# Efficacy, safety and tolerability of lacosamide in patients with gain-of-function Nav1.7 mutations related small fiber neuropathy: a randomized, double-blind, placebo controlled, crossover trial

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Study Rationale and ObjectivesThe objective of the study is to determine the efficacy and safety of lacosamide, a sodium channel blocker, in patients with pain due to SCN9A-associated SFN. The proposed study plans to recruit patients with clinically...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Peripheral neuropathies |
| **Study type** | Observational non invasive |

## Summary

### ID

NL-OMON41621

**Source**
ToetsingOnline

**Brief title**
MaYa-Nav1.7 study

### Condition

- Peripheral neuropathies

**Synonym**
peripheral nerve disorder, Small fiber neuropathy

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Medisch Universitair Ziekenhuis Maastricht
**Source(s) of monetary or material Support:** Princes Beatrix Spierfonds

## Intervention

**Keyword:** lacosamide, Nav1.7 mutations, small fiber neuropathy

## Outcome measures

### Primary outcome

Endpoints

Primary Endpoint

* Change from baseline in the average pain score as measured using a Pain

Intensity Numerical Rating Scale [PI-NRS], an 11-point numerical scale where 0

= no pain and 10 = worst possible pain.

### Secondary outcome

Secondary Endpoints

* Maximum Pain Score on the PI-NRS.

* Neuropathic Pain Scale (NPS).

* Daily Sleep Interference Scale (DSIS).

* Patient Global Impression of Change (PGIC).

* Small Fiber Neuropathy Symptoms Inventory questionnaire (SFN-SIQ).

* Generic short-form SF-36 health survey (SF-36).

* Adverse Events, Laboratory Safety Tests (Hematology, Clinical Chemistry,

Urinalysis), Blood Pressure, Pulse Rate, ECG

# Study description

**Background summary**

Indication
Lacosamide is a functionalized amino acid with antinociceptive properties in inflammatory and neuropathic pain, 1-6 and displays a unique mechanism: it enhances slow inactivation of Nav1.3, Nav1.7, and Nav1.8. 7 8
Rationale
A significant body of evidence implicates sodium channels in mediating the pathophysiological components of both neuropathic and nociceptive pain. 9 10 This is supported by clinical evidence suggesting that local anaesthetics, anticonvulsants and tricyclic compounds that block voltage-gated sodium channels may act as useful therapeutics for managing and treating pain.11 The use of these sodium channel blockers has, however, been limited by the lack of selectivity for different sodium channel subtypes with often additional CNS and cardiovascular side effects. Therefore, a key to improvement on the limitations of most existing sodium channel blockers is to selectively target those that are involved in pain mechanisms whilst sparing those channels involved in cardiovascular function.12
Nav1.7 is expressed predominantly in nociceptive and sympathetic neurons. The role of this channel in nociceptive neurons has been characterized by human genetics, which indicates an essential and non-redundant role in pain transduction and conduction following noxious stimuli. Gain-of-function mutations have been described in Nav1.7 that result in extreme pain disorders such as inherited erythromelalgia (IEM), paroxysmal extreme pain disorder (PEPD) and SCN9A-associated small fiber neuropathy.13-15 In the disease states genetically linked to a gain-of-function of Nav1.7, the channel is mutated to increase the sodium influx resulting in a hyperexcitable sensory neuron, and a resultant sensation of pain.
Lacosamide is a functionalized aminoacid that was synthesized during the development of anticonvulsant drug candidates and has displayed antinociceptive properties in inflammatory and neuropathic pain.1-6 Lacosamide displays a unique mechanism of action in that it seemingly selectively stabilizes channels into the slow- inactivated state.7 Lacosamide inhibited currents from Nav1.3, Nav1.7, and Nav1.8, but only after prolonged depolarizations, consistent with an enhancement in slow-inactivation with no effect on fast inactivation.8 Furthermore, lacosamide was better able to discriminate between resting and inactivated channels compared to lidocaine or carbamazepine, thus likely allowing for improved selectivity over neurons with a depolarized membrane potential, with little tonic block.

Small fiber neuropathy (SFN) is a relatively common disorder of peripheral nerves, primarily affecting small somatic fibers, autonomic fibers, or both.16 In a proportion of patients with SFN, no underlying cause can be identified; these cases are termed idiopathic SFN. Gain-of-function mutations in SCN9A

have recently been reported to be present in 28% of patients with idiopathic SFN,15 suggesting an underlying genetic basis for a proportion of patients with this disease. Electrophysiological analysis demonstrated multiple gain-of-function changes in the mutant channels with each of the mutations resulting in hyperexcitability in dorsal root ganglion (DRG) neurons.15 Moreover, most of these mutations showed impaired slow inactivation of Nav1.7, a finding that provides a rationale to evaluate the possible pain reduction potential of lacosamide in this condition.

## Study objective

Study Rationale and Objectives
The objective of the study is to determine the efficacy and safety of lacosamide, a sodium channel blocker, in patients with pain due to SCN9A-associated SFN. The proposed study plans to recruit patients with clinically diagnosed SFN, where a mutation in SCN9A has been confirmed genetically, and where possible, has been demonstrated on functional testing, to cause hyperexcitability of DRG neurons. This small, precision medicine population provides an opportunity to evaluate the efficacy and safety of lacosamide in treatment of pain due to SCN9A-associated SFN.

Objectives
Primary Objective
* The primary objective of this study is to evaluate the efficacy of lacosamide versus placebo in subjects with SCN9A-associated SFN.
Secondary Objectives
* To evaluate effect on maximum pain of subjects treated with lacosamide versus placebo.
* To evaluate effect on neuropathic pain quality in subjects treated with lacosamide versus *placebo.
* To evaluate subject * reported sleep interference due to pain in subjects treated with lacosamide versus placebo.
* To evaluate subject*s global impression of change in subjects treated with lacosamide versus placebo.
* To determine the effect of lacosamide versus placebo on autonomic symptoms in SCN9A-associated SFN.
* To determine the effect of lacosamide versus placebo on health-related quality of life (HQoL).
* To evaluate the safety and tolerability of lacosamide in subjects with SCN9A-associated SFN.

## Study design

Study Design and Study Treatments
This is a randomized, double-blind, placebo-controlled, 2 period crossover study to evaluate the efficacy, safety, and tolerability of lacosamide compared

to placebo in subjects with SCN9A-associated SFN. Subjects meeting eligibility criteria, aged 18 yrs to 80 yrs will be enrolled in the study. Both males and females will be eligible for this study. Subjects will receive 200 mg lacosamide BID or equivalent placebo for 8 weeks during the study, after a titration period of 3 weeks (for lacosamide: 1st week: 50 mg BID, 2nd week: 100 mg BID, 3rd week: 150 mg BID). As part of the informed consent process, subjects will be informed that they will receive active treatment for 8 weeks (excluding titration and tapering period) during during the 1st or 2nd treatment period, but neither they, nor the study personnel will know when active treatment will be administered. This study does not require subjects to undergo a washout period to discontinue current pain medications in order to be suitable to participate in the study and undergo randomization.

**Study burden and risks**

The burden for the patient exists of visits and telephone calls, a total of approximatly 16 hours, during the 33 weeks of the trial.
There is no invasive treatment, there are no special risks for the patient, there is possibility of side effects from medication.

# Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

Small fiber neuropathy, presence of confirmed abnormality on intra-epidermal nerve fiber density evaluation (IENFD) and/or Quantitative Sensory Testing (QST) and a mutation in the SCN9A gene, confirmed by sequencing.

## Exclusion criteria

-Subjects with predominantly signs of large nerve fiber involvement (muscle weakness, loss of vibration sense, hypo-/-areflexia), clinically significant abnormal nerve conduction studies (NCS).
-History or presence of illnesses known to cause SFN (excluding diabetes mellitus), including liver, kidney or thyroid dysfunction, monoclonal gammopathy, connective tissue disorders, sarcoidosis, Sjogren syndrome, amyloidosis, Fabry disease, celiac disease, HIV and neurotoxic drugs (e.g., chemotherapy).
-Subjects taking medications with activity at sodium channels e.g., lamotrigine, carbamazapine, oxcarbazapine, mexiletine, amitriptyline, topical analgesics e.g., lidocaine patches, capsaicin patches and oral/injectable corticosteroids.

# Study design

## Design

| | |
|---|---|
| Study phase: | 3 |
| Study type: | Observational non invasive |
| Intervention model: | Crossover |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 11-11-2014 |
| Enrollment: | 20 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Vimpat |
| Generic name: | lacosamide |
| Registration: | Yes - NL outside intended use |

# Ethics review

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| Approved WMO Date: | 21-08-2013 |
| Application type: | First submission |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 16-03-2015 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 05-08-2015 |
| Application type: | First submission |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2013-001511-70-NL |
| ClinicalTrials.gov | NCT01911975 |
| CCMO | NL44313.068.13 |

# Study results

Date completed: 30-05-2017

Actual enrolment: 25

**Summary results**
Trial is onging in other countries