensory fibers across any timepoint (Cohen's $d = 0.12$ to -0.01 ; $P = 0.62$ to 0.99). In motor fibers, neither lacosamide nor pregabalin produced statistically significant changes in TEh (peak, –70%; Cohen's $d = 0.16$ to 0.35 ; $P = 0.10$ to 0.45). Tapentadol was associated with a nonsignificant increase at PD4 (Cohen's $d = 0.35$; $P = 0.10$; see supplemental table S9, <https://links.lww.com/ALN/E168>).

Lacosamide statistically significantly increased S2 accommodation in large sensory fibers at all timepoints (Cohen's

$d = 0.90$ to 1.36 ; $P < 0.001$; fig. 6, A and B). Pregabalin and tapentadol did not produce statistically significant changes. No statistically significant changes in motor fibers were observed for any drug (supplemental table S10, <https://links.lww.com/ALN/E168>).

For refractoriness at 2.5 ms, lacosamide showed statistically significant reductions in sensory fibers at PD3 and PD4 (Cohen's $d = -0.67$, -0.64 ; $P = 0.005$, 0.006). Pregabalin and tapentadol were not associated with statistically significant changes at any timepoint (fig. 6C; supplemental table S11, <https://links.lww.com/ALN/E168>).

No statistically significant changes were seen in the relative refractory period (RRP) across treatments at PD2. However, at PD4, lacosamide statistically significantly reduced RRP in both sensory and motor fibers (Cohen's $d = -0.53$ and -0.63 ; $P = 0.020$ and 0.021). Tapentadol also produced a statistically significant reduction in RRP at PD3 in large sensory fibers ($P = 0.034$). Pregabalin did not produce statistically significant changes in RRP at any timepoint (fig. 6C; supplemental table S12, <https://links.lww.com/ALN/E168>).

Exploratory Objectives. Lacosamide statistically significantly increased depolarizing threshold electrotonus (TED) in

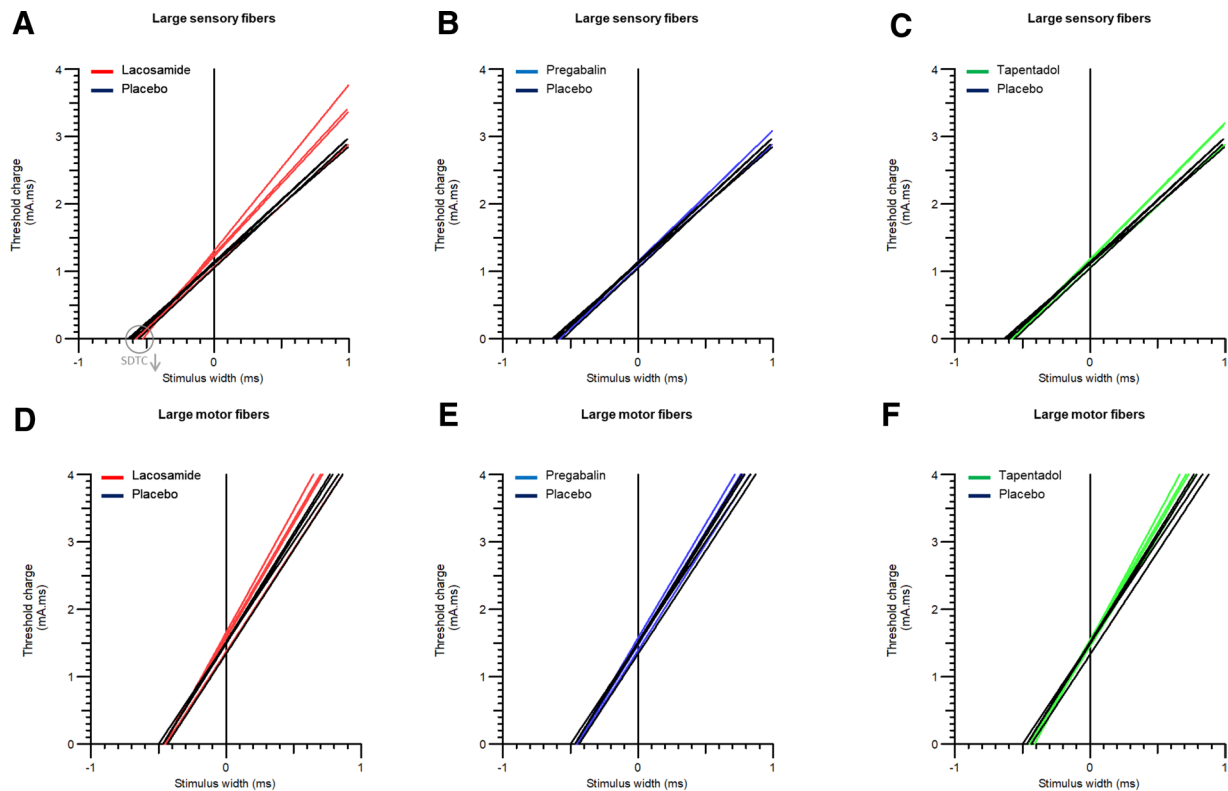


Fig. 4. Strength duration relationship for lacosamide (red), pregabalin (blue), and tapentadol (green) compared to placebo (black) in large sensory (A to C) and motor (D to F) nerve excitability testing recording. Statistically significant reduction in strength–duration time constant induced by lacosamide is highlighted in the graph.

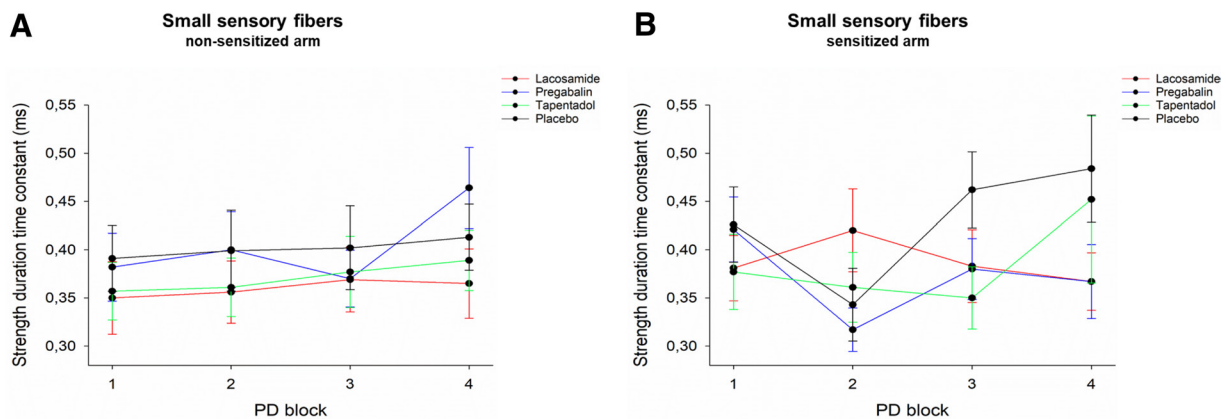


Fig. 5. Strength–duration time constant (SDTC; ms) for lacosamide (red), pregabalin (blue), tapentadol (green), and placebo (black) in small sensory perception threshold tracking (PTT) of nonsensitized arm (A) and sensitized arm (B) across PD1 to PD4. PD, pharmacodynamic.

large sensory fibers compared to placebo at PD2, with effect sizes of 1.13 for TED(peak), $P < 0.001$ and 0.77 for TED(10–20ms) ($P < 0.001$; supplemental table S13, <https://links.lww.com/ALN/E168>). Additionally, a statistically significant increase in TED40(Accom) was observed (Cohen's

$d = 1.06$; $P < 0.001$), and accommodation half-time was statistically significantly shortened from PD2 to PD3 (Cohen's $d = -0.58$, $P = 0.02$; supplemental table S14, <https://links.lww.com/ALN/E168>). In contrast, no statistically significant differences were found for TED20(peak)

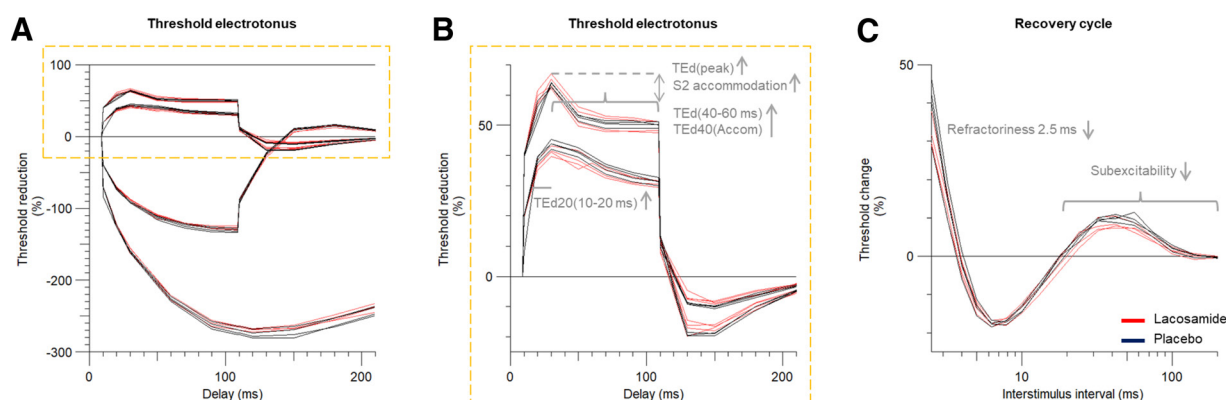


Fig. 6. Sensory nerve excitability threshold tracking recordings. (A to C) Threshold electrotonus (A, B) and recovery cycle (C) of lacosamide (red) compared to placebo (black). Statistically significant changes induced by lacosamide are highlighted in the graphs.

and TE_d20(10–20ms) in either large sensory or motor fibers across all timepoints (supplemental Table S15, <https://links.lww.com/ALN/E168>; fig. 6, A and B).

Lacosamide statistically significantly reduced subexcitability in large sensory fibers at all timepoints compared to placebo, with effect sizes of -0.93 at PD2, -1.08 at PD3, and -1.58 at PD4 ($P < 0.001$). In contrast, no statistically significant differences were observed in superexcitability for either large sensory or motor fibers at any timepoint (supplemental table S16, <https://links.lww.com/ALN/E168>; fig. 6C).

Pain Intensity and Unpleasantness. Pregabalin statistically significantly reduced both pain (-3.6 ; 95% CI, -7.06 to -0.13 ; $P = 0.05$; Cohen's $d = -0.43$) and unpleasantness (-4.94 ; 95% CI, -8.84 to -1.05 ; $P = 0.02$; Cohen's $d = -0.51$) compared to placebo at PD4. No statistically significant differences were observed for lacosamide or tapentadol compared to placebo in either pain or unpleasantness at any timepoint. Additionally, no statistically significant effects were seen for any of the treatments compared to placebo at PD1 or PD2. Detailed pain and unpleasantness scores by treatment group and timepoints are presented in supplemental table S17 (<https://links.lww.com/ALN/E168>).

Pharmacokinetics

Plasma Concentrations and Pharmacokinetic Parameters. The concentrations of the drugs reached their peak levels at the 2.5-h timepoint, *i.e.*, between PD2 and PD3 (fig. 3C). Mean plasma concentrations and pharmacokinetic parameters for lacosamide, pregabalin, and tapentadol after administration of the study drugs are shown in supplemental tables S18 and S19 (<https://links.lww.com/ALN/E168>).

Patient-reported Outcomes

Tiredness scores were statistically significantly higher after all active treatments compared to placebo with mean differences

in lacosamide of 7.76 (95% CI, 1.83 to 13.69 ; $P = 0.011$; Cohen's $d = 0.5$), pregabalin of 11.59 (95% CI, 5.60 to 17.57 ; $P < 0.001$; Cohen's $d = 0.75$), and tapentadol of 14.66 (95% CI, 8.77 to 20.55 ; $P < 0.001$; Cohen's $d = 0.94$). No statistically significant differences in anxiety scores were observed between any active treatment and placebo (supplemental table S20, <https://links.lww.com/ALN/E168>).

