Clinical trial results:
The effect of lacosamide in peripheral neuropathic pain: a randomized, double-blind, placebo-controlled, phenotype-stratified study

Summary

EudraCT number	2018-003110-40
Trial protocol	DK
Global end of trial date	03 June 2022

Results information

Result version number	v1 (current)
This version publication date	18 July 2023
First version publication date	18 March 2023

Trial information

Trial identification

Sponsor protocol code	LACOSAMIDE-2018

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03777956
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aarhus University
Sponsor organisation address	Palle Juul-Jensens Boulevard, Aarhus N, Denmark, 8200
Public contact	Danish Pain Research Center, Aarhus University, 45 93508575, finnerup@clin.au.dk
Scientific contact	Danish Pain Research Center, Aarhus University, 45 78464230, finnerup@clin.au.dk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 June 2022
Global end of trial reached?	Yes
Global end of trial date	03 June 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare the change in pain intensity during treatment with a sodium-channel blocker (lacosamide) in patients with peripheral neuropathic pain with and without the irritable nociceptor phenotype

Protection of trial subjects:

Written informed consent was obtained from patient. The information interview was conducted in an office without disturbances and interruptions, and there was enough time to give information and discuss possible questions. After the interview, the patients were given the possibility of at least 24 hours to decide whether they wanted to participate in the project or not before they signed the informed consent form. The patients were informed that their participation is voluntary, and that they can withdraw from the project at any time.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 February 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 63
Worldwide total number of subjects	63
EEA total number of subjects	63

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	43
From 65 to 84 years	19

85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was performed from February 2019 to July 2022 at 2 centers in Denmark. The study was terminated prematurely due to COVID-19 lockdowns and recruitment problems.

Pre-assignment

Screening details:

We screened 422 patients and based on a clinical evaluation of in- and exclusioncriteria, 93 patients were included and randomized.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Lacosamide

Arm description:

Lacosamide 50 mg tablets, starting at 2 x 50 mg and increased by 50 mg each week until optimal symptom relief (with minimum acceptable level of side effects), not lower than 2 x 100 mg or to maximal dose 2 x 200 mg (400 mg daily)

Arm type	Experimental
Investigational medicinal product name	Lacosamide
Investigational medicinal product code	PR1
Other name	Vimpat, N03AX18
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Lacosamide treatment BID. Gradually increasing dose starting at 2 x 50 mg daily up to a maximum tolerated dose between 200-400 mg daily and then kept in a stable dose for 6 weeks, with a total treatment period of 12 weeks

Arm title	Placebo

Arm description:

Inert placebo, matched to lacosamide. Orally BID for up to 12 weeks

Arm type	Placebo
Investigational medicinal product name	PR1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to investigational product, administered BID orally for 12 weeks.

Number of subjects in period 1	Lacosamide	Placebo
Started	41	22
Completed	35	14
Not completed	6	8
Consent withdrawn by subject	-	1
Adverse event, non-fatal	2	3
Lack of efficacy	3	1
Protocol deviation	1	3

Baseline characteristics

Reporting groups	
Reporting group title	Lacosamide
Reporting group description:	
Lacosamide 50 mg tablets, starting at 2 x 50 mg and increased by 50 mg each week until optimal symptom relief (with minimum acceptable level of side effects), not lower than 2 x 100 mg or to maximal dose 2 x 200 mg (400 mg daily)	
Reporting group title	Placebo
Reporting group description:	
Inert placebo, matched to lacosamide. Orally BID for up to 12 weeks	

Reporting group values	Lacosamide	Placebo	Total
Number of subjects	41	22	63
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	30	13	43
From 65-84 years	11	8	19
85 years and over	0	1	1
Age continuous Units: years			
arithmetic mean	53.9	59.8	
standard deviation	± 15.7	± 12.8	-
Gender categorical Units: Subjects			
Female	23	6	29
Male	18	16	34

End points

End points reporting groups

Reporting group title	Lacosamide
Reporting group description:	
Lacosamide 50 mg tablets, starting at 2 x 50 mg and increased by 50 mg each week until optimal symptom relief (with minimum acceptable level of side effects), not lower than 2 x 100 mg or to maximal dose 2 x 200 mg (400 mg daily)	
Reporting group title	Placebo
Reporting group description:	
Inert placebo, matched to lacosamide. Orally BID for up to 12 weeks	

Primary: Change from baseline to end of week 12 in weekly average neuropathic pain intensity

End point title	Change from baseline to end of week 12 in weekly average neuropathic pain intensity
End point description:	
The patients rated their average neuropathic pain intensity over the past 24 hours using the numerical rating scale (NRS 0-10). A negative change from baseline indicates an improvement. The primary analysis is based on the intent-to-treat (ITT) population which includes all randomised subjects who took at least one dose of randomised study treatment.	
End point type	Primary
End point timeframe:	
Week 12	