Adverse Events

Adverse events were reported by 29% in the lacosamide, 48% in the pregabalin, 73% in the tapentadol, and 7% in the placebo group, which primarily involved nervous system disorders such as dizziness and somnolence, as well as gastrointestinal disorders such as nausea. All adverse events were transient and mild to moderate in severity and did not result in any dropouts (supplemental table S21, <https://links.lww.com/ALN/E168>). No serious adverse events were reported during the study.

Discussion

This study found that lacosamide statistically significantly reduced SDTC in large sensory fibers, suggesting that it effectively modulates peripheral nerve function. This suggests that lacosamide may modulate sodium channel activity, including persistent Na_v currents, which are important for sensory nerve function. Additionally, changes in transient sodium channel inactivation could also contribute to the observed effects.²⁵ Pregabalin and tapentadol did not produce statistically significant changes in SDTC or other nerve excitability parameters for large sensory or motor fibers. These results emphasize the importance of drug-specific mechanisms and their relevance to different types of nerve fibers, suggesting that lacosamide may have utility in conditions related to abnormal nerve excitability.

Lacosamide demonstrated statistically significant effects on nerve excitability parameters, specifically SDTC in

large sensory fibers. SDTC is a membrane–time constant derived from the rate at which the current strength decreases as stimulus durations increase. It is influenced by persistent Na_v currents, which help sustain depolarization, but can also be affected by the availability of transient sodium channels.²⁵ Although rheobase is a viable endpoint for assessing excitability, it was not a primary focus in this study due to its higher susceptibility to variability from external factors such as stimulus intensity and skin resistance. Previous findings have noted that rheobase can reflect changes in required stimulus intensity to elicit a response but may be influenced by nonaxonal factors, limiting its reliability as a biomarker.^{30,38} Furthermore, our data showed no statistically significant or consistent drug-related effects on rheobase (data not shown), supporting the decision to prioritize SDTC as a more robust and pharmacologically relevant endpoint. SDTC, in contrast, directly reflects changes in persistent Na_v currents and membrane properties, aligning well with lacosamide's mechanism of action as a sodium channel modulator. This targeted focus on SDTC allowed us to capture the modulation of nerve excitability with greater sensitivity and reliability. The reductions in SDTC in sensory fibers observed at the first postdose pharmacodynamic session highlight the drug's capacity to modulate peripheral nerve function shortly (1 h for PD2) after administration, with statistically significant and progressively greater reductions observed at 3 (PD3) and 6 (PD4) h after administration. These findings align with the known mechanism of action of lacosamide as a sodium channel modulator and are consistent with the results reported in the study by Ruijs *et al.*,⁴⁴ suggesting its potential efficacy in conditions characterized by abnormal nerve excitability, such as neuropathic pain. Consistent with these findings, a small clinical trial showing some effect of lacosamide in peripheral neuropathic pain showed similar decreases in SDTC and increases in S2 accommodation during lacosamide treatment.¹⁴ Pregabalin and tapentadol did not exhibit statistically significant changes in SDTC for large sensory or motor fibers compared to placebo. This lack of significant effect is consistent with their pharmacologic profiles, where pregabalin primarily targets calcium channels¹⁷ and tapentadol acts on opioid receptors and noradrenaline reuptake.¹⁷

Threshold electrotonus evaluates the changes in threshold due to depolarizing and hyperpolarizing conditioning currents, revealing the properties of the internodal membrane.²⁵ Lacosamide in large sensory fibers statistically significantly increased several threshold electrotonus parameters, including S2 accommodation, TE_d(peak), TE_d(10–20 ms), TE_d40(Accom), and TE_d(40–60 ms). These findings in depolarizing threshold electrotonus contrast with the study by Ruijs *et al.*⁴⁴ The basis for these differences is not entirely clear but may reflect variations in study design, experimental conditions, or population characteristics. Further research is needed to better understand these discrepancies and their

implications for nerve excitability testing. Regarding the hyperpolarizing threshold electrotonus, we did not find any effect of lacosamide similar to Ruijs *et al.*⁴⁴ Additionally, lacosamide statistically significantly decreased subexcitability and shortened refractoriness in the recovery cycle, which is consistent with the findings of Ruijs *et al.*⁴⁴ These changes align with lacosamide's sodium channel modulation mechanism, supporting its potential in treating conditions like neuropathic pain. However, if lacosamide lack statistically significant effects on small sensory fibers, it may partially explain its relatively limited efficacy in neuropathic pain, as small fibers are key contributors to pain mechanisms. This highlights the need for further investigation into lacosamide's effects on small fiber pathways. We observed distinct effects of Na_v blockade on sensory *versus* motor nerve excitability. The effects on threshold electrotonus, and recovery cycle were more pronounced in sensory nerves compared to motor nerve fibers. These differences may be attributed to the physiologic differences in excitability profiles between motor and sensory axons of the median nerve.^{45,46} There are variations in the expression of persistent Na_v channels between motor and sensory nerves.⁴⁷ Additionally, motor axons innervating fast or slow twitch muscle fibers and cutaneous sensory neurons containing different types of afferents could be differentially affected by Na_v blockade. Factors contributing to these differences may include variations in resting membrane potential, expression of transporters like the sodium/potassium ATPase pump, and diverse ion-channel expression profiles.⁴⁴ Despite claims that recording sensory nerve action potential is more challenging than recording compound muscle action potentials, we found similar reliability between motor and sensory recordings.³⁸ Thus, the observed changes in excitability likely reflect inherent mechanistic differences.

None of the drugs statistically significantly reduced the radius or intensity of these pain responses compared to placebo. However, HFS-induced sensitization may have occurred within the first 4 h after stimulation, as suggested by Lebrun *et al.*⁴⁸, which shows increased pinprick sensitivity using similar parameters and electrodes as in this study. In our study, minimal sensitization was observed after 4 h, which may have limited the ability to detect changes and could explain the lack of statistically significant effects on pain responses.

All active drugs caused side effects and tiredness, most severe for tapentadol followed by pregabalin and lacosamide, consistent with known clinical observations.^{49,50} All side effects were mild to moderate, were transient, and did not cause any dropouts.

Although our study involved healthy volunteers, the findings have important implications for clinical practice and trials. NET could potentially be adapted into simplified bedside quantitative sensory testing, helping clinicians select analgesics tailored to individual nerve excitability profiles, for instance, guiding the choice of sodium channel modulators like lacosamide. Additionally, NET may serve as an objective biomarker

for target engagement in clinical trials, predicting treatment response and accelerating analgesic drug development.

While the study provides robust evidence for the pharmacodynamic effects of lacosamide, there are several limitations to consider. The study population consisted of healthy subjects, which may not fully represent the pathophysiologic conditions present in patients with neuropathic pain. Future studies should aim to replicate these findings in clinical populations to confirm the translational relevance of these biomarkers. Additionally, the study focused on single-dose administrations, which may not capture the full therapeutic potential of these drugs, particularly for chronic conditions. Longitudinal studies examining the effects of repeated dosing on nerve excitability are warranted to better understand the sustained impacts of these medications.

A specific limitation lies in the observed lack of statistically significant effects on small sensory fibers, particularly in the sensitized arm. While the limited number of reliable recordings ($N = 31$ on average) may have contributed to variability and reduced statistical power, this alone is unlikely to fully explain the absence of clear effects. Consistent with findings from Pia *et al.*,³⁸ the reliability of small sensory fiber SDTC measurements remains moderate, with intraday and interday intraclass correlation coefficients of 0.68 and 0.69, respectively. These values, derived from the same protocol (TRONDRT4B), fall below the threshold for good reliability (greater than or equal to 0.75) and underscore the technical challenges in obtaining reproducible small fiber data. Small sensory fibers are also inherently more susceptible to noise and variability, which may have further contributed to the observed challenges in detecting drug effects.

While the analysis showed a numerical reduction in SDTC for small sensory fibers, particularly with lacosamide (e.g., effect size of -0.5 at PD4; supplemental table S7, <https://links.lww.com/ALN/E168>), these changes did not reach statistical significance. This likely reflects a combination of variability in small fiber recordings, methodologic challenges associated with the TRONDRT4B protocol, and the pharmacologic selectivity of lacosamide, which may have a stronger impact on larger fibers. Furthermore, the pinprick hyperalgesia induced clinically suggests the facilitation of small fiber pathways, likely involving depolarization of the sensory structures measured by Qtrac. This highlights the need for further studies with improved methodologies, larger data sets, and potentially alternative protocols to better assess small fiber excitability and its modulation by lacosamide.

This study provides important foundational data for advancing nerve excitability testing as a biomarker, but additional approaches will be necessary to achieve consistent detection of drug effects on small sensory fibers, particularly in sensitized conditions. While lacosamide demonstrated statistically significant effects on SDTC and other excitability parameters in large sensory fibers, the absence of consistent effects in small fibers suggests that further methodologic

refinement is needed. Given the complex pharmacology of sodium channel modulation and the limitations of current excitability models, SDTC should be interpreted cautiously as a proxy for sodium channel activity. Nonetheless, these findings represent a critical step toward the development of NET as a tool for early-phase analgesic trials.

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Competing Interests

Dr. Bloms-Funke was an employee of Grünenthal GmbH (Aachen, Germany) when she contributed to the study protocol and reports consultancy fees from Consulech GmbH (Berlin, Germany) during the conduct of the study. Dr. Boesl is an employee of Grünenthal GmbH. Dr. Chapman is an employee of Eli Lilly and Company. Dr. Goetz and Dr. Pelz are employees and shareholders of MRC Systems GmbH (Heidelberg, Germany), a company that manufactures and markets the HFS electrodes used in this study, as well as other instruments for quantitative testing of pain. Dr. Kostenko was an employee of Heidelberg University and received salary as a research assistant when she contributed to the study. Dr. Möller-Grell was an employee of the Heidelberg University Institute for Medical Informatics and the University Hospital Heidelberg Department of Anesthesia. Dr. Pogatzki-Zahn has received payments from Grünenthal, Merck, MSD Sharp and Dohme GmbH, and Medtronic for advisory board activities and lecture fees and has received funding for research from the Gemeinsamer Bundesausschuss, the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No. 777500 (this Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation program and European Federation of Pharmaceutical Industries and Associations), Grünenthal, the (DFG, German Research Foundation, Bonn, Germany), and the Bundesministerium für Bildung und Forschung (BMBF, German Federal Ministry of Education and Research, Berlin, Germany) (all payments were made to the institution Dr. Pogatzki-Zahn works for). Dr. Schubart is an employee of ConsulTech GmbH. Dr. Vincent has received payments to her institution for lectures, consultancy, and associated travel costs from Reckitts, Gesynta, and Gedeon Richter. Dr. Truini has received consultancy fees and research funding from Abbvie, Amgen, Epitech,

Grünenthal, and Viatrix. Dr. Vollert has conducted contract research for Viatrix and AstraZeneca. Dr. Wanigasekera is funded by Oxford Health BioMedical Research Center. Dr. Treede reports grants from the IMI2-PainCare project of the European Union and grants from TEVA and Esteve during the conduct of the study, as well as personal fees from Bayer, Grünenthal, GSK, Merz, Saluda, Sanofi, and Vertex outside the submitted work; in addition, Dr. Treede holds patent No. DE 103 31 250.1-35 with royalties paid by MRC Systems. Dr. Finnerup has received consultancy fees from PharmNovo, Vertex, NeuroPN, Saniona, Nanobiotix, and Neurvati and has undertaken consultancy work for Aarhus University with remunerated work for AKIGAI, Biogen, Merz, and Confo Therapeutics outside the submitted work. The other authors declare no competing interests.

Reproducible Science

Full protocol available at: z.nochi@clin.au.dk. Raw data available at: z.nochi@clin.au.dk.

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Supplemental Digital Content

Supplemental figures and tables, <https://links.lww.com/ALN/E168>

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