End point values	Lacosamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	22		
Units: NRS (0-10)				
arithmetic mean (standard deviation)	-1.3 (± 2.1)	0.6 (± 1.2)		

Statistical analyses

Statistical analysis title	Lacosamide vs placebo
Comparison groups	Lacosamide v Placebo
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.15
Method	t-test, 2-sided
Parameter estimate	Median difference (final values)
Point estimate	-0.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	0.3

Secondary: Pain relief

End point title	Pain relief

End point description:

End point type	Secondary

End point timeframe:

Last week of treatment (week 12)

End point values	Lacosamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	22		
Units: Number				
Complete	2	0		
Good	8	1		
Moderate	1	5		
Mild	3	1		
None	19	13		
Worse	7	1		

Statistical analyses

Statistical analysis title	Lacosamide vs placebo
Comparison groups	Lacosamide v Placebo
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.91
Method	Wilcoxon (Mann-Whitney)

Secondary: Use of escape medication (tablets paracetamol 500 mg)

End point title	Use of escape medication (tablets paracetamol 500 mg)

End point description:

Change in average weekly number of paracetamol tablets from baseline

End point type	Secondary

End point timeframe:
During the 12 week treatment

End point values	Lacosamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	22		
Units: Tablets				
arithmetic mean (standard deviation)	-1.0 (± 7.5)	-0.6 (± 7.7)		

Statistical analyses

Statistical analysis title	Lacosamide vs placebo
Comparison groups	Lacosamide v Placebo
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.87
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	3.8

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Week 1-12 of treatment periods	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	25
Reporting groups	
Reporting group title	Lacosamide
Reporting group description: Lacosamide 50 mg tablets, starting at 2 x 50 mg and increased by 50 mg each week until optimal symptom relief (with minimum acceptable level of side effects), not lower than 2 x 100 mg or to maximal dose 2 x 200 mg (400 mg daily)	
Reporting group title	Placebo
Reporting group description: Inert placebo	

Serious adverse events	Lacosamide	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 41 (2.44%)	0 / 22 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Lacosamide	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 41 (73.17%)	14 / 22 (63.64%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	11 / 41 (26.83%)	1 / 22 (4.55%)	
occurrences (all)	11	1	
Tiredness			

subjects affected / exposed	6 / 41 (14.63%)	4 / 22 (18.18%)	
occurrences (all)	6	4	
Headache			
subjects affected / exposed	4 / 41 (9.76%)	1 / 22 (4.55%)	
occurrences (all)	4	1	
Tremor			
subjects affected / exposed	3 / 41 (7.32%)	0 / 22 (0.00%)	
occurrences (all)	3	0	
Cognitive impairment			
subjects affected / exposed	2 / 41 (4.88%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Paraesthesia			
subjects affected / exposed	1 / 41 (2.44%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Gastrointestinal disturbance			
subjects affected / exposed	3 / 41 (7.32%)	2 / 22 (9.09%)	
occurrences (all)	3	2	
Nausea			
subjects affected / exposed	2 / 41 (4.88%)	2 / 22 (9.09%)	
occurrences (all)	2	2	
Mucous membrane disorder			
subjects affected / exposed	0 / 41 (0.00%)	3 / 22 (13.64%)	
occurrences (all)	0	3	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 41 (4.88%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
itch			
subjects affected / exposed	3 / 41 (7.32%)	0 / 22 (0.00%)	
occurrences (all)	3	0	
perspiration excessive			
subjects affected / exposed	2 / 41 (4.88%)	1 / 22 (4.55%)	
occurrences (all)	2	1	
Psychiatric disorders			

Mood change			
subjects affected / exposed	2 / 41 (4.88%)	4 / 22 (18.18%)	
occurrences (all)	2	4	
sleep disturbance			
subjects affected / exposed	1 / 41 (2.44%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Involuntary urination			
subjects affected / exposed	2 / 41 (4.88%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Urinary tract infection			
subjects affected / exposed	0 / 41 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
swollen joints			
subjects affected / exposed	3 / 41 (7.32%)	1 / 22 (4.55%)	
occurrences (all)	3	1	
Restless legs syndrome			
subjects affected / exposed	2 / 41 (4.88%)	2 / 22 (9.09%)	
occurrences (all)	2	2	
Metabolism and nutrition disorders			
Weight gain			
subjects affected / exposed	4 / 41 (9.76%)	0 / 22 (0.00%)	
occurrences (all)	4	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated prematurely due to COVID-19 lockdowns and recruitment problems. The results presented here are for lacosamide vs placebo. For the primary objective, there was no statistically significant differences between IN and NIN grps

Notes: